PROTEASE SCREENING METHODS AND PROTEASES IDENTIFIED THEREBY

RELATED APPLICATIONS

Benefit of priority is claimed to U.S. Provisional Application Serial No. 60/818,804, to Edwin Madison, entitled "Protease Screening Methods and Proteases Identified Thereby," filed July 05, 2006, and to U.S. Provisional Application Serial No. 60/818,910, to Edwin Madison, entitled "Modified Urinary-Plasminogen Activator (u-PA) Proteases," filed July 05, 2006. Where permitted, the subject matter of the above-noted applications are incorporated by reference in its entirety.

This application is related to U.S. Application Serial No. (Attorney Dkt. No. 19049-002001/ 4902) to Edwin Madison, entitled "Protease Screening Methods and Proteases Identified Thereby," filed July 05, 2007, which claims priority to U.S. Provisional Application Serial No. 60/818,804 and to U.S. Provisional Application Serial No. 60/818,910.

This application also is related to U.S. Application Serial No. 10/677,977, filed October 02, 2003 and published as U.S. Application No. US-2004-0146938 on July 29, 2004, entitled "*Methods of Generating and Screening for Proteases with Altered Specificity*" to J Nguyen, C Thanos, S Waugh-Ruggles, and C Craik, and to corresponding published International PCT Application No. WO2004/031733, published April 15, 2004, which claim benefit to U.S. Provisional Application Serial No. 60/415,388 filed October 02, 2002.

This application also is related to U.S. Application Serial No. 11/104,110, filed April 02, 2005 and published as U.S. Application No. US-2006-0002916 on January 05, 2006, entitled "*Cleavage of VEGF and VEGF Receptor by Wild-Type and Mutant MTSP-1*" to J Nguyen and S Waugh-Ruggles, and to corresponding published International PCT Application No. WO2005/110453, published November 24, 2005, which claim benefit to U.S. Provisional Application Serial No. 60/561,720 filed April 12, 2004.

This application also is related to U.S. Application Serial No. 11/104,111, filed April 12, 2005 and published as U.S. Application No. US-2006-0024289 on February 02, 2006, entitled "*Cleavage of VEGF and VEGF Receptor by Wild-Type and Mutant Proteases*" to J Nguyen and S Waugh-Ruggles, and to corresponding published International PCT Application No. WO2005/100556, published October 27,

2005, which claim benefit to U.S. Provisional Application Serial No. 60/561,671 filed April 12, 2004.

This application also is related to U.S. Provisional Application Serial No. 60/729,817 filed October 21, 2005, entitled "*Modified Proteases that Inhibit Complement Activation*" to Edwin L. Madison. This application also is related to U.S. Application Serial No. 11/584,776 filed October 20, 2006, entitled "*Modified Proteases that Inhibit Complement Activation*" to Edwin L. Madison, Jack Nguyen, Sandra Waugh Ruggles and Christopher Thanos, and to corresponding published International PCT Application No. WO2007/047995, published April 26, 2007, which each claim benefit to U.S. Provisional Application No. 60/729,817.

Where permitted, the subject matter of each of the above-noted related applications is incorporated by reference in its entirety.

Incorporation by reference of Sequence Listing provided on compact discs

An electronic version on compact disc (CD-R) of the Sequence Listing is filed herewith in four copies (labeled COPY 1, COPY 2, COPY 3, and CRF), the contents of which are incorporated by reference in their entirety. The computer-readable file on each of the aforementioned compact discs, created on July 05, 2007, is identical, 1,809 kilobytes in size, and titled 4902SEQ.PC1.txt.

FIELD OF THE INVENTION

Methods for identifying modified proteases with modified substrate specificity or other properties are provided. The methods screen candidate and modified proteases by contacting them with a substrate that traps them upon cleavage of the substrate.

BACKGROUND

Proteases are protein-degrading enzymes. Because proteases can specifically interact with and inactivate or activate a target protein, they have been employed as therapeutics. Naturally-occurring proteases often are not optimal therapeutics since they do not exhibit the specificity, stability and/or catalytic activity that renders them suitable as biotherapeutics (see, *e.g.*, Fernandez-Gacio *et al.* (2003) *Trends in Biotech.* 21: 408-414). Among properties of therapeutics that are important are lack of immunogenicity or reduced immunogenicity; specificity for a target molecule, and limited side-effects. Naturally-occurring proteases generally are deficient in one or more of these properties.

Attempts have been made to engineer proteases with improved properties. Among these approaches include 1) rational design, which requires information about the structure, catalytic mechanisms, and molecular modeling of a protease; and 2) directed evolution, which is a process that involves the generation of a diverse mutant repertoire for a protease, and selection of those mutants that exhibit a desired characteristic (Bertschinger *et al.* (2005) in *Phage display in Biotech. and Drug Discovery* (Sidhu s, ed), pp. 461-491). For the former approach, a lack of information regarding the structure-function relationship of proteases limits the ability to rationally design mutations for most proteases. Directed evolution methodologies have been employed with limited success.

Screening for improved protease activity often leads to a loss of substrate selectivity and vice versa. An optimal therapeutic protease should exhibit a high specificity for a target substrate and a high catalytic efficiency. Because of the limited effectiveness of available methods to select for proteases with optimized specificity and optimized activity, there remains a need to develop alternate methods of protease selection. Accordingly, it is among the objects herein to provide methods for selection of proteases or mutant proteases with desired substrate specificities and activities.

SUMMARY

Provided are methods for selection or identification of proteases or mutant proteases or catalytically active portions thereof with desired or predetermined substrate specificities and activities. In particular, provided herein are protease screening methods that identify proteases that have an altered, improved, or optimized or otherwise altered substrate specificity and/or activity for a target substrate or substrates. The methods can be used, for example, to screen for proteases that have an altered substrate specificity and/or activity for a target substrate involved in the etiology of a disease or disorder. By virtue of the altered, typically increased, specificity and/or activity for a target substrate, the proteases identified or selected in the methods provided herein are candidates for use as reagents or therapeutics in the treatment of diseases or conditions for which the target substrate is involved. In practicing the methods provided herein, a collection of proteases or catalytically active portion thereof is contacted with a protease trap polypeptide resulting in the formation of stable complexes of the protease trap polypeptide with proteases or

catalytically active portion thereof in the collection. In some examples, the protease trap polypeptide is modified to be cleaved by a protease having a predetermined substrate specificity and/or activity for a target substrate, for example, a target substrate involved in a disease or disorder. The method can further comprise screening the complexes for substrate specificity for the cleavage sequence of the target substrate. In such examples, the identified or selected protease has an altered activity and/or specificity towards the target substrate. In one example, the stable complex is formed by covalent linkage of a selected protease with a protease trap polypeptide. The selected proteases or catalytically active portion thereof are identified or selected from the complex in the methods provided herein. The methods provided herein can further include the step of separating the complexed proteases from the uncomplexed protease members of the collection. In one example, the protease trap polypeptide is labeled for detection or separation and separation is effected by capture of complexes containing the detectable protease trap polypeptide and the protease or catalytically active portion thereof. Capture can be effected in suspension, solution or on a solid support. In instances where capture is by a solid support, the protease trap polypeptide is attached to the solid support, which can be effected before, during or subsequent to contact of the protease trap polypeptide with the collection of proteases or catalytically active portions thereof. The solid support can include, for example, a well of a 96-well plate. In some examples, the protease trap polypeptide is labeled with biotin. In other examples, the protease trap polypeptide can be labeled with a His tag and separation can be effected by capture with a metal chelating agent such as, but not limited to, nickel sulphate ($NiSO_4$), cobalt chloride ($CoCl_2$), copper sulphate ($CuSO_4$) and zinc chloride ($ZnCl_2$). The metal chelating agent can be conjugated to a solid support, such as for example, on beads such as sepharose beads or magnetic beads.

In the methods provided herein, the method can further include a step of amplifying the protease or catalytically active portion thereof in the separated complexes. In some examples, the protease or catalytically active portion thereof in the separated complex is displayed on a phage, and amplification is effected by infecting a host cell with the phage. The host cells can include a bacteria, for example, E.coli. The amplified protease, either from bacterial cell medium, bacterial periplasm, phage supernatant or purified protein, can be screened for specificity

and/or activity towards a target substrate. Typically, the target substrate is a polypeptide or cleavage sequence in a polypeptide involved in the etiology of a disease or disorder.

Also provided herein is a multiplexing method whereby the collection of proteases are contacted with a plurality of different protease trap polypeptides, including modified forms thereof, where each of the protease trap polypeptides are labeled such that they can be identifiably detected. In such methods, at least two protease trap polypeptides are identifiable labeled such that more than one stable complex can form and more than one protease is identified.

In the methods provided herein, the methods also include successive rounds of screening to optimize protease selection where proteases are amplified following their identification or selection in a first round of the screening methods herein, to thereby produce a second collection of proteases or catalytically active portions thereof. The second collection of proteases are contacted with a protease trap polypeptide, that is the same or different than the first protease trap polypeptide, to produce a second set of stable complexes. The proteases in the second set of stable complexes are identified or selected.

In the methods provided herein, the protease trap polypeptide is a serpin, a member of the alpha macroglobulin family, or a member of the p35 family. Such a polypeptide molecule used in the methods provided herein forms a stable complex by covalent linkage of a protease or catalytically active portion thereof with the protease trap polypeptide.

In one aspect of the method provided herein, proteases are identified that have a desired substrate specificity by contacting a collection of protease and/or proteolytically active portions of proteases with a protease trap polypeptide to form stable complexes of the protease trap polypeptide with a protease upon cleavage of the protease trap polypeptide. The protease trap polypeptide, or modified form thereof, is selected for use in the methods for purposes of being cleaved by a protease having the desired substrate specificity. In the methods, the protease or proteolytically active portion thereof is identified to select for a protease having a desired substrate specificity.

The collection of proteases used in the methods provided herein are any collection of proteases or catalytically active portions thereof and include members

with at least, about, or equal to 5, 10, 50, 100, 10^3, 10^4, 10^5, 10^6 or more different members. In some aspects, the proteases are serine and/or cysteine proteases. In the methods provided herein, the collection of proteases or catalytically active portions thereof are displayed for contact with a protease trap polypeptide. In one example, the protease or proteolytically active portion thereof are displayed on a solid support, cell surface, or on a surface of a microorganism. The protease can be displayed on yeast, bacterium, a virus, a phage, a nucleic acid, an mRNA molecule, or on ribosomes. Where the protease or proteolytically active portion thereof is displayed on a microorganism the microorganism includes, but is not limited to, E. coli, S.cerevisiae, or a virus such as an M13, fd, or T7 phage, or a baculovirus. In the methods provided herein, the proteases or proteolytically active portions thereof are displayed on a phage display library and the protease collection is a protease phage display library. In some embodiments, the proteases are provided in the collections, such as by display, as proteolytically active portions of a full-length protease. In some examples, contact of a protease collection with a protease trap polypeptide is in a homogenous mixture.

Provided herein is a method of protease selection where at least two different protease trap polypeptides are contacted with the collection, but where only one of the protease trap polypeptides is detectably labeled. The protease trap polypeptide that is detectably labeled permits the capture of stable complexes containing the detectable protease trap polypeptide and a protease or catalytically active portion thereof. In some examples of this method, the one or more other protease trap polypeptides that are not detectably labeled are present in excess in the reaction compared to the detectably labeled protease trap polypeptide. In the methods, the label is any label for detection thereof, such as a fluorescent label or an epitope label such as a His tag. In other examples, the detectable label is biotin.

The collection of proteases for which selection is made in the methods provided herein include any collection of proteases. In some examples, the proteases are serine or cysteine proteases. The collection of proteases include those that are members of the chymotrypsin and subtilisin family of serine proteases or from the caspases of the papain family of cysteine proteases. The proteases include any proteases, or catalytically active portion thereof, set forth in Table 7. In some examples, the protease or catalytically active portion thereof are collections of

urokinase plasminogen activator (u-PA) proteases, tissue plasminogen activator (t-PA) proteases, or MT-SP1 proteases.

In one aspect, the protease trap polypeptides used in the methods provided herein are serpins, p35 family members, alpha-macroglobulin family members, or any modified forms thereof. A protease trap polypeptide used in the methods provided herein include, but is not limited to, plasminogen inhibitor-1 (PAI-1), antithrombin (AT3), or alpha 2-macroglobulin, or modified forms thereof. Modified forms of a protease trap polypeptide used in the methods provided herein included those containing amino acid replacement, deletions, or substitutions in the reactive site of the protease trap polypeptide. In some examples, the modification is any one or more amino acid replacements corresponding to a cleavage sequence of a target substrate. The target substrate can be any protein involved in an etiology of a disease or disorder. Examples of target substrates include, but are not limited to, a VEGFR, a t-PA cleavage sequence, or a complement protein. For example, target substrates include, but are not limited to, VEGFR2 or complement protein C2. The cleavage sequence of a target substrate includes, but is not limited to, any set forth in any of SEQ ID NOS: 389, 479 and 498. In some aspects, the protease trap polypeptide is a serpin and the one or more amino acid replacements is/are in the reactive site loop of the serpin polypeptide. The one or more replacements in the reactive site loop (RSL) include those in any one or more of the P4-P2' positions. Exemplary of such serpins used in the methods provided herein are any set forth in any of SEQ ID NOS: 497, 499, 610 and 611. In another example, the protease trap polypeptide is an alpha 2 macroglobulin and the one or more amino acid replacements are in the bait region of the polypeptide. The proteases identified or selected in the methods herein against a modified protease trap polypeptide can be screened or selected for altered substrate specificity for the target substrate as compared to a non-target substrate. In such examples, the non-target substrate includes a substrate of the corresponding template protease. Typically, the substrate specificity of the identified or selected protease is increased by 1.5-fold, 2-fold, 5-fold, 10-fold, 50-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold or more.

The methods provided herein include those that are iterative where the method of identifying and/or selecting for proteases with a desired substrate specificity is repeated or performed a plurality of times. In such methods, a plurality of different

proteases can be identified in the first iteration, or the first round, of the method. In other examples, a plurality of proteases are generated and prepared after the first iteration based on the identified proteases selected in the first round of iteration. Additionally, in some examples, the amino acid sequences of selected proteases identified in the first round or iteration and/or in successive rounds are compared to identify hot spots. Hot spots are those positions that are recognized as a modified locus in multiple rounds, such as occur in at least 2, 3, 4, 5 or more identified proteases, such as compared to a wild-type or template protease, from a collection of modified proteases used in the method.

Also provided in the method herein is a further step of, after identifying a protease or proteases, preparing a second collection of proteases, where an identified protease is used a template to make further mutations in the protease sequence or catalytically active portion thereof such that members of the second collection (are based on) contain polypeptides having mutations of the identified proteases and additional mutations; then contacting the second collection with a protease trap polypeptide that is either identical or different from the protease trap used to isolate the first protease or proteases, where the protease trap is modified to be cleaved by a protease having the desired substrate specificity; and identifying a protease(s) or proteolytically active portion(s) of a protease from the collection in a complex, whereby the identified protease(s) has greater activity or specificity towards the desired substrate than the first identified protease. The second collection can contain random or focused mutations compared to the sequence of amino acids of the identified template protease(s) or proteolytically active portion of a protease. Focused mutations, include, for example, hot spot positions, such as positions 30, 73, 89 and 155, based on chymotrypsin numbering, in a serine protease, such as u-PA.

In practicing the methods, the reaction for forming stable complexes can be modulated by controlling one or more parameters. Such parameters are any that alter the rate or extent of reaction or efficiency of the reaction, such as, but are not limited to, reaction time, temperature, pH, ionic strength, library concentration and protease trap polypeptide concentration.

The reactions can be performed in the presence of a competitor of the reaction between a protease trap polypeptide and a protease or proteolytically active portion thereof to thereby enhance selectivity of identified protease(s) or proteolytically

active portion(s). Competitors include, for example, serum or plasma. Such as human serum or human plasma, a cell or tissue extract, a biological fluid, such as urine or blood, a purified or partially purified wild type form (or other modified form) of the protease trap. Exemplary of such competitors is a purified or partially purified wild-type form of a protease trap polypeptide or one or more specific variants of a protease trap polypeptide.

Iterative methods for evolving or selecting or identifying a protease or proteolytically active portion thereof with specificity/selectivity and/or activity for at least two cleavage sequences are provided. The methods include the steps of: a) contacting a collection of proteases and/or proteolytically active portions of proteases with a first protease trap polypeptide to form, upon cleavage of the protease trap polypeptide by the protease or proteolytically active portion thereof, stable complexes containing the protease trap polypeptide with a protease or catalytically active portion thereof in the collection, wherein contacting is effected in the presence of a competitor; b) identifying or selecting proteases or proteolytically active portions thereof that form complexes with the first protease trap polypeptide; c) contacting proteases or proteolytically active portion thereof that form complexes with the first protease trap polypeptide with a second protease trap polypeptide in the presence of a competitor; and d) identifying or selecting proteases or proteolytically active portions thereof that form complexes with the first protease trap polypeptide. The two cleavage sequences can be in one target substrate or can be in two different target substrates. The identified, selected or evolved protease or proteolytically active portion thereof has substrate specificity and/or cleavage activity for at least two different cleavage sequences in one or two different target substrates. The first and second protease trap polypeptide can be the same or different. Typically, the first and second protease trap polypeptide used in the method are different and each are modified to be cleaved by a protease having the predetermined substrate specificity for different target substrates. The method can further include repeating steps a) and b) or a)-d) at least once more until a protease with a desired or predetermined substrate specificity and cleavage activity to at least two recognition sequences is isolated. Substrate specificity and cleavage activity typically are increased compared with a template protease.

Competitors for use in the methods include anything with which the protease trap polypeptide can interact, typically with lesser stability than a target protease. Competitors include, but are not limited to, serum, plasma, human serum or human plasma, a cell or tissue extract, a biological fluid such as urine or blood, a purified or partially purified wild-type form of the protease trap, and one or more specific variants of a protease trap polypeptide.

Also provided are methods of protease selection that include the steps of: a) contacting a collection of proteases or proteolytically active portions thereof with a first protease trap polypeptide to form, upon cleavage of the protease trap polypeptide, covalent complexes of the protease trap polypeptide with any protease or catalytically active portion thereof in the collection; b) separating the complexed proteases from uncomplexed protease trap polypeptide(s); c) isolating or selecting or identifying the complexed proteases; d) generating a second collection of proteases or proteolytically active portions of proteases based on the selected proteases; and e) repeating steps a) - c) by contacting the second collection of proteases or proteolytically active portions thereof with a second protease trap polypeptide that is different from the first protease trap polypeptide to form complexes; separating the complexes; and isolating, selecting or identifying complexed proteases. The first and second protease trap polypeptides can be modified to contain two different target substrate recognition sequences, whereby the identified or selected protease has specificity and high cleavage activity to at least two recognition sequences. These methods can be repeated a plurality of times. In these methods, the collection of proteases or proteolytically active portions thereof can be contacted with the first and/or second protease trap polypeptide in the presence of a competitor (see above).

In any of the methods of protease selection provided herein, the collections can contain modified proteases. The modifications in the proteases can be random or focused or in a target region of the polypeptide.

Also provided are combinations that contain a collection of proteases and/or proteolytically active portions thereof; and at least one protease trap polypeptide. The components can be provided separately or as a mixture. The protease trap polypeptide include, among serpins, p35 family members, alpha-macroglobulin family members, modified forms of each, and mixtures thereof.

The collection of proteases and/or catalytically active portions thereof can be provided in solution or suspension or in a solid phase or otherwise displayed, such as on a solid support (matrix material) or in a display library, such as, but not limited to, a phage display library, where members display at least a proteolytically active portion of a protease.

Kits containing the combinations are provided. Typically the kits contain the packaged components and, optionally, additional reagents and instructions for performing the methods.

Also provided are methods for modifying the substrate specificity of a serine protease, such as u-PA, by modifying one or more of residues selected from 30, 73, 89 and 155 based on chymotrypsin numbering.

Also provided are modified proteases identified by the methods herein. The modified proteases provided herein exhibit altered substrate specificity and/or activity by virtue of the identified modification. Any of the modifications provided herein identified using the selection method can be made in a wild-type protease, any allelic or species variant thereof, or in any other variant of the protease. In addition, also provided herein are modified proteases containing 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to a wild-type protease, or allelic or species variant thereof, so long as the modification identified in the methods herein is present.

Among such proteases are modified proteases, including modified serine proteases in the chymotrypsin family, such as urinary plasminogen activator (u-PA) polypeptides, or catalytically active fragments thereof containing one or more mutations in hot spot positions selected from among positions 30, 73, 89, and 155, based on chymotrypsin numbering, whereby substrate specificity is altered.

Provided herein also include modified urinary plasminogen activator (u-PA) proteases identified in the method herein that exhibit increased specificity and/or activity towards a target substrate involved in the etiology of a disease or disorder. Such target substrates include, but are not limited to, a VEGFR or a tissue plasminogen activator (t-PA) substrate. Hence, also provided are modified serine proteases or catalytically active portions thereof that cleave a t-PA substrate. In particular, among such proteases are modified urinary plasminogen activator (u-PA) polypeptides in which the u-PA polypeptide or catalytically active portion thereof

contains one or more modifications in positions selected from among positions 21, 24, 30, 39, 61(A), 80, 82, 84, 89, 92, 156, 158, 159, and 187, based on chymotrypsin numbering. Also provided are such modified u-PA polypeptides or catalytically active portions thereof containing one or more mutations selected from among F21V, I24L, F30V, F30L, T39A, Y61(A)H, E80G, E82E, E84K, I89V, K92E, K156T, T158A, V159A, and K187E. Also provided are these modified u-PA polypeptides where the u-PA polypeptide or catalytically active portions thereof contain two or more mutations selected from among F30V/Y61(a)H; F30V/K82E; F30V/K156T; F30V/K82E/V159A; F30V/K82E/T39A/V159A; F30V/K82E/T158A/V159A; F30V/Y61(a)H/K92E; F30V/K82E/V159A/E80G/I89V/K187E; and F30V/K82E/V159A/E80G/E84K/I89V\K187E.

Also provided are modified serine proteases or catalytically active portions thereof that cleave VEGFR, particularly VEGFR-2. In particular, provided are modified urinary plasminogen activator (u-PA) polypeptides and catalytically active portions thereof, wherein the u-PA polypeptide or catalytically active portion thereof contains one or more modifications in positions selected from among positions 38, 72, 73, 75, 132, 133, 137, 138, 155, 160, and 217, based on chymotrypsin numbering, whereby substrate specificity to a VEGFR-2, or sequence thereof, is altered. Also provided are such polypeptides that contain one or more mutations selected from among V38D, R72G, L73A, L73P, S75P, F132L, G133D, E137G, I138T, L155P, L155V, L155M, V160A, and R217C. These polypeptides can further include a modification at position 30 and/or position 89, based on chymotrypsin numbering, such as modifications selected from among F30I, F30T, F30L, F30V, F30G, F30M, and I89V. Also provided are these u-PA polypeptides or catalytically active portions thereof that contain one or more mutations, and in some instances two or more mutations selected from among L73A/I89V; L73P; R217C; L155P; S75P/I89V/I138T; E137G; R72G/L155P; G133D; V160A; V38D; F132L/V160A; L73A/I89V/F30T; L73A/I89V/F30L; L73A/I89V/F30V; L73A/I89V/F30G; L73A/I89V/L155V; L73A/I89V/F30M; L73A/I89V/L155M; L73A/I89V/F30L/L155M; and L73A/I89V/F30G/L155M.

Also provided are modified u-PA polypeptide, wherein the u-PA polypeptide or catalytically active portion thereof contains one or more mutations selected from among F30I, F30T, F30G, and F30M.

Also provided herein are modified MT-SP1 polypeptides identified by the methods herein. Such modified polypeptides include any having one or more amino acid modifications selected from among D23E, I41F, I41T, L52M, Y60(g)s, T56K, H71R, F93L, N95K, F97Y, F97L, T98P, F99L, A126T, V129D, P131S, I136T, I136V, H143R, T144I, I154V, N164D, T166A, L171F, P173S, F184(a)L, Q192H, S201I, Q209L, Q221(a)L, R230W, F234L, and V244G, based on chymotrypsin numbering, in an MT-SP1 polypeptide set forth in SEQ ID NO:253. In some examples, the modifications are in a catalytically active portion of an MT-SP1 having a sequence of amino acids set forth in SEQ ID NO:505. In other examples, the modifications are in an MT-SP1 polypeptide further comprising a mdofication corresponding to modification of C122S in an MT-SP1 polypeptide set forth in SEQ ID NO:253, based on chymotrypsin numberiner, for example, an MT-SP1 set forth in SEQ ID NO: 507 or 517. In particular of modifications provided herein are any selected from among I41F, F97Y, L171F and V244G. The modified MT-SP1 polypeptides provided herein can further include one or more modifications corresponding to Q175R or D217V in an MT-SP1 polypeptide set forth in SEQ ID NO:253. Such modifications include any selected from among I136T/N164D/T166A/F184(A)L/D217V; I41F; I41F/ A126T/V244G; D23E/I41F/T98P /T144I; I41F/ L171F/V244G; H143R/Q175R; I41F/ L171F; R230W; I41F /I154V/V244G; I141F/L52M/ V129D/Q221(A)L; F99L; F97Y/ I136V/Q192H/S201I; H71R/ P131S/D217V; D217V; T65K/F93L/F97Y/ D217V; I41T/ P173S/Q209L; F97L/ F234L; Q175R; N95K; and Y60(G)S. Any of the above modified MT-SP1 polypeptides exhibit modifications that increase one or both of specificity for a C2 complement protein or activity towards C2 complement protein.

Also provided are pharmaceutical compositions containing the modified proteases, including modified serine proteases, such as the modified u-PA polypeptides or modified MT-SP1 polypeptides. The pharmaceutical compositions contain pharmaceutically acceptable excipients, and can be formulated for any suitable route of administration, including, but not limited to, systemic, oral, nasal, pulmonary, local and topical administration. Also provided are kits containing any of the pharmaceutical compositions, a device for administration of the composition and, optionally, instructions for administration.

Nucleic acid molecules encoding the modified proteases, including the u-PA proteases and MT-SP1 proteases and catalytically active portions thereof are provided. Also provided are vectors containing the nucleic acid molecules and cells containing the nucleic acid molecules or vectors.

Methods of treatment of subjects having a disease or condition, such as, but not limited to, a disease or condition selected from among arterial thrombosis, venous thrombosis and thromboembolism, ischemic stroke, acquired coagulation disorders, disseminated intravascular coagulation, bacterial infection and periodontitis, and neurological conditions, that is treated by administration of t-PA, by administering the pharmaceutical compositions containing the modified u-PA proteases or proteolytically active portions thereof or encoding nucleic acid molecules or the cells are provided. The methods are effected by administering a nucleic acid molecule, a cell or a pharmaceutical composition to the subject.

Also provided are methods of treating a subject having a disease or condition that is mediated by a VEGFR, particularly a VEGFR-2. Such diseases and conditions include, but are not limited to, cancer, angiogenic diseases, ophthalmic diseases, such as macular degeneration, inflammatory diseases, and diabetes, particularly complications therefrom, such as diabetic retinopathies. The methods are effected by administering a nucleic acid molecule or cell or composition containing or encoding the modified u-PA proteases that exhibit substrate specificity, particularly increased compared to the unmodified form, for VEGFR-2. The methods optionally include administering another agent for treatment of the disease or condition, such as administering an anti-tumor agent where the disease is cancer.

Also provided are methods of treating a subject having a disease or condition that is mediated by a complement protein, particularly C2. Such diseases and conditions include, but are not limited to sepsis, Rheumatoid arthritis (RA), membranoproliferative glomerulonephritis (MPGN), Multiple Sclerosis (MS), Myasthenia gravis (MG), asthma, inflammatory bowel disease, immune complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), Ischemia-reperfusion injury, and Guillan-Barre syndrome. In some examples, the ischemia-reperfusion injury is caused by an event or treatment, such as, but not limited to, myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis. The methods are effected by

administering a nucleic acid molecule or cell or composition containing or encoding the modified MT-SP1 proteases that exhibit substrate specificity, particularly increased compared to the unmodified form, for C2. In other examples, the disease or conditions results from treatment of a subject. For example, the treatment can result in complement-mediated ischemia-reperfusion injury. Such treatments include, but are not limited to, angioplasty or coronary artery bypass graft. In such examples, a modified MT-SP1 protease is administered prior to treatment of a subject. The modified MT-SP1 polypeptides can be administered by contacting a body fluid or tissue sample in vitro, ex vivo or in vivo.

Also provided herein are modified serpin polypeptides used in the methods provided herein. Such modified serpin polypeptides are modified in its reactive site loop at positions corresponding to positions P4-P2' with a cleavage sequence for a target substrate. Typically, the target substrate is involved in the etiology of a disease or disorder. Such target substrates include, but are not limited to, a VEGFR, a complement protein or a t-PA substrates. For example, target substrates include VEGFR2 and complement protein C2. Exemplary of modified serpins provided herein are modified plasminogen-activator inhibitor-1 (PAI-1) and antithrombin-3 (AT3). Exemplary modified serpins are set forth in any of SEQ ID NOS: 497, 499, 610 and 611.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the mechanism of inhibition of a protease by a serpin and the generation of a stable inhibited complex. Following contact, a serpin (**I**) and protease (**E**) initially form a noncovalent, Michaelis-like complex (**EI**). This is followed by cleavage of the P1-P1' scissile bond and nucleophilic attack by the catalytic serine of a protease on a reactive site loop (RSL) carbonyl of a serpin and the formation of a covalent acyl-enzyme intermediate ($\mathbf{EI}^{\#}$). The kinetically trapped covalent inhibitory product ($\mathbf{EI}^{+}$) is the result of RSL insertion, protease translocation, protease active site distortion, and deformation of the overall protease structure. The minor non-inhibitory pathway releases normal cleavage product, serpin (**I***), and reactive protease (**E**).

DETAILED DESCRIPTION

Outline

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A. DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the invention(s) belong. All patents, patent applications, published applications and publications, Genbank sequences, databases, websites and other published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

As used herein, a "protease trap" or "protease trap polypeptide", refers to a substrate that is cleaved by a protease and that, upon cleavage, forms a stable complex with the protease to thereby trap the proteases as the protease goes through an actual transition state to form an enzyme complex, thereby inhibiting activity of the proteases and capturing it. Thus, protease traps are inhibitors of proteases. Protease traps are polypeptides or molecules that include amino acid residues that are cleaved by a protease such that upon cleavage a stable complex is formed. The complex is sufficiently stable to permit separation of complexes from unreacted trap or from trap that has less stable interactions with the proteases. Protease traps include any molecule, synthetic, modified or naturally-occurring that is cleaved by the protease and, upon cleavage, forms a complex with the protease to permit separation of the reacted protease or complex from unreacted trap. Exemplary of such protease traps are serpins, modified serpins, molecules that exhibit a mechanism similar to serpins, such as for example, p35, and any other molecule that is cleaved by a protease and traps the protease as a stable complex, such as for example, alpha 2 macroglobulin. Also included as protease traps are synthetic polypeptides that are cleaved by a protease (or proteolytically active portion thereof) and, upon cleavage, form a stable complex with the protease or proteolytically active portion thereof.

As used herein, serpins refer to a group of structurally related proteins that inhibit proteases following cleavage of their reactive site by a protease resulting in the formation of a stable acyl-enzyme intermediate and the trapping of the protease in a stable covalent complex. Serpins include allelic and species variants and other

variants so long as the serpin molecule inhibits a protease by forming a stable covalent complex. Serpins also include truncated or contiguous fragments of amino acids of a full-length serpin polypeptide that minimally includes at least a sufficient portion of the reactive site loop (RSL) to facilitate protease inhibition and the formation of a stable covalent complex with the protease. Exemplary serpins are set forth in Table 2 and/or have a sequence of amino acids set forth in any one of SEQ ID NOS: 1-38, allelic variants, or truncated portions thereof.

As used herein a "mutant" or "variant" serpin refers to a serpin that contains amino acid modifications, particularly modifications in the reactive site loop of the serpin. The modifications can be replacement, deletion, or substitution of one or more amino acids corresponding to P_n-P_{15}-P_{14}-P_{13}....P_4-P_3-P_2-P_1-P_1'-P_2'-P_3'...Pn'-positions. Typically, the serpin contains amino acid replacements in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid positions in the reactive site loop as compared to a wild-type serpin. Most usually, the replacements are in one or more amino acids corresponding to positions P4-P2'. For example, for the exemplary PAI-1 serpin set forth in SEQ ID NO:11, the P4-P1' positions (VSARM) corresponding to amino acid positions 366-370 in SEQ ID NO:11 can be modified. Example 1 describes modification of the VSARM amino acid residues to RRVRM or PFGRS.

As used herein, a "scissile bond" refers to the bond in a polypeptide cleaved by a protease and is denoted by the bond formed between the P1-P1' position in the cleavage sequence of a substrate.

As used herein, reactive site refers to the portion of the sequence of a target substrate that is cleaved by a protease. Typically, a reactive site includes the P1-P1' scissile bond sequence.

As used herein, reactive site loop (RSL; also called reactive center loop, RCL) refers to a sequence of amino acids in a serpin molecule (typically 17 to 22 contiguous amino acids) that serve as the protease recognition site and generally contain the sole or primary determinants of protease specificity. Cleavage of the RSL sequence and conformational changes thereof are responsible for the trapping of the protease by the serpin molecule in a stable covalent complex. For purposes herein, any one or more amino acids in the RSL loop of a serpin can be modified to correspond to cleavage sequences in a desired target protein. Such modified serpins,

or portions thereof containing the variant RSL sequence, can be used to select for proteases with altered substrate specificity.

As used herein, partitioning refers to the process by which serpins partition between a stable serpin-protease complex versus cleaved serpins. The reason for partitioning in serpins pertains to the nature of the inhibitory pathway, which results from a large translocation of the cleaved reactive-site loop across the serpin surface. If the protease has time to dissociate (i.e. deacylate the enzyme-serpin complex) before adopting the inhibited location, then partitioning occurs. The outcome of a given serpin–protease interaction, therefore, depends on the partitioning ratio between the inhibitory (k_4) and substrate (k_5) pathways (such as is depicted in Figure 1), which is represented by the stoichiometry of inhibition (SI = 1 + k_5/k_4); good inhibitors have the value of 1 because most of the serpin molecules partition into complex formation and k_5/k_4 is close to 0. If the RSL loop, however, is not inserted fast enough into the protease, partitioning occurs and the reaction proceeds directly to the cleaved product.

As used herein, catalytic efficiency or kcat/km is a measure of the efficiency with which a protease cleaves a substrate and is measured under steady state conditions as is well known to those skilled in the art.

As used herein, second order rate constant of inhibition refers to the rate constant for the interaction of a protease with an inhibitor. Generally the interaction of a protease with an inhibitor, such as a protease trap, such as a serpin, is a second order reaction proportional to the product of the concentration of each reactant, the inhibitor and the protease. The second order rate constant for inhibition of a protease by a tight binding or irreversible inhibitor or a protease trap is a constant, which when multiplied by the enzyme concentration and the inhibitor concentration yields the rate of enzyme inactivation by a particular inhibitor. The rate constant for each protease trap and enzyme pair uniquely reflects their interaction. As a second order reaction, an increase in the second order rate constant means that the interaction between a modified selected protease and inhibitor is faster compared to the interaction of an unmodified protease and the inhibitor. Thus, a change in the second order rate constant reflects a change in the interaction between the components, the protease and/or inhibitor, of the reaction. An increased second order rate constant when screening for proteases can reflect a desired selected modification in the protease.

As used herein, acyl enzyme intermediate refers to the covalent intermediate formed during the first step in the catalysis between a substrate and an essential serine in the catalytic center of a serine protease (typically Ser195, based on chymotrypsin numbering). The reaction proceeds as follows: the serine –OH attacks the carbonyl carbon at the P1 position of the substrate, the nitrogen of the histidine accepts the hydrogen from the –OH of the serine, and a pair of electrons from the double bond of the carbonyl oxygen moves to the oxygen. This results in the generation of a negatively charged tetrahedral intermediate. The bond joining the nitrogen and the carbon in the peptide bond of the substrate is now broken. The covalent electrons creating this bond move to attack the hydrogen of the histidine thereby breaking the connection. The electrons that previously moved from the carbonyl oxygen double bond move back from the negative oxygen to recreate the bond resulting in the formation of a covalent acyl enzyme intermediate. The acyl enzyme intermediate is hydrolyzed by water, resulting in deacylation and the formation of a cleaved substrate and free enzyme.

As used herein, a collection of proteases refers to a collection containing at least 10 different proteases and/or proteolytically active portions thereof, and generally containing at least 50, 100, 500, 1000, 10^4, 10^5 or more members. The collections typically contain proteases (or proteolytically active portions thereof) to be screened for substrate specificity. Included in the collections are naturally occurring proteases (or proteolytically active portions thereof) and/or modified proteases (or proteolytically active portions thereof). The modifications include random mutations along the length of the proteases and/or modifications in targeted or selected regions (*i.e* focused mutations). The modifications can be combinatorial and can include all permutations, by substitution of all amino acids at a particular locus or at all loci or subsets thereof. The collections can include proteases of full length or shorter, including only the protease domain. The proteases can include any proteases, such as serine proteases and cysteine proteases. The size of the collection and particular collection is determined by the user. In other embodiments, the collection can contain as few as 2 proteases.

As used herein, "combinatorial collections" or "combinatorial libraries" refers to a collection of protease polypeptides having distinct and diverse amino acid mutations in its sequence with respect to the sequence of a starting template protease

polypeptide sequence. The mutations represented in the collection can be across the sequence of the polypeptide or can be in a specified region or regions of the polypeptide sequence. The mutations can be made randomly or can be targeted mutations designed empirically or rationally based on structural or functional information.

As used herein, a "template protease" refers to a protease having a sequence of amino acids that is used for mutagenesis thereof. A template protease can be the sequence of a wild-type protease, or a catalytically active portion thereof, or it can be the sequence of a variant protease, or catalytically active portion thereof, for which additional mutations are made. For example, a mutant protease identified in the selection methods herein, can be used as a starting template for further mutagenesis to be used in subsequent rounds of selection.

As used herein, random mutation refers to the introduction of one or more amino acid changes across the sequence of a polypeptide without regard or bias as to the mutation. Random mutagenesis can be facilitated by a variety of techniques known to one of skill in the art including, for example, UV irradiation, chemical methods, and PCR methods (*e.g.*, error-prone PCR).

As used herein, a focused mutation refers to one or more amino acid changes in a specified region (or regions) or a specified position (or positions) of a polypeptide. For example, targeted mutation of the amino acids in the specificity binding pocket of a protease can be made. Focused mutagenesis can be performed, for example, by site directed mutagenesis or multi-site directed mutagenesis using standard recombinant techniques known in the art.

As used herein, a stable complex between a protease trap and a protease or a proteolytically active portion thereof refers to a complex that is sufficiently stable to be separated from proteases that did not form complexes with the protease trap (*i.e.* uncomplexed proteases). Such complexes can be formed via any stable interaction, including covalent, ionic and hydrophobic interactions, but are sufficiently stable under the reaction conditions to remain complexed for sufficient time to separate complexes for isolation. Typically such interactions, such as between serpins and cleaved proteases, are covalent bonds.

As used herein, a "hot spot" refers to a position that is mutated in multiple variants resulting from the protease selection that exhibit improved activity and/or

selectivity for the desired new substrate sequence. One or more "hot spots" can be identified during protease selection. Hence, such positions are specificity and/or selectivity determinants for the protease and thereby contribute to substrate specificity and also can occur as broad specificity and/or selectivity determinants across the corresponding locus in more than one member of a protease family, such as a serine protease family or a particular protease family, such as based on chymotrypsin numbering.

As used herein, desired specificity with reference to substrate specificity refers to cleavage specificity for a predetermined or preselected or otherwise targeted substrate.

As used herein, "select" or grammatical variations thereof refers to picking or choosing a protease that is in complex with a protease trap polypeptide. Hence, for purposes herein, select refers to pulling out the protease based on its association in stable complexes with a protease trap polypeptide. Generally, selection can be facilitated by capture of the covalent complexes, and if desired, the protease can be isolated. For example, selection can be facilitated by labeling the protease trap polypeptide, for example, with a predetermined marker, tag or other detectable moiety, to thereby identify the protease based on its association in the stable complex.

As used herein, "identify" and grammatical variations thereof refers to the recognition of or knowledge of a protease in a stable complex. Typically, in the methods herein, the protease is identified by its association in a stable complex with a protease trap polypeptide, which can be accomplished , for example, by amplification (i.e. growth in an appropriate host cell) of the bound proteases in the complex followed by DNA sequencing.

As used herein, labeled for detection or separation means that that the molecule, such as a protease trap polypeptide, is associated with a detectable label, such as a fluorophore, or is associated with a tag or other moiety, such as for purification or isolation or separation. Detectably labeled refers to a molecule, such as a protease trap polypeptide, that is labeled for detection or separation.

As used herein, reference to amplification of a protease or proteolytically active portion of a protease, means that the amount of the protease or proteolytically active portion is increased, such as through isolation and cloning and expression, or, where the protease or proteolytically active portion is displayed on a microorganism,

the microorganism is introduced into an appropriate host and grown or cultured so that more displayed protease or proteolytically active portion is produced.

As used herein, homogeneous with reference to a reaction mixture means that the reactants are in the liquid phase as a mixture, including as a solution or suspension.

As used herein, recitation that a collection of proteases or proteolytically active portions of proteases is "based on" a particular protease means that the collection is derived from the particular protease, such as by random or directed mutagenesis or rational design or other modification scheme or protocol, to produce a collection.

As used herein, a disease or condition that is treated by administration of t-PA refers to a disease or condition for which one of skill in the art would administer t-PA. Such conditions include, but are not limited to, fibrinolytic conditions, such as arterial thrombosis, venous thrombosis and thromboembolism, ischemic stroke, acquired coagulation disorders, disseminated intravascular coagulation, and precursors thereto, such as bacterial or viral infections, periodontitis, and neurological conditions.

As used herein, a disease or condition that is mediated by VEGFR-2 is involved in the pathology or etiology. Such conditions include, but are not limited to, inflammatory and angiogenic conditions, such as cancers, diabetic retinopathies, and ophthalmic disorders, including macular degeneration.

As used herein, "proteases," "proteinases" and "peptidases" are interchangeably used to refer to enzymes that catalyze the hydrolysis of covalent peptidic bonds. These designations include zymogen forms and activated single-, two- and multiple-chain forms thereof. For clarity, reference to protease refers to all forms. Proteases include, for example, serine proteases, cysteine proteases, aspartic proteases, threonine and metallo-proteases depending on the catalytic activity of their active site and mechanism of cleaving peptide bonds of a target substrate.

As used herein, a zymogen refers to a protease that is activated by proteolytic cleavage, including maturation cleavage, such as activation cleavage, and/or complex formation with other protein(s) and/or cofactor(s). A zymogen is an inactive precursor of a proteolytic enzyme. Such precursors are generally larger, although not necessarily larger than the active form. With reference to serine proteases, zymogens are converted to active enzymes by specific cleavage, including catalytic and

autocatalytic cleavage, or by binding of an activating co-factor, which generates an active enzyme. A zymogen, thus, is an enzymatically inactive protein that is converted to a proteolytic enzyme by the action of an activator. Cleavage can be effected autocatalytically Zymogens, generally, are inactive and can be converted to mature active polypeptides by catalytic or autocatalytic cleavage of the proregion from the zymogen.

As used herein, a "proregion," "propeptide," or "pro sequence," refers to a region or a segment that is cleaved to produce a mature protein. This can include segments that function to suppress enzymatic activity by masking the catalytic machinery and thus preventing formation of the catalytic intermediate (*i.e.*, by sterically occluding the substrate binding site). A proregion is a sequence of amino acids positioned at the amino terminus of a mature biologically active polypeptide and can be as little as a few amino acids or can be a multidomain structure.

As used herein, an activation sequence refers to a sequence of amino acids in a zymogen that are the site required for activation cleavage or maturation cleavage to form an active protease. Cleavage of an activation sequence can be catalyzed autocatalytically or by activating partners.

Activation cleavage is a type of maturation cleavage in which a conformational change required for activity occurs. This is a classical activation pathway, for example, for serine proteases in which a cleavage generates a new N-terminus which interacts with the conserved regions of catalytic machinery, such as catalytic residues, to induce conformational changes required for activity. Activation can result in production of multi-chain forms of the proteases. In some instances, single chain forms of the protease can exhibit proteolytic activity as a single chain.

As used herein, domain refers to a portion of a molecule, such as proteins or the encoding nucleic acids, that is structurally and/or functionally distinct from other portions of the molecule and is identifiable.

As used herein, a protease domain is the catalytically active portion of a protease. Reference to a protease domain of a protease includes the single, two- and multi-chain forms of any of these proteins. A protease domain of a protein contains all of the requisite properties of that protein required for its proteolytic activity, such as for example, its catalytic center.

As used herein, a catalytically active portion or proteolytically active portion of a protease refers to the protease domain, or any fragment or portion thereof that retains protease activity. Significantly, at least *in vitro*, the single chain forms of the proteases and catalytic domains or proteolytically active portions thereof (typically C-terminal truncations) exhibit protease activity.

As used herein, a "nucleic acid encoding a protease domain or catalytically active portion of a protease" refers to a nucleic acid encoding only the recited single chain protease domain or active portion thereof, and not the other contiguous portions of the protease as a continuous sequence.

As used herein, recitation that a polypeptide consists essentially of the protease domain means that the only portion of the polypeptide is a protease domain or a catalytically active portion thereof. The polypeptide can optionally, and generally will, include additional non-protease-derived sequences of amino acids.

As used herein, "S1-S4" refers to amino acid residues that form the binding sites for P1-P4 residues of a substrate (see, *e.g.*, Schecter and Berger (1967) *Biochem Biophys Res Commun* 27:157-162). Each of S1-S4 contains one, two or more residues, which can be non-contiguous. These sites are numbered sequentially from the recognition site N-terminal to the site of proteolysis, referred to as the scissile bond.

As used herein, the terms "P1-P4" and "P1'-P4'" refer to the residues in a substrate peptide that specifically interact with the S1-S4 residues and S1'-S4' residues, respectively, and are cleaved by the protease. P1-P4 refer to the residue positions on the N-terminal side of the cleavage site; P1'-P4' refer to the residue positions to the C-terminal side of the cleavage site. Amino acid residues are labeled from N to C termini of a polypeptide substrate (Pi, ..., P3, P2, P1, P1', P2', P3', ..., Pj). The respective binding sub-sites are labeled (Si,..., S3, S2, S1, S1', S2', S3',..., Sj). The cleavage is catalyzed between P1 and P1.'

As used herein, a "binding pocket" refers to the residue or residues that interact with a specific amino acid or amino acids on a substrate. A "specificity pocket" is a binding pocket that contributes more energy than the others (the most important or dominant binding pocket). Typically, the binding step precedes the formation of the transition state that is necessary for the catalytic process to occur. S1-S4 and S1'- S4' amino acids make up the substrate sequence binding pocket and

facilitate substrate recognition by interaction with P1-P4 and P1'-P4'amino acids of a peptide, polypeptide or protein substrate, respectively. Whether a protease interacts with a substrate is a function of the amino acids in the S1-S4 and S1'-S4' positions. If the amino acids in any one or more of the S1, S2, S3, S4, S1', S2', S3' and S4' sub-sites interact with or recognize any one or more of the amino acids in the P1, P2, P3, P4, P1', P2', P3' and P4' sites in a substrate, then the protease can cleave the substrate. A binding pocket positions a target amino acid with a protease so that catalysis of a peptide bond and cleavage of a substrate is achieved. For example, serine proteases typically recognize P4-P2' sites in a substrate; other proteases can have extended recognition beyond P4-P2'.

As used herein, amino acids that "contribute to extended substrate specificity" refers to those residues in the active site cleft in addition to the specificity pocket. These amino acids include the S1-S4, S1'-S4' residues in a protease.

As used herein, secondary sites of interaction are outside the active site cleft. These can contribute to substrate recognition and catalysis. These amino acids include amino acids that can contribute second and third shell interactions with a substrate. For example, loops in the structure of a protease surrounding the S1-S4. S1'-S4' amino acids play a role in positioning P1-P4, P1'-P4' amino acids in the substrate thereby registering the scissile bond in the active site of a protease.

As used herein, active site of a protease refers to the substrate binding site where catalysis of the substrate occurs. The structure and chemical properties of the active site allow the recognition and binding of the substrate and subsequent hydrolysis and cleavage of the scissile bond in the substrate. The active site of a protease contains amino acids that contribute to the catalytic mechanism of peptide cleavage as well as amino acids that contribute to substrate sequence recognition, such as amino acids that contribute to extended substrate binding specificity.

As used herein, a "catalytic triad" or "active site residues" of a serine or cysteine protease refers to a combination of amino acids, typically three amino acids, that are in the active site of a serine or cysteine protease and contribute to the catalytic mechanism of peptide cleavage. Generally, a catalytic triad is found in serine proteases and provides an active nucelophile and acid/base catalysis. The catalytic triad of serine proteases contains three amino acids, which in chymotrypsin are

Asp^{102}, His^{57}, and Ser^{195}. These residues are critical for the catalytic efficiency of a serine protease.

As used herein, the "substrate recognition site" or "cleavage sequence" refers to the sequence recognized by the active site of a protease that is cleaved by a protease. Typically, for example, for a serine protease, a cleavage sequence is made up of the P1-P4 and P1'-P4' amino acids in a substrate, where cleavage occurs after the P1 position. Typically, a cleavage sequence for a serine protease is six residues in length to match the extended substrate specificity of many proteases, but can be longer or shorter depending upon the protease. For example, the substrate recognition site or cleavage sequence of MT-SP1 required for autocatalysis is RQARVV, where R is at the P4 position, Q is at the P3 position, A is at the P2 position and R is at the P1 position. Cleavage in MT-SP1 occurs after position R followed by the sequence VVGG.

As used herein, target substrate refers to a substrate that is specifically cleaved at its substrate recognition site by a protease. Minimally, a target substrate includes the amino acids that make up the cleavage sequence. Optionally, a target substrate includes a peptide containing the cleavage sequence and any other amino acids. A full-length protein, allelic variant, isoform, or any portion thereof, containing a cleavage sequence recognized by a protease, is a target substrate for that protease. Additionally, a target substrate includes a peptide or protein containing an additional moiety that does not affect cleavage of the substrate by a protease. For example, a target substrate can include a four amino acid peptide or a full-length protein chemically linked to a fluorogenic moiety.

As used herein, cleavage refers to the breaking of peptide bonds by a protease. The cleavage site motif for a protease involves residues N- and C-terminal to the scissile bond (the unprimed and primed sides, respectively, with the cleavage site for a protease defined as ... P3-P2-P1-P1'-P2'-P3' ..., and cleavage occurs between the P1 and P1' residues). Typically, cleavage of a substrate is an activating cleavage or an inhibitory cleavage. An activating cleavage refers to cleavage of a polypeptide from an inactive form to an active form. This includes, for example, cleavage of a zymogen to an active enzyme, and/or cleavage of a progrowth factor into an active growth factor. For example, MT-SP1 can auto-activate by cleaving a target substrate at the P1-P4 sequence of RQAR. An activating cleavage also is cleavage whereby a

protein is cleaved into one or more proteins that themselves have activity. For example, activating cleavage occurs in the complement system, which is an irreversible cascade of proteolytic cleavage events whose termination results in the formation of multiple effector molecules that stimulate inflammation, facilitate antigen phagocytosis, and lyse some cells directly.

As used herein, an inhibitory cleavage is cleavage of a protein into one or more degradation products that are not functional. Inhibitory cleavage results in the diminishment or reduction of an activity of a protein. Typically, a reduction of an activity of a protein reduces the pathway or process for which the protein is involved. In one example, the cleavage of any one ore more target proteins, such as for example a VEGFR, that is an inhibitory cleavage results in the concomitant reduction or inhibition of any one or more functions or activities of the target substrate. For example, for cleavage of a VEGFR, activities that can be inhibited include, but are not limited to, ligand binding, kinase activity, or angiogenic activity such as angiogenic activity *in vivo* or *in vitro*. To be inhibitory, the cleavage reduces activity by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99.9% or more compared to a native form of the protein. The percent cleavage of a protein that is required for the cleavage to be inhibitory varies among proteins but can be determined by assaying for an activity of the protein.

As used herein, a protease polypeptide is a polypeptide having an amino acid sequence corresponding to any one of the candidate proteases, or variant proteases thereof described herein.

As used herein, a "modified protease," or "mutein protease" refers to a protease polypeptide (protein) that has one or more modifications in primary sequence compared to a wild-type or template protease. The one or more mutations can be one or more amino acid replacements (substitutions), insertions, deletions and any combination thereof. A modified protease polypeptide includes those with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more modified positions. A modified protease can be a full-length protease, or can be a catalytically active portion thereof of a modified full length protease as long as the modified protease is proteolytically active. Generally, these mutations change the specificity and activity of the wild-type or template proteases for cleavage of any one or more desired or predetermined target substrates. In addition to containing modifications in regions

that alter the substrate specificity of a protease, a modified protease also can tolerate other modifications in regions that are non-essential to the substrate specificity of a protease. Hence, a modified protease typically has 60%, 70%, 80 %, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to a corresponding sequence of amino acids of a wildtype or scaffold protease. A modified full-length protease or a catalytically active portion thereof of a modified protease can include proteases that are fusion proteins as long as the fusion itself does not alter substrate specificity of a protease.

As used herein, chymotrypsin numbering refers to the amino acid numbering of a mature chymotrypsin polypeptide of SEQ ID NO:391. Alignment of a protease of the chymotrypsin family (*i.e.* u-PA, t-PA, MT-SP1, and others), including the protease domain, can be made with chymotrypsin. In such an instance, the amino acids of the protease that correspond to amino acids of chymotrypsin are given the numbering of the chymotrypsin amino acids. Corresponding positions can be determined by such alignment by one of skill in the art using manual alignments or by using the numerous alignment programs available (for example, BLASTP). Corresponding positions also can be based on structural alignments, for example by using computer simulated alignments of protein structure. Recitation that amino acids of a polypeptide correspond to amino acids in a disclosed sequence refers to amino acids identified upon alignment of the polypeptide with the disclosed sequence to maximize identity or homology (where conserved amino acids are aligned) using a standard alignment algorithm, such as the GAP algorithm. For example, upon alignment of u-PA with the mature chymotrypsin polypeptide amino acid C168 in the precursor sequence of u-PA set forth in SEQ ID NO:191 aligns with amino acid C1 of the mature chymotrypsin polypeptide. Thus, amino acid C168 in u-PA also is C1 based on chymotrypsin numbering. Using such a chymotrypsin numbering standard, amino acid L244 in the precursor u-PA sequence set forth in SEQ ID NO:191 is the same as L73 based on chymotrypsin numbering and amino acid and I260 is the same as I89 based on chymotrypsin numbering. In another example, upon alignment of the serine protease domain of MT-SP1 (corresponding to amino acids 615 to 855 in SEQ ID NO:253) with mature chymotrypsin, V at position 615 in MT-SP1 is given the chymotrypsin numbering of V16. Subsequent amino acids are numbered accordingly. Thus, an F at amino acid position 708 of full-length MT-SP1 (SEQ ID NO:253),

corresponds to F99 based on chymotrypsin numbering. Where a residue exists in a protease, but is not present in chymotrypsin, the amino acid residue is given a letter notation. For example, residues in chymotrypsin that are part of a loop with amino acid 60 based on chymotrypsin numbering, but are inserted in the MT-SP1 sequence compared to chymotrypsin, are referred to for example as Asp60b or Arg60c.

As used herein, specificity for a target substrate refers to a preference for cleavage of a target substrate by a protease compared to another substrate, referred to as a non-target substrate. Specificity is reflected in the second order rate constant or specificity constant (k_{cat}/K_m), which is a measure of the affinity of a protease for its substrate and the efficiency of the enzyme.

As used herein, a specificity constant for cleavage is (k_{cat}/K_m), wherein K_m is the Michaelis-Menton constant ([S] at one half V_{max}) and K_{cat} is the $V_{max}/[E_T]$, where E_T is the final enzyme concentration. The parameters k_{cat}, K_m and k_{cat}/K_m can be calculated by graphing the inverse of the substrate concentration versus the inverse of the velocity of substrate cleavage, and fitting to the Lineweaver-Burk equation ($1/velocity=(K_m/V_{max})(1/[S]) + 1/V_{max}$; where $V_{max}=[E_T]k_{cat}$). Any method to determine the rate of increase of cleavage over time in the presence of various concentrations of substrate can be used to calculate the specificity constant. For example, a substrate is linked to a fluorogenic moiety, which is released upon cleavage by a protease. By determining the rate of cleavage at different enzyme concentrations, k_{cat} can be determined for a particular protease. The specificity constant can be used to determine the site specific preferences of an amino acid in any one or more of the S1-S4 pockets of a protease for a concomitant P1-P4 amino acid in a substrate using standard methods in the art, such as a positional scanning combinatorial library (PS-SCL). Additionally, the specificity constant also can be used to determine the preference of a protease for one target substrate over another substrate.

As used herein, a substrate specificity ratio is the ratio of specificity constants and can be used to compare specificities of two or more proteases or a protease for two more substrates. For example, substrate specificity of a protease for competing substrates or of competing proteases for a substrate can be compared by comparing k_{cat}/K_m. For example, a protease that has a specificity constant of 2×10^6 $M^{-1}sec^{-1}$ for a target substrate and 2×10^4 $M^{-1}sec^{-1}$ for a non-target substrate is more specific for

the target substrate. Using the specificity constants from above, the protease has a substrate specificity ratio of 100 for the target protease.

As used herein, preference for a target substrate can be expressed as a substrate specificity ratio. The particular value of the ratio that reflects a preference is a function of the substrates and proteases at issue. A substrate specificity ratio that is greater than 1 signifies a preference for a target substrate and a substrate specificity less than 1 signifies a preference for a non-target substrate. Generally, a ratio of at least or about 1 reflects a sufficient difference for a protease to be considered a candidate therapeutic.

As used herein, altered specificity refers to a change in substrate specificity of a modified or selected protease compared to a starting wild-type or template protease. Generally, the change in specificity is a reflection of the change in preference of a modified protease for a target substrate compared to a wildtype substrate of the template protease (herein referred to as a non-target substrate). Typically, modified proteases or selected proteases provided herein exhibits increased substrate specificity for any one or more predetermined or desired cleavage sequences of a target protein compared to the substrate specificity of a template protease. For example, a modified protease or selected protease that has a substrate specificity ratio of 100 for a target substrate versus a non-target substrate exhibits a 10-fold increased specificity compared to a scaffold protease with a substrate specificity ratio of 10. In another example, a modified protease that has a substrate specificity ratio of 1 compared to a ratio of 0.1, exhibits a 10-fold increase in substrate specificity. To exhibit increased specificity compared to a template protease, a modified protease has a 1.5-fold, 2-fold, 5-fold, 10-fold, 50-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold or more greater substrate specificity for any one of more of the predetermined target substrates.

As used herein, "selectivity" can be used interchangeably with specificity when referring to the ability of a protease to choose and cleave one target substrate from among a mixture of competing substrates. Increased selectivity of a protease for a target substrate compared to any other one or more target substrates can be determined, for example, by comparing the specificity constants of cleavage of the target substrates by a protease. For example, if a protease has a specificity constant of

cleavage of 2 X 10^6 $M^{-1}sec^{-1}$ for a target substrate and 2 X 10^4 $M^{-1}sec^{-1}$ for any other one of more substrates, the protease is more selective for the former target substrate.

As used herein, activity refers to a functional activity or activities of a polypeptide or portion thereof associated with a full-length (complete) protein. Functional activities include, but are not limited to, biological activity, catalytic or enzymatic activity, antigenicity (ability to bind to or compete with a polypeptide for binding to an anti-polypeptide antibody), immunogenicity, ability to form multimers, and the ability to specifically bind to a receptor or ligand for the polypeptide.

As used herein, catalytic activity or cleavage activity refers to the activity of a protease as assessed in *in vitro* proteolytic assays that detect proteolysis of a selected substrate. Cleavage activity can be measured by assessing catalytic efficiency of a protease.

As used herein, activity towards a target substrate refers to cleavage activity and/or functional activity, or other measurement that reflects the activity of a protease on or towards a target substrate. Cleavage activity can be measured by assessing catalytic efficiency of a protease. For purposes herein, an activity is increased if a protease exhibits greater proteolysis or cleavage of a target substrate and/or modulates (*i.e.* activates or inhibits) a functional activity of a target substrate protein as compared to the absence of the protease.

As used herein, serine protease or serine endopeptidases refers to a class of peptidases, which are characterized by the presence of a serine residue in the active center of the enzyme. Serine proteases participate in a wide range of functions in the body, including blood clotting, inflammation as well as digestive enzymes in prokaryotes and eukaryotes. The mechanism of cleavage by "serine proteases," is based on nucleophilic attack of a targeted peptidic bond by a serine. Cysteine, threonine or water molecules associated with aspartate or metals also can play this role. Aligned side chains of serine, histidine and aspartate form a catalytic triad common to most serine proteases. The active site of serine proteases is shaped as a cleft where the polypeptide substrate binds. Exemplary serine proteases include urinary plasminogen activator (u-PA) set forth in SEQ ID NO: 433 and MT-SP1 set forth in SEQ ID NO:253, and catalytically active portions thereof, for example the MT-SP1 protease domain (also called the B-chain) set forth in SEQ ID NO:505.

As used herein, a human protein is one encoded by a nucleic acid molecule, such as DNA, present in the genome of a human, including all allelic variants and conservative variations thereof. A variant or modification of a protein is a human protein if the modification is based on the wildtype or prominent sequence of a human protein.

As used herein, the residues of naturally occurring α-amino acids are the residues of those 20 α-amino acids found in nature which are incorporated into protein by the specific recognition of the charged tRNA molecule with its cognate mRNA codon in humans.

As used herein, non-naturally occurring amino acids refer to amino acids that are not genetically encoded.

As used herein, nucleic acids include DNA, RNA and analogs thereof, including peptide nucleic acids (PNA) and mixtures thereof. Nucleic acids can be single or double-stranded. When referring to probes or primers, which are optionally labeled, such as with a detectable label, such as a fluorescent or radiolabel, single-stranded molecules are contemplated. Such molecules are typically of a length such that their target is statistically unique or of low copy number (typically less than 5, generally less than 3) for probing or priming a library. Generally a probe or primer contains at least 14, 16 or 30 contiguous nucleotides of sequence complementary to or identical to a gene of interest. Probes and primers can be 10, 20, 30, 50, 100 or more nucleic acids long.

As used herein, a peptide refers to a polypeptide that is from 2 to 40 amino acids in length.

As used herein, the amino acids which occur in the various sequences of amino acids provided herein are identified according to their known, three-letter or one-letter abbreviations (Table 1). The nucleotides which occur in the various nucleic acid fragments are designated with the standard single-letter designations used routinely in the art.

As used herein, an "amino acid" is an organic compound containing an amino group and a carboxylic acid group. A polypeptide contains two or more amino acids. For purposes herein, amino acids include the twenty naturally-occurring amino acids, non-natural amino acids and amino acid analogs (i.e., amino acids wherein the α-carbon has a side chain).

As used herein, "amino acid residue" refers to an amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are presumed to be in the "L" isomeric form. Residues in the "D" isomeric form, which are so designated, can be substituted for any L-amino acid residue as long as the desired functional property is retained by the polypeptide. NH_2 refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxyl terminus of a polypeptide. In keeping with standard polypeptide nomenclature described in *J. Biol. Chem.*, 243: 3552-3559 (1969), and adopted 37 C.F.R. §§ 1.821-1.822, abbreviations for amino acid residues are shown in Table 1:

Table 1 – Table of Correspondence

SYMBOL		
1-Letter	**3-Letter**	**AMINO ACID**
Y	Tyr	Tyrosine
G	Gly	Glycine
F	Phe	Phenylalanine
M	Met	Methionine
A	Ala	Alanine
S	Ser	Serine
I	Ile	Isoleucine
L	Leu	Leucine
T	Thr	Threonine
V	Val	Valine
P	Pro	proline
K	Lys	Lysine
H	His	Histidine
Q	Gln	Glutamine
E	Glu	glutamic acid
Z	Glx	Glu and/or Gln
W	Trp	Tryptophan
R	Arg	Arginine
D	Asp	aspartic acid
N	Asn	asparagines
B	Asx	Asn and/or Asp
C	Cys	Cysteine
X	Xaa	Unknown or other

It should be noted that all amino acid residue sequences represented herein by formulae have a left to right orientation in the conventional direction of amino-terminus to carboxyl-terminus. In addition, the phrase "amino acid residue" is broadly defined to include the amino acids listed in the Table of Correspondence

(Table 1) and modified and unusual amino acids, such as those referred to in 37 C.F.R. §§ 1.821-1.822, and incorporated herein by reference. Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino acid residues, to an amino-terminal group such as NH_2 or to a carboxyl-terminal group such as COOH.

As used herein, "naturally occurring amino acids" refer to the 20 L-amino acids that occur in polypeptides.

As used herein, "non-natural amino acid" refers to an organic compound that has a structure similar to a natural amino acid but has been modified structurally to mimic the structure and reactivity of a natural amino acid. Non-naturally occurring amino acids thus include, for example, amino acids or analogs of amino acids other than the 20 naturally-occurring amino acids and include, but are not limited to, the D-isostereomers of amino acids. Exemplary non-natural amino acids are described herein and are known to those of skill in the art.

As used herein, an isokinetic mixture is one in which the molar ratios of amino acids has been adjusted based on their reported reaction rates (see, *e.g.*, Ostresh et al., (1994) Biopolymers 34:1681).

As used herein, a DNA construct is a single or double stranded, linear or circular DNA molecule that contains segments of DNA combined and juxtaposed in a manner not found in nature. DNA constructs exist as a result of human manipulation, and include clones and other copies of manipulated molecules.

As used herein, a DNA segment is a portion of a larger DNA molecule having specified attributes. For example, a DNA segment encoding a specified polypeptide is a portion of a longer DNA molecule, such as a plasmid or plasmid fragment, which, when read from the 5' to 3' direction , encodes the sequence of amino acids of the specified polypeptide.

As used herein, the term ortholog means a polypeptide or protein obtained from one species that is the functional counterpart or a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

As used herein, the term polynucleotide means a single- or double-stranded polymer of deoxyribonucleotides or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and can be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic

molecules. The length of a polynucleotide molecule is given herein in terms of nucleotides (abbreviated "nt") or base pairs (abbreviated "bp"). The term nucleotides is used for single- and double-stranded molecules where the context permits. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term base pairs. It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide can differ slightly in length and that the ends thereof can be staggered; thus all nucleotides within a double-stranded polynucleotide molecule can not be paired. Such unpaired ends will, in general, not exceed 20 nucleotides in length.

As used herein, "similarity" between two proteins or nucleic acids refers to the relatedness between the sequence of amino acids of the proteins or the nucleotide sequences of the nucleic acids. Similarity can be based on the degree of identity and/or homology of sequences of residues and the residues contained therein. Methods for assessing the degree of similarity between proteins or nucleic acids are known to those of skill in the art. For example, in one method of assessing sequence similarity, two amino acid or nucleotide sequences are aligned in a manner that yields a maximal level of identity between the sequences. "Identity" refers to the extent to which the amino acid or nucleotide sequences are invariant. Alignment of amino acid sequences, and to some extent nucleotide sequences, also can take into account conservative differences and/or frequent substitutions in amino acids (or nucleotides). Conservative differences are those that preserve the physico-chemical properties of the residues involved. Alignments can be global (alignment of the compared sequences over the entire length of the sequences and including all residues) or local (the alignment of a portion of the sequences that includes only the most similar region or regions).

"Identity" per se has an art-recognized meaning and can be calculated using published techniques. (See, *e.g.*: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data*, Part I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). While there exists a number of methods to

measure identity between two polynucleotide or polypeptides, the term "identity" is well known to skilled artisans (Carillo, H. & Lipton, D., *SIAM J Applied Math 48*:1073 (1988)).

As used herein, homologous (with respect to nucleic acid and/or amino acid sequences) means about greater than or equal to 25% sequence homology, typically greater than or equal to 25%, 40%, 50%, 60%, 70%, 80%, 85%, 90% or 95% sequence homology; the precise percentage can be specified if necessary. For purposes herein the terms "homology" and "identity" are often used interchangeably, unless otherwise indicated. In general, for determination of the percentage homology or identity, sequences are aligned so that the highest order match is obtained (see, *e.g.*: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part I*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; Carillo *et al.* (1988) *SIAM J Applied Math 48*:1073). By sequence homology, the number of conserved amino acids is determined by standard alignment algorithms programs, and can be used with default gap penalties established by each supplier. Substantially homologous nucleic acid molecules would hybridize typically at moderate stringency or at high stringency all along the length of the nucleic acid of interest. Also contemplated are nucleic acid molecules that contain degenerate codons in place of codons in the hybridizing nucleic acid molecule.

Whether any two molecules have nucleotide sequences or amino acid sequences that are at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% "identical" or "homologous" can be determined using known computer algorithms such as the "FASTA" program, using for example, the default parameters as in Pearson *et al.* (1988) *Proc. Natl. Acad. Sci. USA 85*:2444 (other programs include the GCG program package (Devereux, J., *et al., Nucleic Acids Research 12(I)*:387 (1984)), BLASTP, BLASTN, FASTA (Atschul, S.F., *et al., J Molec Biol 215*:403 (1990)); Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo *et al.* (1988) *SIAM J Applied Math 48*:1073). For example, the BLAST function of the National Center for Biotechnology Information database

can be used to determine identity. Other commercially or publicly available programs include, DNAStar "MegAlign" program (Madison, WI) and the University of Wisconsin Genetics Computer Group (UWG) "Gap" program (Madison WI). Percent homology or identity of proteins and/or nucleic acid molecules can be determined, for example, by comparing sequence information using a GAP computer program (*e.g.*, Needleman *et al.* (1970) *J. Mol. Biol.* 48:443, as revised by Smith and Waterman ((1981) *Adv. Appl. Math.* 2:482). Briefly, the GAP program defines similarity as the number of aligned symbols (i.e., nucleotides or amino acids), which are similar, divided by the total number of symbols in the shorter of the two sequences. Default parameters for the GAP program can include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) and the weighted comparison matrix of Gribskov *et al.* (1986) *Nucl. Acids Res.* 14:6745, as described by Schwartz and Dayhoff, eds., *ATLAS OF PROTEIN SEQUENCE AND STRUCTURE*, National Biomedical Research Foundation, pp. 353-358 (1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

Therefore, as used herein, the term "identity" or "homology" represents a comparison between a test and a reference polypeptide or polynucleotide. As used herein, the term at least "90% identical to" refers to percent identities from 90 to 99.99 relative to the reference nucleic acid or amino acid sequence of the polypeptide. Identity at a level of 90% or more is indicative of the fact that, assuming for exemplification purposes a test and reference polypeptide length of 100 amino acids are compared. No more than 10% (i.e., 10 out of 100) of the amino acids in the test polypeptide differs from that of the reference polypeptide. Similar comparisons can be made between test and reference polynucleotides. Such differences can be represented as point mutations randomly distributed over the entire length of a polypeptide or they can be clustered in one or more locations of varying length up to the maximum allowable, *e.g.* 10/100 amino acid difference (approximately 90% identity). Differences are defined as nucleic acid or amino acid substitutions, insertions or deletions. At the level of homologies or identities above about 85-90%, the result should be independent of the program and gap parameters set; such high levels of identity can be assessed readily, often by manual alignment without relying on software.

As used herein, an aligned sequence refers to the use of homology (similarity and/or identity) to align corresponding positions in a sequence of nucleotides or amino acids. Typically, two or more sequences that are related by 50% or more identity are aligned. An aligned set of sequences refers to 2 or more sequences that are aligned at corresponding positions and can include aligning sequences derived from RNAs, such as ESTs and other cDNAs, aligned with genomic DNA sequence.

As used herein, "primer" refers to a nucleic acid molecule that can act as a point of initiation of template-directed DNA synthesis under appropriate conditions (e.g., in the presence of four different nucleoside triphosphates and a polymerization agent , such as DNA polymerase, RNA polymerase or reverse transcriptase) in an appropriate buffer and at a suitable temperature. It will be appreciated that a certain nucleic acid molecules can serve as a "probe" and as a "primer." A primer, however, has a 3' hydroxyl group for extension. A primer can be used in a variety of methods, including, for example, polymerase chain reaction (PCR), reverse-transcriptase (RT)-PCR, RNA PCR, LCR, multiplex PCR, panhandle PCR, capture PCR, expression PCR, 3' and 5' RACE, in situ PCR, ligation-mediated PCR and other amplification protocols.

As used herein, "primer pair" refers to a set of primers that includes a 5' (upstream) primer that hybridizes with the 5' end of a sequence to be amplified (e.g. by PCR) and a 3' (downstream) primer that hybridizes with the complement of the 3' end of the sequence to be amplified.

As used herein, "specifically hybridizes" refers to annealing, by complementary base-pairing, of a nucleic acid molecule (e.g. an oligonucleotide) to a target nucleic acid molecule. Those of skill in the art are familiar with *in vitro* and *in vivo* parameters that affect specific hybridization, such as length and composition of the particular molecule. Parameters particularly relevant to *in vitro* hybridization further include annealing and washing temperature, buffer composition and salt concentration. Exemplary washing conditions for removing non-specifically bound nucleic acid molecules at high stringency are 0.1 x SSPE, 0.1% SDS, 65°C, and at medium stringency are 0.2 x SSPE, 0.1% SDS, 50°C. Equivalent stringency conditions are known in the art. The skilled person can readily adjust these parameters to achieve specific hybridization of a nucleic acid molecule to a target nucleic acid molecule appropriate for a particular application.

As used herein, substantially identical to a product means sufficiently similar so that the property of interest is sufficiently unchanged so that the substantially identical product can be used in place of the product.

As used herein, it also is understood that the terms "substantially identical" or "similar" varies with the context as understood by those skilled in the relevant art.

As used herein, an allelic variant or allelic variation references any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and can result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or can encode polypeptides having altered amino acid sequence. The term "allelic variant" also is used herein to denote a protein encoded by an allelic variant of a gene. Typically the reference form of the gene encodes a wildtype form and/or predominant form of a polypeptide from a population or single reference member of a species. Typically, allelic variants, which include variants between and among species typically have at least 80%, 90% or greater amino acid identity with a wildtype and/or predominant form from the same species; the degree of identity depends upon the gene and whether comparison is interspecies or intraspecies. Generally, intraspecies allelic variants have at least about 80%, 85%, 90% or 95% identity or greater with a wildtype and/or predominant form, including 96%, 97%, 98%, 99% or greater identity with a wildtype and/or predominant form of a polypeptide. Reference to an allelic variant herein generally refers to variations n proteins among members of the same species.

As used herein, "allele," which is used interchangeably herein with "allelic variant" refers to alternative forms of a gene or portions thereof. Alleles occupy the same locus or position on homologous chromosomes. When a subject has two identical alleles of a gene, the subject is said to be homozygous for that gene or allele. When a subject has two different alleles of a gene, the subject is said to be heterozygous for the gene. Alleles of a specific gene can differ from each other in a single nucleotide or several nucleotides, and can include substitutions, deletions and insertions of nucleotides. An allele of a gene also can be a form of a gene containing a mutation.

As used herein, species variants refer to variants in polypeptides among different species, including different mammalian species, such as mouse and human.

As used herein, a splice variant refers to a variant produced by differential processing of a primary transcript of genomic DNA that results in more than one type of mRNA.

As used herein, modification is in reference to modification of a sequence of amino acids of a polypeptide or a sequence of nucleotides in a nucleic acid molecule and includes deletions, insertions, and replacements of amino acids and nucleotides, respectively. Methods of modifying a polypeptide are routine to those of skill in the art, such as by using recombinant DNA methodologies.

As used herein, a peptidomimetic is a compound that mimics the conformation and certain stereochemical features of the biologically active form of a particular peptide. In general, peptidomimetics are designed to mimic certain desirable properties of a compound, but not the undesirable properties, such as flexibility, that lead to a loss of a biologically active conformation and bond breakdown. Peptidomimetics can be prepared from biologically active compounds by replacing certain groups or bonds that contribute to the undesirable properties with bioisosteres. Bioisosteres are known to those of skill in the art. For example the methylene bioisostere CH2S has been used as an amide replacement in enkephalin analogs (see, e.g., Spatola (1983) pp. 267-357 in Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, Weinstein, Ed. volume 7, Marcel Dekker, New York). Morphine, which can be administered orally, is a compound that is a peptidomimetic of the peptide endorphin. For purposes herein, cyclic peptides are included among peptidomimetics as are polypeptides in which one or more peptide bonds is/are replaced by a mimic.

As used herein, a polypeptide comprising a specified percentage of amino acids set forth in a reference polypeptide refers to the proportion of contiguous identical amino acids shared between a polypeptide and a reference polypeptide. For example, an isoform that comprises 70% of the amino acids set forth in a reference polypeptide having a sequence of amino acids set forth in SEQ ID NO:XX, which recites 147 amino acids, means that the reference polypeptide contains at least 103 contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:XX.

As used herein, the term promoter means a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of

transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding region of genes.

As used herein, isolated or purified polypeptide or protein or biologically-active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue from which the protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. Preparations can be determined to be substantially free if they appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis and high performance liquid chromatography (HPLC), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound, however, can be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

The term substantially free of cellular material includes preparations of proteins in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly-produced. In one embodiment, the term substantially free of cellular material includes preparations of protease proteins having less that about 30% (by dry weight) of non-protease proteins (also referred to herein as a contaminating protein), generally less than about 20% of non-protease proteins or 10% of non-protease proteins or less that about 5% of non-protease proteins. When the protease protein or active portion thereof is recombinantly produced, it also is substantially free of culture medium, *i.e.*, culture medium represents less than about or at 20%, 10% or 5% of the volume of the protease protein preparation.

As used herein, the term substantially free of chemical precursors or other chemicals includes preparations of protease proteins in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. The term includes preparations of protease proteins having less than about 30% (by dry weight) 20%, 10%, 5% or less of chemical precursors or non-protease chemicals or components.

As used herein, synthetic, with reference to, for example, a synthetic nucleic acid molecule or a synthetic gene or a synthetic peptide refers to a nucleic acid molecule or polypeptide molecule that is produced by recombinant methods and/or by chemical synthesis methods.

As used herein, production by recombinant means by using recombinant DNA methods means the use of the well known methods of molecular biology for expressing proteins encoded by cloned DNA.

As used herein, vector (or plasmid) refers to discrete elements that are used to introduce a heterologous nucleic acid into cells for either expression or replication thereof. The vectors typically remain episomal, but can be designed to effect integration of a gene or portion thereof into a chromosome of the genome. Also contemplated are vectors that are artificial chromosomes, such as yeast artificial chromosomes and mammalian artificial chromosomes. Selection and use of such vehicles are well known to those of skill in the art.

As used herein, an expression vector includes vectors capable of expressing DNA that is operatively linked with regulatory sequences, such as promoter regions, that are capable of effecting expression of such DNA fragments. Such additional segments can include promoter and terminator sequences, and optionally can include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, and the like. Expression vectors are generally derived from plasmid or viral DNA, or can contain elements of both. Thus, an expression vector refers to a recombinant DNA or RNA construct, such as a plasmid, a phage, recombinant virus or other vector that, upon introduction into an appropriate host cell, results in expression of the cloned DNA. Appropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells and/or prokaryotic cells and those that remain episomal or those which integrate into the host cell genome.

As used herein, vector also includes "virus vectors" or "viral vectors." Viral vectors are engineered viruses that are operatively linked to exogenous genes to transfer (as vehicles or shuttles) the exogenous genes into cells.

As used herein, an adenovirus refers to any of a group of DNA-containing viruses that cause conjunctivitis and upper respiratory tract infections in humans. As used herein, naked DNA refers to histone-free DNA that can be used for vaccines and

gene therapy. Naked DNA is the genetic material that is passed from cell to cell during a gene transfer processed called transformation. In transformation, purified or naked DNA is taken up by the recipient cell which will give the recipient cell a new characteristic or phenotype.

As used herein, operably or operatively linked when referring to DNA segments means that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator.

As used herein, protein binding sequence refers to a protein or peptide sequence that is capable of specific binding to other protein or peptide sequences generally, to a set of protein or peptide sequences or to a particular protein or peptide sequence.

As used herein, epitope tag refers to a short stretch of amino acid residues corresponding to an epitope to facilitate subsequent biochemical and immunological analysis of the epitope tagged protein or peptide. Epitope tagging is achieved by adding the sequence of the epitope tag to a protein-encoding sequence in an appropriate expression vector. Epitope tagged proteins can be affinity purified using highly specific antibodies raised against the tags.

As used herein, metal binding sequence refers to a protein or peptide sequence that is capable of specific binding to metal ions generally, to a set of metal ions or to a particular metal ion.

As used herein the term assessing is intended to include quantitative and qualitative determination in the sense of obtaining an absolute value for the activity of a protease, or a domain thereof, present in the sample, and also of obtaining an index, ratio, percentage, visual or other value indicative of the level of the activity. Assessment can be direct or indirect and the chemical species actually detected need not of course be the proteolysis product itself but can for example be a derivative thereof or some further substance. For example, detection of a cleavage product of a complement protein, such as by SDS-PAGE and protein staining with Coomasie blue.

As used herein, biological activity refers to the *in vivo* activities of a compound or physiological responses that result upon *in vivo* administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmaceutical activity of such compounds, compositions and

mixtures. Biological activities can be observed in *in vitro* systems designed to test or use such activities. Thus, for purposes herein a biological activity of a protease is its catalytic activity in which a polypeptide is hydrolyzed.

As used herein equivalent, when referring to two sequences of nucleic acids, means that the two sequences in question encode the same sequence of amino acids or equivalent proteins. When equivalent is used in referring to two proteins or peptides, it means that the two proteins or peptides have substantially the same amino acid sequence with only amino acid substitutions that do not substantially alter the activity or function of the protein or peptide. When equivalent refers to a property, the property does not need to be present to the same extent (*e.g.*, two peptides can exhibit different rates of the same type of enzymatic activity), but the activities are usually substantially the same. Complementary, when referring to two nucleotide sequences, means that the two sequences of nucleotides are capable of hybridizing, typically with less than 25%, 15% or 5% mismatches between opposed nucleotides. If necessary, the percentage of complementarity will be specified. Typically the two molecules are selected such that they will hybridize under conditions of high stringency.

As used herein, an agent that modulates the activity of a protein or expression of a gene or nucleic acid either decreases or increases or otherwise alters the activity of the protein or, in some manner, up- or down-regulates or otherwise alters expression of the nucleic acid in a cell.

As used herein, a pharmaceutical effect or therapeutic effect refers to an effect observed upon administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

As used herein, "modulate" and "modulation" or "alter" refer to a change of an activity of a molecule, such as a protein. Exemplary activities include, but are not limited to, biological activities, such as signal transduction. Modulation can include an increase in the activity (*i.e.*, up-regulation or agonist activity) a decrease in activity (*i.e.*, down-regulation or inhibition) or any other alteration in an activity (such as a change in periodicity, frequency, duration, kinetics or other parameter) . Modulation can be context dependent and typically modulation is compared to a designated state, for example, the wildtype protein, the protein in a constitutive state, or the protein as expressed in a designated cell type or condition.

As used herein, inhibit and inhibition refer to a reduction in an activity relative to the uninhibited activity.

As used herein, a composition refers to any mixture. It can be a solution, suspension, liquid, powder, paste, aqueous, non-aqueous or any combination thereof.

As used herein, a combination refers to any association between or among two or more items. The combination can be two or more separate items, such as two compositions or two collections, can be a mixture thereof, such as a single mixture of the two or more items, or any variation thereof. The elements of a combination are generally functionally associated or related. A kit is a packaged combination that optionally includes instructions for use of the combination or elements thereof.

As used herein, "disease or disorder" refers to a pathological condition in an organism resulting from cause or condition including, but not limited to, infections, acquired conditions, genetic conditions, and characterized by identifiable symptoms. Diseases and disorders of interest herein are those involving complement activation, including those mediated by complement activation and those in which complement activation plays a role in the etiology or pathology. Diseases and disorders also include those that are caused by the absence of a protein such as an immune deficiency, and of interest herein are those disorders where complement activation does not occur due to a deficiency in a complement protein.

As used herein, "treating" a subject with a disease or condition means that the subject's symptoms are partially or totally alleviated, or remain static following treatment. Hence treatment encompasses prophylaxis, therapy and/or cure. Prophylaxis refers to prevention of a potential disease and/or a prevention of worsening of symptoms or progression of a disease. Treatment also encompasses any pharmaceutical use of a modified interferon and compositions provided herein.

As used herein, a therapeutic agent, therapeutic regimen, radioprotectant, or chemotherapeutic mean conventional drugs and drug therapies, including vaccines, which are known to those skilled in the art. Radiotherapeutic agents are well known in the art.

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

As used herein therapeutic effect means an effect resulting from treatment of a subject that alters, typically improves or ameliorates the symptoms of a disease or condition or that cures a disease or condition. A therapeutically effective amount refers to the amount of a composition, molecule or compound which results in a therapeutic effect following administration to a subject.

As used herein, the term "subject" refers to an animal, including a mammal, such as a human being.

As used herein, a patient refers to a human subject.

As used herein, amelioration of the symptoms of a particular disease or disorder by a treatment, such as by administration of a pharmaceutical composition or other therapeutic, refers to any lessening, whether permanent or temporary, lasting or transient, of the symptoms that can be attributed to or associated with administration of the composition or therapeutic.

As used herein, prevention or prophylaxis refers to methods in which the risk of developing disease or condition is reduced.

As used herein, an effective amount is the quantity of a therapeutic agent necessary for preventing, curing, ameliorating, arresting or partially arresting a symptom of a disease or disorder.

As used herein, administration of a protease, such as a modified protease, refers to any method in which the protease is contacted with its substrate. Adminstration can be effected *in vivo* or *ex vivo* or *in vitro*. For example, for *ex vivo* administration a body fluid, such as blood, is removed from a subject and contacted outside the body with the modified non-complement protease. For *in vivo* administration, the modified protease can be introduced into the body, such as by local, topical, systemic and/or other route of introduction. *In vitro* administration encompasses methods, such as cell culture methods.

As used herein, unit dose form refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art.

As used herein, a single dosage formulation refers to a formulation for direct administration.

As used herein, an "article of manufacture" is a product that is made and sold. As used throughout this application, the term is intended to encompass modified protease polypeptides and nucleic acids contained in articles of packaging.

As used herein, fluid refers to any composition that can flow. Fluids thus encompass compositions that are in the form of semi-solids, pastes, solutions, aqueous mixtures, gels, lotions, creams and other such compositions.

As used herein, a "kit" refers to a combination of a modified protease polypeptide or nucleic acid molecule provided herein and another item for a purpose including, but not limited to, administration, diagnosis, and assessment of a biological activity or property. Kits optionally include instructions for use.

As used herein, a cellular extract or lysate refers to a preparation or fraction which is made from a lysed or disrupted cell.

As used herein, animal includes any animal, such as, but are not limited to primates including humans, gorillas and monkeys; rodents, such as mice and rats; fowl, such as chickens; ruminants, such as goats, cows, deer, sheep; ovine, such as pigs and other animals. Non-human animals exclude humans as the contemplated animal. The proteases provided herein are from any source, animal, plant, prokaryotic and fungal. Most proteases are of animal origin, including mammalian origin.

As used herein, a control refers to a sample that is substantially identical to the test sample, except that it is not treated with a test parameter, or, if it is a sample plasma sample, it can be from a normal volunteer not affected with the condition of interest. A control also can be an internal control.

As used herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to compound, comprising "an extracellular domain"" includes compounds with one or a plurality of extracellular domains.

As used herein, ranges and amounts can be expressed as "about" a particular value or range. About also includes the exact amount. Hence "about 5 bases" means "about 5 bases" and also "5 bases."

As used herein, "optional" or "optionally" means that the subsequently described event or circumstance does or does not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not. For example, an optionally substituted group means that the group is unsubstituted or is substituted.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage,

recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) Biochem. 11:1726).

B. METHOD FOR SCREENING PROTEASES

Provided are methods for screening for proteases with altered properties, particularly substrate specificity and selectivity. The methods also provide such altered proteases that exhibit substantially unchanged or with sufficient activity for a therapeutic use. The methods provided herein can be employed with any method for protease modification and design of modified proteases. Such methods include random methods for producing libraries, use of existing libraries, and also directed evolution methods

A variety of selection schemes to identify proteases having altered substrate specificity/selectivity have been employed, but each has limitations. The methods provided herein overcome such limitations. Generally, selection schemes include those that 1) select for protease binding or 2) select for protease catalysis. Examples of strategies that take advantage of protease binding include, for example, the use of transition state analogues (TSAs) and those that employ small molecule suicide substrates. A TSA is a stable compound that mimics the electronic and structural features of the transition state of a protease: substrate reaction. The strongest interaction between a protease and the substrate typically occurs at the transition state of a reaction. A TSA is employed as a model substrate to select for proteases with high binding affinity. A TSA is never a perfect mimic of a true transition state and their syntheses are difficult (Bertschinger *et al.* (2005) in *Phage display in Biotech. and Drug Discovery* (Sidhu S, ed), pp. 461-491). Such a strategy has identified protease variants with altered substrate specificity, but such proteases generally exhibit reduced activity because a requirement for protease catalysis is not part of the selection scheme.

In an alternate strategy, small molecule suicide substrates (also called mechanism-based inhibitors) have been used to select for proteases based on binding. Such suicide substrates typically are small molecule inhibitors that bind covalently to the active site of an enzyme. These suicide substrates contain a reactive electrophile that reacts with an enzymes nucleophile to form a covalent bond. Cleavage of a natural peptide bond by the protease is not required for this reaction. Typically, such inhibitors produce a reactive nucleophile only upon binding to the correct enzyme and

undergoing normal catalytic steps (see, *e.g.*, Bertschinger *et al.* (2005) in *Phage display in Biotech. and Drug Discovery* (Sidhu S, ed), pp. 461-491). In many cases, the substrate inhibitor mimics the conformation of the first transition state involved in catalysis, but do not allow completion of the catalytic cycle. As a result, the use of such inhibitors effectively selects for strong binding instead of catalysis and results in the selection of inactive enzymes with impaired dissociation of the substrate (Droge *et al.* (2006) ChemBioChem, 7:149-157). Also, due to their size and the lack of requirement for cleavage of the substrate, they do not recapitulate the interaction of a protease with a natural protein substrate.

A protease selection strategy that selects for catalysis instead of binding also has been attempted (see, *e.g.*, Heinis *et al.* (2001), *Protein Engineering*, 14: 1043-1052). One of the major limitations in assaying for catalysis is that reaction products diffuse away quickly after the reaction is complete making it difficult to isolate the catalytically active enzyme. Consequently, strategies that select for catalysis rely on anchoring the substrate and the enzyme to phage such that they are in close proximity. For example, the protein calmodulin has been used as an immobilization agent (Demartis (1999) J Mol. Biol., 286:617-633). Reaction substrates are non-covalently anchored on calmodulin-tagged phage enzymes using calmodulin-binding peptide derivatives. Following catalysis, phage displaying the reaction product are isolated from non-catalytically active phage using anti-product affinity reagents. Since the substrate is attached to the phage particle, however, the catalysis reaction can be hindered. Therefore, these and other methods for protease selection, suffer limitations and do not identify proteases with altered specificity and substantially unchanged with sufficient activity for therapeutic applications. The methods provided herein address these limitations.

Provided herein are method of protease selection to identify proteases and/or protease variants with altered, optimized or improved substrate specificity. Such proteases are identified for optimization and use as therapeutic proteases that can cleave and inactivate (or activate) desired protein targets such as, for example, protein targets involved in the etiology of a disease or disorder. In the methods for screening proteases provided herein, candidate proteases are trapped as stable intermediate complexes of the protease enzymatic reaction, and then identified. The stable intermediate complexes typically are covalent complexes or other complexes that

permit separation thereof from non-complexed molecules. Such intermediates, include, for example, an acyl enzyme intermediate, that permits capture and ultimately identification of the proteases that have a selected or predetermined substrate specificity. Capture (trapping) of the protease is effected by contacting a collection of proteases with a protease trap polypeptide that is cleaved by the protease, and, upon cleavage, forms the stable complex. Exemplary of such protease trap polypeptides are serpins, alpha 2 macroglobulin, and other such molecules. The protease trap polypeptide can be naturally-occurring and/or can be modified to select for a particular target substrate.

In practicing the methods, collections of proteases, typically modified or mutant proteases and/or collections of natural proteases, are contacted with a protease trap polypeptide that reacts with the protease following substrate cleavage to form the complex containing the trapped intermediate. These methods can be used to identify proteases having a desired substrate specificity/selectivity. To achieve identification of proteases having a desired substrate specificity/selectivity, the amino acid sequence of the scissile bond, and/or surrounding sequences in the reactive site, such as the reactive loop sequence or analogous sequence, can be modified in the protease trap polypeptide to mimic the substrate cleavage sequence of a desired target substrate.

The screening reaction is performed by contacting a collection of proteases with the protease trap polypeptide under conditions whereby stable complexes, typically covalent complexes form. The complexes are of sufficient stability to permit their separation from other less stable complexes and unreacted protease trap polypeptides.

The protease trap polypeptides can be identifiable labeled or affinity-tagged to facilitate identification of complexes. For example, labeling of the protease trap polypeptides, such as by a fluorescent moiety, affinity tag or other such labeling/tagging agent facilitates the isolation of the protease-inhibitor complex and identification of the selected protease. Selected proteases can be analyzed for activity to assess proteolytic efficiency and substrate specificity. The identified or selected proteases also can be identified, such as by sequencing or other identification protocol, including mass spectrometric methods, or by other labeling methods, to identify selected proteases in the complexes.

The methods provided herein also include optional iterative screening steps, such that the method can be performed once, or can be performed in multiple rounds hone in on proteases of a desired or predetermined specificity/selectivity and/or cleavage activity. For example, proteases selection can include randomly or empirically or systematically modifying the selected protease (in targeted regions and/or along the length), and repeating (in one, two, three, four or more rounds) the method of contacting the proteases collection with one or more protease trap polypeptide.

The methods provided herein can be multiplexed, such as by including two or more differentially labeled or differentially identifiable protease trap polypeptides.

In the methods provided herein, it is not necessary that the protease trap polypeptide exhibit 100% or even very high efficiency in the complexing reaction as long as at least a detectable percentage, typically at least 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more, can form a stable complex that can be separated or otherwise identified from among less stable complexes or unreacted protease trap polypeptides. Thus, proteases can be selected where partitioning occurs in the reaction in which there is than 100% inhibition by the protease trap polypeptide, such as for example, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% 90%, 95%, 99% or more inhibition of protease catalyzed reaction. In the methods provided herein, the stringency of the selection and other parameters can be modulated, such as by controlling reaction time, temperature, pH, ionic strength, and/or library and substrate concentrations. Specificity constraints also can be modulated during selection by including competitors such as, for example, specific competitors containing an undesired substrate cleavage sequence or broader classes of competitors, such as for example, human plasma.

The method provided herein also can be performed by contacting a collection of proteases with one protease trap polypeptide or mixtures of different protease trap polypeptides such as by multiplexing. Where a plurality of different protease trap polypeptides are used, each protease trap polypeptide can be individually and distinctly labeled so that they can be identifiably detected. Such a method enables the isolation and identification of multiple proteases from a collection of proteases in a single reaction.

The methods provided herein permit collections of proteases to be screened at once to identify those having a desired or predetermined substrate specificity. The collections of proteases include, any collection of proteases, including collections of various wild-type proteases, modified proteases, mixtures thereof, and also proteolytically active portions thereof. Any collection can be employed. The collections also can be made as a set of mutant proteases, or proteolytically active portions thereof that contain the mutation. Such collections include, combinatorial collections in which members in the collection contain diverse mutations. The mutation can be random along the length of a protease (or catalytically active portion thereof) or can be targeted to a particular position or region, such as for example, the specificity binding pocket of the protease. The methods provided herein can identify and discover non-contact residues not previously appreciated to be involved as specificity determinants (*i.e.* buried residues). Hence, the protease selection technology method provided herein can be used to create proteases with entirely new specificities and activities and/or to optimize the specificity or activity of an existing protease lead.

C. PROTEASE TRAP POLYPEPTIDES

A protease trap polypeptide used in the methods provided herein is a polypeptide, or a polypeptide portion containing a reactive site, that serves as a substrate for a protease that upon cleavage results in the formation of a protease-substrate intermediate complex, that is stable. Generally, such a protease trap polypeptide is one that requires cleavage of a scissile bond (P1-P1') by the protease to yield the generation of a trapped substrate-protease complex. The stable complex is typically an irreversible complex formed through the tight interactions between the protease and the protease trap polypeptide, such as due to covalent, ionic, hydrophobic, or other tight linkages. As such the complex is generally stable for hours, days, weeks, or more thereby permitting isolation of the complex. In one example, the stable intermediate complex can be an acyl enzyme intermediate that is formed upon reaction of a serine or cysteine protease with a protease trap polypeptide. Most usually, following protease trap polypeptide cleavage a rapid conformational change in the complex distorts the protease and prevents deacylation of the acyl-enzyme complex. Thus, panning proteases with protease trap polypeptides allows selection for the rate limiting step of catalysis (*i.e.* cleavage of the P1-P1' bond and

acylation of the enzyme) while at the same time forming very tight (*i.e.* covalent) complexes that are easily isolated from collection mixtures.

Typically, such protease trap polypeptides are large (greater than 100 amino acids), single domain proteins containing a reactive site sequence recognized by a protease. Generally, the reactive site cleavage sequence is part of a larger reactive loop that is flexible, exposed, and long to make it a target substrate (Otlewski *et al.* (2005) *The EMBO J.* 24: 1303-1310), however, so long as the protease trap contains a reactive site sequence that can be cleaved by a protease, thereby mimicking substrate cleavage, it can be used in the methods provided herein. Thus, any large polypeptide or synthetically produced polypeptide that contains a scissile bond cleaved by a protease resulting in the trapping of a protease in a long-lasting, stable complex can be used in the methods provided herein. Exemplary of such protease trap polypeptides are serpins, such as any described herein. Other protease trap polypeptides also can be used in the methods provided herein, such as any whose mechanism of action is similar to those of serpin molecules. These include, for example, synthetic or recombinantly generated serpin-like molecules, or polypeptides containing contiguous fragments or sequences of a serpin molecule including a sufficient portion of a reactive site loop of a serpin molecule. In addition, other protease inhibitors whose mechanism of inhibition is similar to that of serpins can be used, such as for example, the baculovirus p35 protein that inhibits caspases (Xu *et al.* (2001) *Nature*, 410:494-497; Otlewski *et al.* (2005) *The EMBO J.* 24: 1303-1310). Other protease trap polypeptides include any that trap a protease in a stable complex that can be easily isolated, such as, but not limited to, alpha 2 macroglobulin.

1. SERPINS: Structure, Function, and Expression

Serpins (serine protease inhibitors) are protease inhibitors that are large protein molecules (about 330-500 amino acids) compared to other serine protease inhibitors that are normally about less than 60 amino acids. The serpin superfamily is the largest and most broadly distributed of protease inhibitors. Over 1,500 serpin family members have been identified to date in a variety of different animals, poxviruses, plants, bacteria, and archaea (Law *et al.* (2006) *Genome Biology*, 7:216), with over thirty different human serpins studied thus far. Most human serpins are found in the blood where they function in a wide range of regulatory roles including, for example, inflammatory, complement, coagulation, and fibrinolytic cascades.

Serpins also function intracellularly to perform cytoprotective roles, such as for example, regulating the inappropriate release of cytotoxic proteases. Although most serpins have an inhibitory role on protease activity, some serpins perform other non-inhibitory roles such as but not limited to, hormone transport, corticosteroid binding globulin, and blood pressure regulation (Silverman *et al.* (2001) *JBC*, 276: 33293-33296). Among non-inhibitory serpins are steroid binding globulins and ovalbumin. Typically, serpins inhibit the action of serine proteases, although several serpins have been identified that are inhibitors of papain-like cysteine proteases or caspases (Whisstock et al. (2005) FEBS Journal, 272: 4868-4873).

The sequence identity among serpin family members is weak, however, their structures are highly conserved. For example, members of the serpin family share about 30% amino acid sequence homology with the serpin alpha1-antitrypsin and have a conserved tertiary structure. Structurally, serpins are made up of three β sheets (A, B, and C) and 8-9 α-helices (A-I), which are organized into an upper β-barrel domain and a lower helical domain. The two domains are bridged by the five stranded B-sheet A, which is the main structural feature of serpins (Huntington *et al.* (2003), *J. Thrombosis and Haemostasis*, 1: 1535-1549). Serpins are metastable proteins such that they are only partially stable in their active form; they require protease to adopt a completely stable conformation. A loop, termed the reactive site loop (RSL), is responsible for the altered conformation of the serpin molecule. The RSL is an exposed stretch of about 17 amino acid residues that protrudes out from the top of the molecule in a region between the A and C β-sheets. The RSL serves as the protease recognition site, and generally contains the sole determinants of protease specificity. The most stable form of the serpin structure is the RSL-cleaved form. Following protease cleavage, the amino terminal portion of the RSL inserts into the center of β-sheet A to become strand four of the six-stranded β-sheet. This conformational change is termed the "stressed" to "relaxed" (or S to R) transition. This transformation is characterized by an increase in thermal stability of the molecule owing to the reorganization of the five-stranded β-sheet A to a six-stranded anti-parallel form (Lawrence *et al.* (2000), *J Biol. Chem.*, 275: 5839-5844). In other words, the native structure of serpins is equivalent to a latent intermediate, which is

only converted to a more stable structure following protease cleavage (Law *et al.* (2006) *Genome Biology*, 7:216).

Typically, serpins target serine proteases, although some serpins inhibit cysteine proteases using a similar mechanism. The RSL loop determines which proteases are targeted for inhibition as it provides a pseudo-substrate for the target protease. In effect, the inhibitory specificity of a particular serpin is mediated by the RSL sequence, which is the most variable region among serpins (Travis *et al.* (1990) *Biol. Chem. Hoppe Seyler*, 371: 3-11). The RSL mimics the substrate recognition sequence of a protease and thereby contains a reactive site numbered as ...P_n-P_3-P_2-P_1-P_1'-P_2'-P_3'-P'_n..., where the reactive site is the scissile bond between P_1 and P_1'. For mature α1-antitrypsin, cleavage at the P1-P1' bond occurs at the Met_{358}-Ser_{359} bond (corresponding to amino acids Met_{382} and Ser_{389} of the sequence of amino acids set forth in SEQ ID NO:1). The corresponding binding site for the residues on the protease are ...S_n-S_3-S_2-S_1-S_1', S_2', S_3', S_n'-... In the method provided herein, modification of the RSL sequence is made to select for proteases from a display library exhibiting altered substrate specificity, as discussed in detail below.

2. Protease Catalysis, Inhibitory Mechanism of Serpins, and Formation of Acyl Enzyme Intermediate

The protease selection method provided herein exploits the ability of polypeptides to trap proteases, such as is exemplified by serpins, to identify proteases with altered substrate specificity. Mechanisms of protease catalysis differ slightly between classes of proteolytic enzymes: serine, cysteine, aspartic, threonine, or metallo-proteases. For example, serine peptidases have a serine residue involved in the active center, the aspartic have two aspartic acids in the catalytic center, cysteine - type peptidases have a cysteine residue, threonine-type peptidases have a threonine residue, and metallo-peptidases use a metal ion in the catalytic mechanism. Generally, those proteases families that form covalent intermediates are the target of the protease selection method provided herein. These include, for example, members of the serine and cysteine protease family. As an example, for serine proteases, the first step in catalysis is the formation of an acyl enzyme intermediate between the substrate and the serine in the catalytic center of the protease. Formation of this covalent intermediate proceeds through a negatively charged tetrahedral transition state intermediate and then the P1-P1' peptide bond of the substrate is cleaved.

During the second step or deacylation, the acyl-enzyme intermediate is hydrolyzed by a water molecule to release the peptide and to restore the Ser-hydroxyl of the enzyme. The deacylation, which also involves the formation of a tetrahedral transition state intermediate, proceeds through the reverse reaction pathway of acylation. For deacylation, a water molecule is the attacking nucleophile instead of the Ser residue. The His residue in the catalytic center of a serine protease provides a general base and accepts the OH group of the reactive Ser.

Serpins inhibit the catalysis reaction of both serine and cysteine target proteases using the S to R transition as mentioned above. Their mechanism of action is unique among protease inhibitors by destroying the active site of the protease before deacylation progresses, thereby irreversibly impeding proteolysis following the formation of the acyl-enzyme intermediate (Otlewski *et al.* (2005) *The EMBO Journal*, 24: 1303). The kinetic model of the reaction of a serpin with a protease is identical to that of proteolysis of a substrate (see *e.g.*, Figure 1; Zhou *et al.* (2001) *J. Biol. Chem.*, 276: 27541-27547). Following interaction with a target protease, the serpin initially forms a non-covalent Michaelis-like complex through interactions of residues in the RSL flanking the P1-P1' scissile bond (Silverman *et al.* (2001), *J. Biol. Chem.*, 276: 33293-33296). The serine residue (for serine proteases), in the active site of the protease attacks the P1-P1' bond, facilitating cleavage of the peptide bond and formation of a covalent ester linkage between the serine residue and the backbone carbonyl of the P1 residue. After the RSL is cleaved, the RSL inserts into β-sheet A of the serpin molecule. The first residue to insert is P14 (*i.e.* amino acid 345 in mature α1-antitrypsin, which corresponds to amino acid position T369 in the sequence of amino acids set forth in SEQ ID NO:1), and is followed by the flexible hinge region (P15-P9) of the RSL (Buck *et al.* (2005) *Mol. Biol. Evol.*, 22: 1627-1634). Insertion of the RSL transports the covalently bound protease with it, resulting in a conformational change of the protease characterized by a distorted active site (see Figure 1) as well as a transition of the serpin into a "relaxed" state. The conformational change of the protease alters the catalytic triad of the active site such that the P1 side chain is removed from the S1 pocket. The net result of the conformational rearrangements is trapping of the acyl enzyme intermediate (Silverman *et al.* (2001), *J. Biol. Chem.*, 276: 33293-33296).

The formation of an acyl enzyme is important to the serpin interaction, and therefore, serpins are typically specific for classes of proteases that have acyl enzyme intermediates in catalysis. Among these classes of proteases are predominantly members of the serine protease family including those in the chymotrypsin superfamily and those in the subtilisin superfamily of proteases, which are described in more detail below. Additionally, serpins also are reactive against cysteine proteases including, for example, those in the papain family and the caspases family of serine proteases. Typically, serpins do not inhibit proteases of the metallo-, threonine, or aspartic families. For example, interactions of serpins with metalloproteases do not result in a covalent trapped intermediate, but instead the metalloprotease cleaves the inhibitor without the formation of any complex (Li *et al.* (2004) *Cancer Res.* 64: 8657-8665).

Thus, although most serpins inhibit serine proteases of the chymotrypsin family, cross-class inhibitors do exist that inhibit cysteine proteases. Among cross-class inhibitors are the viral serpin CrmA and PI9 (SEPRINB9) that both inhibit caspases 1, and SCCA1 (SERPINB3) that inhibits papain-like cysteine proteases including cathepsins L, K, and S. The mechanism of serpin-mediated inhibition of serine proteases appears to be adapted to cysteine proteases as well. The difference, however, is that the kinetically trapped intermediate is a thiol ester rather than an oxy ester as is the case for serine proteases (Silverman *et al.* (2001) *J. Biol. Chem.*, 276:33293-33296). The existence of a stable, covalent thiol ester-type linkage is supported by the detection of an SDS-stable complex between SCCA1 and cathepsin S (Silverman *et al.* (2001) *J. Biol. Chem.*, 276:33293-33296; Schick *et al.* (1998) *Biochemistry*, 37:5258-5266).

The serpin-protease pair is highly stable for weeks up to years depending on the serpin-protease pair, however, dissociation eventually will occur to yield the products of normal proteolysis (*i.e.* the cleaved serpin and the active protease; see e.g., Zhou *et al.* (2001) *J. Biol. Chem.*, 276: 27541-27547). Further, if the RSL loop is not inserted fast enough into the protease, the reaction proceeds directly to the cleaved product. This phenomenon is termed partitioning and reflects the existence of a branched pathway that can occur leading to either a stable inhibitory complex or turnover of the serpin into a substrate such as is depicted in Figure 1 as the formation of an inhibited complex versus the non-inhibitory pathway (Lawrence *et al.* (2000), *J.*

Biol. Chem., 275: 5839-5844). Partitioning of a serpin can be modulated by changing residues in the RSL loop, particularly in the hinge region of the RSL which initiates loop insertion (*i.e.* P14), or by altering the protease for which the serpin optimally interacts. For example, the inhibitory activity of the serpin plasminogen activator inhbitor-1 (PAI-1) differs between the proteases uPA, tPA, and thrombin, with a targeted preference for uPA and tPA. Further, variation of the RSL loop at, for example, the P14 position of the hinge region alters the targeted preference of PAI-1: mutation to charged amino acids (*i.e.* Arg, Lys, Asp, Glu) reduces the inhibitory activity of PAI-1 to each of uPA, tPA, and thrombin; mutation to neutral amino acids (*i.e.* His, Tyr, Gln, Asn) or to Gly which lacks a side chain results in a 10-100-fold reduced inhibitory activity of PAI-1 to tPA and thrombin as compared to uPA; and mutation to hydrophobic amino acids does not change the inhibitory activity of PAI-1 as compared to wildtype PAI-1 (Lawrence *et al.* (2000), *J. Biol. Chem.*, 275: 5839-5844).

An important factor in the success of the serpin-mediated inhibition of protease catalysis is the length of the RSL loop, which must be of a precise length to ensure that the serpin and protease interact in a way that provides leverage between the body of the serpin and protease to allow for displacement of the catalytic serine from the active site and deformation of the protease (Zhou *et al.* (2001) *J. Biol. Chem.*, 276: 27541-27547; Huntington *et al.* (2000) *Nature,* 407:923-926). In effect, the protease is crushed against the body of the serpin. Most serpins have an RSL that is 17 residues in length, while only a few have been identified with loops of 16 residues (i.e. α2-antiplasmin, C1-inhibitor, and CrmA). An α2-antiplasmin variant serpin having an 18 residue loop also has been identified from a patient with a bleeding disorder, although this variant is not a functional inhibitory serpin (Zhou *et al.* (2001) *J. Biol. Chem.*, 276: 27541-27547). Thus, the serpin inhibitory mechanism can accommodate a shortening, but not a lengthening, of the RSL (Zhou *et al.* (2001) *J. Biol. Chem.*, 276: 27541-27547). In addition to a conservation of loop length among serpin family members, the RSLs of serpins also generally retain a conserved hinge region (P15-P9) composition and do not typically contain charged or bulky P residues.

a. Exemplary Serpins

Serpins used in the method provided herein can be any serpin polypeptide, including but not limited to, recombinantly produced polypeptides, synthetically produced polypeptides and serpins extracted from cells, tissues, and blood. Serpins also include allelic variants and polypeptides from different species including, but not limited to, animals of human and non-human origin, poxviruses, plants, bacteria, and archaea. Typically, an allelic or species variant of a serpin differs from a native or wildtype serpin by about or at least 40%, 50%, 60%, 70%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. Human serpins include any serpin provided herein (*e.g.*, in Table 2 below), allelic variant isoforms, synthetic molecules from nucleic acids, proteins isolated from human tissues, cells, or blood, and modified forms of any human serpin polypeptide. Serpins also include truncated polypeptide fragments so long as a sufficient portion of the RSL loop is present to mediate interaction with a protease and formation of a covalent acyl enzyme intermediate.

TABLE 2: Exemplary Serpins

	Serpin	Protein name	Nick-name	Function	Acc. #	Mature Poly-peptide (aa)	SEQ ID NO
Extra-cellular inhibitory Serpins	SERPINA1	Alpha-1-antitrypsin	AIAT	Inhibits elastase	P01009	25-418	1
	SERPINA2	Alpha-1-antitrypsin-related protein	A1AU	May be a pseudogene	P20848	22-420	2
	SERPINF2	Alpha-2-antiplasmin	A2AP	Inhibits plasmin and trypsin	P08697	40-491	3
	SERPINA3	Alpha-1-antichymotrypsin	AACT	Inhibits neutrophil cathepsin G and mast cell cymase	P01011	24-423	4
	SERPINC1	Antithrombin-III	ANT3	Regulates blood coagulation cascade; thrombin and factor Xa inhibitor	P01008	33-464	5
	SERPIND1	Heparin cofactor II	HEP2	Regulates blood coagulation cascade; thrombin inhibitor	P05546	20-499	6
	SERPING1	Plasma protease C1 inhibitor	IC1	Regulation of complement activation,	P05155	23-500	7

				blood coagulation, fibrinolysis and the generation of kinins; C1 esterase inhibitor			
	SERPINA5	Plasma serine protease inhibitor, Protein C inhibitor	IPSP, PAI-3	Inhibits activated protein C and plasminogen activators	P05154	20-406	8
	SERPINA4	Kallistatin	KAIN, PI4	Inhibits amidolytic and kininogenase activities of human tissue kallikrein	P29622	21-427	9
	SERPINI1	Neuroserpin	NEUS, PI12	Formation or reorganization of synaptic connections and synaptic plasticity; inhibitor of tPA, uPA, and plasmin	Q99574	17-410	10
	SERPINE1	Plasminogen activator inhibitor-1	PAI1	Regulation of fibrinolysis; inhibitor of thrombin, uPA, tPA, and plasmin	P05121	24-402	11
	SERPIN12	Myoepithelium-derived serine proteinase inhibitor	PI14	Inhibition of cancer metastasis	O75830	19-405	12
	SERPINA10	Protein Z-dependent protease inhibitor	ZP1	Inhibits factor Z and XI	Q9UK55	22-444	13
	SERPINE2	Protease nexin I, glia-derived nexin precursor	PI7, GDN, PN-1	Inhibition of uPA and tPA	P07093	20-398	14
Intra-cellular inhibitory Serpins	SERPINB1	Leukocyte elastase inhibitor, monocytes neutrophil elastase inhibitor	ILEU	Inhibition of neutrophil protease	P30740	1-379	15
	SERPINB2	Plasminogen activator inhibitor-2	PAI2	Tissue-type plasminogen activator, intracellular signaling; inhibition of uPA	P05120	1-415	16
	SERPINB6	Placental	PTI6	Inhibits	P35237	1-376	17

		thrombin inhibitor		thrombin			
	SERPINB10	Bomapin	SB10, P110	Haematopoiesis, inhibition of thrombin and trypsin	P48595	1-397	18
	SERPINB11	epipin	SB11		Q96P15	1-392	19
	SERPINB12	Yukopin	SB12	Inhibits trypsin and plasmin	Q96P63	1-405	20
	SERPINB13	Headpin	SB13, P113	Proliferation or differentiation of keratinocytes, inhibition of cathepsins L and K	Q9UIV8	1-391	21
	SERPINB3	Squamous cell carcinoma antigen 1	SCC1	Modulates immune response towards tumors, inhibition of cathepsins L, K, S and V, and papain	P29508	1-390	22
	SERPINB4	Squamous cell carcinoma antigen 2	SCC2	Modulates immune response towards tumors, inhibition of Cathepsin G and chymase	P48594	1-390	23
	SERPINB7	Megsin	SPB7	Maturation of megakaryocytes	O75635	1-390	24
	SERPINB8	Cytoplasmic antiproteinase 8	SPB8, PI8	Inhibition of Furin	P50452	1-374	25
	SERPINB9	Cytoplasmic antiproteinase 9	SPB9, PI9	Granzyme B inhibitor	P50453	1-376	26
	SERPINB6	Proteinase inhibitor-6, placental thrombin inhibitor	PI6, PTI	Inhibition of cathepsin G, inhibits thrombin	P35237	1-376	27
Non-inhibitory serpins	SERPINA8	Angiotensinogen	ANGT	Blood pressure regulation, hormone precursor	P01019	34-485	28
	SERPINA6	Corticosteroid-binding globulin	CBG	Hormone carrier (glucocorticoids and progestins), cortisol binding	P08185	23-405	29
	SERPINH1	47 kDa heat shock protein	HS47	Molecular chaperone for collagen	P29043	18-417	30
	SERPINF1	Pigment epithelium-derived factor	PEDF	Induces neuronal differentiation	P36955	20-418	31

				in retinoblastoma cells; inhibitor of angiogenesis			
	SERPINB5	Maspin	MASP	Tumor suppressor, prevents metastasis	P36952	1-375	32
	SERPINH2	Collagen-binding protein 2	SIH2	Molecular chaperone for collagen	P50454	19-418	33
	SERPINA7	Thyroxine-binding protein	THBG	Thyroid hormone transport, thyroxine binding	P05543	21-415	34
	SERPINA9	Germinal center B-cell expressed transcript 1 protein	GCET1	Maintenance of naïve B cells	Q86WD7	24-417	35
	SERPINA12	Vaspin		Insulin-sensitizing adipocytokine	Q8IW75	21-414	36
	SERPINA11				Q86U17	20-422	37
	SERPINA13				Q6UXR4	22-307	38

Typically, a serpin used in the method provided herein is an inhibitory serpin, or fragment thereof, capable of forming a covalent acyl enzyme intermediate between the serpin and protease. Generally, such a serpin is used to select for proteases normally targeted by the serpin where close to complete inhibition of the protease occurs and partitioning is minimized between the inhibitory complex and cleaved serpin substrate. Table 3 depicts examples of serine proteases and their cognate serpin inhibitors. Such serpin/protease pairs are expected to have a high association constant or second ordered rate constant of inhibition and low or no partitioning into a non-inhibitory complex. For example, the major physiological inhibitor of t-PA is the serpin PAI-1, a glycoprotein of approximately 50 kD (Pannekoek *et al.* (1986) *EMBO J.*, 5:2539-2544; Ginsberg *et al.*, (1980) *J. Clin. Invest.*, 78:1673-1680; and Carrell *et al. In: Proteinase Inhibitors*, Ed. Barrett, A.J. et al., Elsevier, Amsterdam, pages 403-420 (1986). Other serpin/protease pairs also can be used in the methods provided herein, however, even where association constants are lower and partitioning is higher. For example, although the association constants of other serpins, such as C1 esterase inhibitor and alpha-2-antiplasmin with tPA are orders of magnitude lower

than that of PAI-1 (Ranby *et al.* (1982) *Throm. Res.*, 27:175-183; Hekman *et al.* (1988) *Arch. Biochem. Biophys.*, 262:199-210), these serpins nevertheless inhibit tPA (see *e.g.*, Lucore *et al.* (1988) *Circ.* 77:660-669).

TABLE 3:	
Serine Protease	**Cognate Serpin Inhibitor**
Activated protein C	Protein C inhibitor PAI-1
C1 esterase	C1 esterase inhibitor
Cathepsin G	Alpha-1-antitrypsin Alpa-1-antichymotrypsin
Chymase	Alpha-1-antichymotrypsin
Chymotrypsin	Alpha-1-antichymotrypsin Alpha-2-antiplasmin Contrapsin
Coagulation Factors (VIIa, Xa, XIa, XIIa)	Antithrombin III C1 esterase inhibitor
Elastase	Alpha-1-antitrypsin
Kallikrein	C1 esterase inhibitor Alpha-1-antitrypsin
Plasmin	Alpha-2-antiplasmin
Thrombin	Antithrombin III Heparin cofactor II
tPA	PAI-1, PAI-2, PAI-3
Trypsin	Alpha-1-antitrypsin Growth hormone regulated protein
Trypsin-like protease	Protease nexin I
u-PA	PAI-1, PAI-2, PAI-3

Thus, generally a serpin used for selection of a protease in the methods provided herein yields a reaction product where 80%, 90%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the reaction product is the formation of the inhibitory complex. In some cases, however, increased partitioning between a serpin and protease can occur in the methods provided herein, such as if the serpin used in the method does not optimally target the protease. Thus, in the method provided herein a serpin can be used to select a protease where the resulting reaction leads to at or about 20%, 30%, 40%, 50%, 60%, 70%, 75%, or more of a stable inhibitory complex and the remaining product is a cleaved serpin substrate. Factors that can be altered to optimize for protease selection where partitioning occurs include, for example, increased serpin concentration and increased reaction time. In some instances, other

non-inhibitory serpins, or mutants thereof as discussed below, can be used in the methods provided herein so long as the target protease for selection is able to interact with the serpin substrate to yield a covalent inhibitory complex that can be captured.

i. PAI-1

Exemplary of serpins used in the protease selection methods is plasminogen activator inhibitior-1 (PAI-1), or variants thereof. PAI-1 is the main inhibitor of tissue plasminogen activator (t-PA) and urokinase or urinary-plasminogen activator (u-PA), which are proteases involved in fibrinolyis due to the activation of plasminogen. PAI-1 has a second order rate constant for t-PA and u-PA of about 2 X 10^7 $M^{-1}s^{-1}$. PAI-1 is involved in tumor invasion, fibrinolysis, cell migration, tissue remodeling, tissue involution, ovulation, inflammation, trophoblast invasion, and malignant transformation (Salonen *et al.* (1988) *J Biol. Chem.*, 264: 6339-6343). PAI-1 is mainly produced by the endothelium, but also is secreted by other tissue types, such as for example, adipose tissue. Other related plasminogen activator inhibitors include PAI-2 and PAI-3. PAI-2, for example, also is an inhibitor of u-PA and t-PA, but is secreted by the placenta and typically is only present in high amounts during pregnancy.

PAI-1 is a single chain glycoprotein having a precursor sequence set forth in SEQ ID NO:11, including a 23 amino acid signal sequence, which when cleaved results in a 379 amino acid mature sequence. Like other serpins, PAI-1 transitions from a latent form into an active form following cleavage by a protease at its P1-P1' reactive site located at Arg^{346}-Met^{347} (*i.e.* corresponding to amino acids Arg^{369} and Met^{370} of a precursor sequence set forth in SEQ ID NO:11), thereby resulting in the formation of a stable covalent complex and the inactivation of the bound protease. Unlike other serpins, however, PAI-1 adopts a latent transition spontaneously resulting in an inactive, highly stable but covalently intact form whereby residues P15 to P4 of the RSL insert into the β-sheet A to form strand four of the β-sheet (*i.e.* s4A), and residues P3 to P10' form an extended loop at the surface of the molecule (De Taeye *et al.* (2003) *J Biol. Chem.*, 278: 23899-23905). Thus, active PAI-1 is relatively unstable at 37°C exhibiting a half-life of only 2.5 hours before spontaneous conversion to a latent conformation. This latent form, however, can be re-activated by denaturation, such as by denaturation with sodium dodecyl sulfate, guanidinium chloride, and urea (Declerek *et al.* (1992) *J. Biol. Chem.*, 267: 11693-11696) and heat

(Katagiri et al. (1988) Eur J. Biochem., 176: 81-87). The active form of PAI-1 also is stabilized by interaction with vitronectin. Mutant PAI-1 have been identified that are unable to undergo conversion to a latent conformation and are therefore more stable at elevated temperature and pH for extended times periods (see e.g., Berkenpas *et al.* (1995) *The EMBO J.*, 14:2969-2977).

Modifications of serine proteases (*i.e.* t-PA or u-PA) and/or of the inhibitory serpin (*i.e.* PAI-1) have been made to modulate or alter the secondary rate constants of inhibition so as to make proteases resistant to inhibition by their cognate serpin inhibitor, or variant thereof, such as for use in therapeutic applications where activity of the wild-type protease is desired (see *e.g*, U.S. Patent Serial Nos. 5,866,413; 5,728,564; 5,550,042; 5,486602; 5,304,482).

ii. Antithrombin (AT3)

Another exemplary serpin, or variant thereof, for use in the methods herein is antithrombin (AT3). AT3 also is a member of the serpin family and inactivates a number of enzymes, including for example, those from the coagulation system such as, but not limited to, Factor X, Factor IX, Factor II (thrombin), Factor VII, Factor XI, and Factor XII. Typically, antithrombin is predominantly found in the blood where it, for example, prevents or inhibits coagulation by blocking the function of thrombin. The activity of AT3 is increased by the presence of one or more cofactors, typically heparin. Upon interaction with heparin, AT3 undergoes a conformational rearrangement involving loop expulsion away from serpin structure and P1 exposure resulting in an AT3 structure having an exposed protease-accessible conformation. In addition, heparin can bind to both the protease and inhibitor thereby accelerating the inhibitory mechanism (Law *et al.* (2006) *Genome Biology*, 7(216): 1-11).

The gene sequence for AT3 codes for a seven exon spanning DNA, encoding a precursor protein set forth in SEQ ID NO:5. Cleavage of the signal sequence corresponding to amino acids 1-32 of the sequence set forth in SEQ ID NO:5 results in a mature protein of 432 amino acids that has a molecular weight of about 58,000 daltons. Six of the amino acids are cysteines, which results in the formation of three intramolecular disulfide bonds. The P4-P2' positions in the RSL of AT3 contain the amino acid residues IAGRSL (SEQ ID NO:478), which correspond to amino acids 422-427 in the sequence of amino acids set forth in SEQ ID NO:5, where cleavage at the reactive site P1-P1' occurs between amino acids Arg^{425}-Ser^{426}.

3. Other Protease Trap Polypeptides

Additional protease trap polypeptides are known in the art or can be identified that exhibit a mechanism of inhibition similar to serpins (*e.g.* cleavage of the target substrate by a protease that produces a stable intermediate and a conformational change in the structure of the protease). Such protease trap polypeptides are contemplated for use in the method provided herein. Exemplary of such a protease trap polypeptide is p35. In addition, any other molecule that is cleaved by a protease resulting in the trapping of a protease in a long-lasting, stable complex can be used in the methods provided herein.

a. p35

For example, the baculovirus p35 protein (SEQ ID NO: 473), which is a broad spectrum caspase inhibitor, can inhibit caspases in this manner (Xu *et al.* (2001) *Nature* 410:494-497; Xu *et al.* (2003) *J. Biol. Chem.* 278(7):5455-5461). Cleavage of the P_1-P_1' bond of p35 (at the caspase cleavage site $DQMD^{87}$) by caspases produces a covalent thioester intermediate between the amino segment of p35 loop (Asp87) and the cysteine residue of the caspase catalytic triad (Cys350 in caspase-8). Upon formation of the thioester linkage, the protease undergoes a conformational change allowing the amino segment of the cleaved loop to bury into the caspase, while the N-terminus of p35 containing a Cys residue at position 2 inserts into the caspase active site, thus blocking solvent accessibility of His 317 residue in caspase-8. Inaccessibility to the hydrolytic water molecule thus prevents subsequent hydrolysis of thioester bond.

Similar viral caspase inhibitors in addition to p35 include, but are not limited to, p49 (SEQ ID NO: 491) and the serpin CrmA cowpox gene (SEQ ID NO: 492). The p49 inhibitor exhibits a caspase inhibition mechanism similar to that of p35 in that a stable thioester linkage is formed with the active site of the caspase upon cleavage of the p49 caspase recognition sequence $TVTD^{94}$.

Target substrates for the screening using the methods provided herein can include a viral caspase inhibitor polypeptide, such as a p35, p49 or CrmA polypeptide. Methods of modification of the RSL loop of serpins provided herein can be easily adapted to modification of viral caspase inhibitor polypeptides. For example, the target site for cleavage in the p35 RSL can be modified to so as to select for proteases that have an altered reactivity or specificity for a target substrate. In wild-type p35,

caspase recognition is found at amino acid positions 84-87 ($DQMD^{87}$). Modifications to viral caspase inhibitor polypeptides can thus include modifications that alter the cleavage sequence and/or surrounding amino acid residues. For example, such modified caspase inhibitor polypeptides, such as for example a p35, p49 or CrmA polypeptide, can be designed to mimic the cleavage sequence of a desired target substrate, such as for example, a target substrate involved in the etiology of a disease or disorder. Any modification in the RSL loop sequence of a viral caspase inhibitor polypeptide can be made in the methods provided herein.

Viral caspase inhibitor polypeptides such as a p35, p49 or CrmA polypeptide, used in the methods provided herein can be any viral caspase inhibitor polypeptide, including but not limited to, recombinantly produced polypeptides, synthetically produced polypeptides and p35 pr p49 polypeptide produced by baculovirus purification methods. Viral caspase inhibitor polypeptides also include allelic variants of polypeptides, such as p35, p49 or CrmA polypeptide variants.

b. Alpha Macroglobulins (aM)

The alpha macroglobulin (aM) family of proteases include protease inhibitors such as the exemplary protease inhibitor alpha-2-macroglobulin (a2M; SEQ ID NO:490), and are contemplated for use as protease traps in the methods provided herein. aM molecules inhibit all classes of proteases. aM protease traps are characterized by a similar inhibition mechanism involving cleavage of a bait region of the inhibitor by a protease. The bait region is a segment that is susceptible to proteolytic cleavage, and which, upon cleavage, initiates a conformational change in the aM molecule resulting in the collapse of the structure around the protease. For the exemplary a2M sequence set forth in SEQ ID NO:490, the bait region corresponds to amino acids 690-728. In the resulting aM-protease stable complex, the active site of the protease is sterically shielded, thereby decreasing access to normal protease substrates. Typically, the trapped protease remains active against small peptide substrates, but loses its ability to interact with large protein substrates or inhibitors. In addition, aM molecules are characterized by the presence of a reactive thiol ester, which inactivates the inhibitory capacity by reaction of the thiol ester with amines. Further, the conformational change that occurs upon cleavage of the bait region exposes a conserved COOH-terminal receptor binding domain (RBD). Exposure of

the RBD sequence facilitates the removal of the aM-protease complex from circulation.

4. Protease Trap Competitors

Competitors can be used in the methods provided herein to modulate the specificity and selectivity constraints of a selected protease for a target substrate. The competitors can be contacted with the protease, or collections thereof, at any time, such as before or after contact of the protease with the desired protease trap polypeptide or the competitor and desired protease trap polypeptide can be contacted with the protease simultaneously. Competitors can be specific competitors or broad competitors.

Specific competitors are designed that mimic a predetermined non-target substrate and thereby act as predetermined potential off-targets. Typically, such competitors are not labeled, so that stable protease complexes that form are not selected for. In addition, such competitors are added in large excess, typically molar excess, over the designed protease trap polypeptide used in the selection scheme, such that the competitors bind up the undesired proteases in the collection. In one example of specific competition, two different protease trap polypeptides, each designed to mimic different substrate recognition, are contacted with a collection of proteases where only one of the protease trap polypeptides is detectably labeled. For example, a competitor can include a polypeptide protease trap that is designed to have its reactive site mimic the cleavage sequence of a non-target substrate. Thus, a competitor, such as a serpin, can be designed to have its P4-P1' RSL residues replaced by the cleavage sequence of a predetermined non-target substrate. The competitor can be used in methods in combination with a protease trap polypeptide, such as for example another serpin polypeptide, whose RSL sequence has been modified to contain amino acids in the P4-P1' positions that mimic the cleavage sequence of a desired or predetermined target substrate, and that is labeled for isolation thereof. Thus, both protease trap polypeptides select for proteases exhibiting selectivity for the target or non-target cleavage sequence, but only those stable protease complexes that exhibit the desired target substrate specificity and that are detectably labeled can be isolated from the reaction. Other examples of specific competitors include, for example, the native protease trap polypeptide for which the reactive site has been modified in the methods

provided herein. Example 6 exemplifies such a strategy where a plasma purified AT3 serpin is used as a competitor against the modified serpin $AT3^{SLGR-KI}$.

Broad competitors also can be used in the methods provided herein to constrain the specificity and selectivity of selected proteases. Examples of broad competitors include, for example, human plasma or human serum which contains a variety of natural protease inhibitors. Alternatively, a broad small molecule library of protease trap polypeptides can be generated where every position of P2, P3, or P4 is made to be different, such as for example an Acxxx-Thiaphine library.

5. Variant Protease Trap Polypeptides

Protease trap polypeptides that have been modified in their reactive site to have an altered cleavage sequence can be used in the methods provided herein to select for proteases with a desired or predetermined target substrate. Thus, protease traps are modified in the region of their sequence that serves as the recognized cleavage site of a protease so as to select for proteases that have an altered reactivity or specificity for a target substrate. For example, serpins can be modified to have an altered cleavage sequence at or around the scissile bond in the RSL loop. In another example, a2M can be modified in its bait region to have an altered cleavage sequence. Such modified protease traps can be designed to mimic the cleavage sequence of a desired target substrate, such as for example, a target substrate involved in the etiology of a disease or disorder.

Any modification in the RSL loop sequence of a serpin molecule can be made in the methods provided herein. Alignments of RSL sequences of exemplary wild-type serpins are set forth in Table 4 below. In the Table below, the numbers designating the P15 to P5' positions are with respect to a mature α1-antitrypsin molecule (corresponding to amino acids 367- 387 of the sequence of amino acids set forth in SEQ ID NO:1). The identity of the RSL loop sequences are known to those of skill in the art and/or can be determined by alignments such as by alignment with serpins as set forth in Table 4 below.

TABLE 4: RSL LOOP SEQUENCE ALIGNMENT*

SERPIN	RSL loop sequence	SEQ ID NO
	343 P_{15} P_{10} P_4 P_1P_1' P_5' 363	

Manduca sexta serpin 1B	EGAEAAAANAFGIVPKSLILY	397
Manduca sexta serpin 1K	EGAEAAAANAFKITTYSFHFV	398
α1-antichymotrypsin	EGTEASAATAVKITLLSALVE	399
Antithrombin-III	EGSEAAASTAVVIAGRSLNPN	400
PAI-II	EGTEAAAGTGGVMTGRTGHGG	401
α1-antitrypsin	KGTEAAGAMFLEAIPMSIPPE	402
PAI-I	SGTVASSSTAVIVSARMAPEE	403
PAI-III	SGTRAAAATGTIFTFRSARLN	404
Ovalbumin	AGREVVGSAEAGVDAASVSEE	405

* adapted from Ye et al. (2001) Nature Structural Biology 8: 979

Thus, amino acid sequences within the RSL loop of a serpin corresponding to any one or more of amino acids in the reactive site of a serpin (*i.e.* any one or more of amino acids corresponding to P15 to P5' positions such as set forth, for example, in Table 4 above) can be modified. Typically, amino acids that are part of the hinge region of the RSL loop sequence are not modified (*i.e.* amino acids corresponding to P15-P9 positions). In one example, one or more amino acid in the P1 and/or P1' position are modified corresponding to those amino acids that flank the scissile bond. In another example, any one or more amino acids corresponding to reactive site positions P4-P2' are modified. For example, the P4-P1' of PAI-1 is VSARM (SEQ ID NO:378), where cleavage occurs between the R (P1) and M (P1') amino acids. Modification of any or more of amino acids of the VSARM sequence can be made to modify the cleavage sequence of PAI-I to select for proteases with altered specificity. Example 1 exemplifies modification of PAI-I where the VSARM sequence in the reactive site loop is modified to be RRARM (SEQ ID NO:379). In another example, the reactive site loop the VSARM sequence can be modified to the known efficient peptide substrate PFGRS (SEQ ID NO:389). Exemplary of such mutant PAI-1 are set forth in SEQ ID NOS:610 and 611.

In another example, modifications can be made in the RSL of antithrombin III (AT3). For example, the P4-P1' of AT3 is IAGRSL (SEQ ID NO:478), where cleavage occurs between the R (P1) and S (P1') amino acids. Modification of any one or more of amino acids of the IAGRSL sequence can be made to modify the cleavage sequence of AT3 to select for proteases with altered specificity. Examples 6 and 7 exemplify modification of AT3 where the IAGRSL sequence in the reactive site loop is modified to be RRVRKE (SEQ ID NO:498). In another example, the IAGRSL amino acid sequence in the reactive site loop can be modified to SLGRKI (SEQ ID

NO:479). Other modified AT3 polypeptides were made containing replacement of the IAGRSL amino acid sequence with the amino acid sequence SKGRSL (SEQ ID NO:501) or the amino acid sequence PRFKII (SEQ ID NO: 503). Exemplary of such mutant AT3 molecules are set forth in any of SEQ ID NOS:497, 499, 500, and 502.

Alternatively, and if necessary, the modification in any one or more amino acid positions P4-P2' can be made one at a time, two at a time, three at a time, etc., and the resulting modified serpin can be separately tested in successive rounds of selection so as to optimize for proteases that exhibit substrate specificity and/or selectivity at each of the modified positions.

In most cases, amino acid residues that replace amino acid residues in the reactive site loop of a wild-type serpin, or analogous sequence in another protease trap, are chosen based on cleavage sequences in a desired target substrate. A target substrate protein is one that is normally involved in a pathology, where cleaving the target protein at a given substrate sequence serves as a treatment for the pathology (see e.g. U.S. patent publication No. US 2004/0146938, US2006/0024289, US2006/0002916, and provisional application serial No. 60/729,817). For example, the target protein can be one involved in rheumatoid arthritis (*i.e.* TNFR), sepsis (*i.e.* protein C), tumorigenicity (*i.e.* a growth factor receptor, such as a VEGFR), or inflammation (*i.e.* a complement protein). A target substrate also can be a viral protein such that upon cleavage of the viral protein the viruses would be unable to infect cells. Table 5 below sets forth exemplary target substrates.

TABLE 5: Exemplary Target Substrates

Target	Indication	Molecule Class
IL-5/IL-5R	Asthma	Cytokine
IL-1/IL-1R	Asthma, inflammation, Rheumatic disorders	Cytokine
IL-13/IL-13R	Asthma	Cytokine
IL-12/IL-12R	Immunological disorders	Cytokine
IL-4/IL-4R	Asthma	Cytokine
TNF/TNFR	Asthma, Crohn's disease, HIV infection, inflammation, psoriasis, rheumatoid arthritis, inflammatory bowel disease	Cytokine
CCR5/CXCR4	HIV infection	GPCR
gp120/gp41	HIV infection	Fusion protein
CD4	HIV infection	Immune Receptor

Hemaglutinin	Influenza infection	Fusion Protein
RSV fusion protein	RSV infection	Fusion Protein
B7/CD28	Graft-v-host disorder, rheumatoid arthritis, transplant rejection, diabetes mellitus	Immune Receptor
IgE/IgER	Graft-v-host disorder, transplant rejection	Antibody receptor
CD2, CD3, CD4, CD40	Graft-v-host disorder, transplant rejection, psoriasis	Immune Receptor
IL-2/ IL-2R	Autoimmune disorders, graft-v-host disorders, rheumatoid arthritis	Cytokine
VEGF, FGF, EGF, TGF	Cancer	Growth Factor
HER2/Neu	Cancer (*i.e.* breast cancer)	Growth Factor Receptor
CCR1	Multiple sclerosis	GPCR
CXCR3	Multiple sclerosis, rheumatoid arthritis	GPCR
CCR2	Atherosclerosis, rheumatoid arthritis	GPCR
Src	Cancer, osteoporosis	Kinase
Akt	Cancer	Kinase
Bcl-2	Cancer	Protein-protein
BCR-Abl	Cancer	Kinase
GSK-3	Diabetes	Kinase
Cdk-2/cdk-4	Cancer	Kinase
EGFR	Lung, breast, bladder, prostate, colorectal, kidney, head & neck cancer	
VEGFR-1, VEGFR-2	neck cancer	Growth Factor Receptor
Complement	Inflammatory diseases	Immune molecules

Cleavage sites within target proteins are known or can be easily identified. Cleavage sites within target proteins are identified by the following criteria: 1) they are located on the exposed surface of the protein; 2) they are located in regions that are devoid of secondary structure (i.e. not in P sheets of helices), as determined by atomic structure of structure prediction algorithms (these regions tend to be loops on the surface of proteins or stalk on cell surface receptors); 3) they are located at sites that are likely to inactive (or activate) the protein, based on its known function. Cleavage sequences are *e.g.*, four residues in length (*i.e.* P1-P4 positions) to match the extended substrate specificity of proteases, but can be longer or shorter. For example, the P4-P1 amino acid residues for a cleavage sequence in complement factor C2 is

SLGR (SEQ ID NO:431), but also can be represented as the P4-P2' sequence of SLGRKI (SEQ ID NO:479), where cleavage occurs between the P1 and P1' position (i.e. between R/K). Hence, any one or more residues within a cleavage sequence, including any one or more of residues P4-P2', including P4-P1, can be introduced into a protease trap polypeptide, such as in the RSL of a serpin to generate a mutant protease trap polypeptide.

Cleavage sequences can be identified in a target substrate by any method known in the art (see *e.g.*, published U.S. Application No. US 2004/0146938). In one example, cleavage of a target substrate is determined by incubating the target substrate with any protease known to cleave the substrate. Following incubation with the protease, the target protein can be separated by SDS-PAGE and degradative products can be identified by staining with a protein dye such as Coomassie Brilliant Blue. Proteolytic fragments can be sequenced to determine the identity of the cleavage sequences, for example, the 6 amino acid P4-P2' cleavage sequence, and in particular, the four amino acid P4-P1 cleavage sequence residues. Table 6 identifies cleavage sequences corresponding to positions P4-P1 for exemplary target substrates.

TABLE 6: Cleavage Sequence for Exemplary Target Substrates (P4-P1 residues)

Target	**Cleavage sequence**
TNF-α	AEAK (406)
TNF-R1	ENVK (407); GTED (408)
TNF-R2	SPTR (409); VSTR (410); STSF (411)
HER-2	KFPD (412); AEQR (413)
EGFR	KYAD (414); NGPK (415)
VEGFR-1	SSAY (416); GTSD (417)
VEGFR-2	AQEK (418); RIDY (419); VLKD (480); LVED (481); WFKD (482); RIYD (483); KVGR (484); RVRK (485); RKTK (486); KTKK (487); TKKR (488); RRVR (489)
C3	REFK (420); GLAR (421); RLGR (422); AEGK (423); QHAR (424); LPSR (425); SLLR (426); LGLA (427); LSVV (428)
C4	HRGR (429)
C2	GATR (430); SLGR (431); VFAK (432)

Hence, modification of an RSL of a serpin, or analogous sequence in other protease traps, can be modified to any desired or predetermined cleavage sequence of a target substrate. In one example, the selected cleavage sequence can be one that is a particularly efficient cleavage sequence of t-PA. Such a cleavage sequence is, for example, PFGRS (SEQ ID NO:389; see *e.g.*, Ding *et al.* (1995) *PNAS*, 92:7627-7631). Thus, for example, a protease can be selected for that has an altered substrate specificity that is made to replicate the substrate specificity of t-PA. Since t-PA is an often used therapeutic for the treatment of fibrinolytic disorders, such a selected protease can be optimized to be an alternative t-PA therapeutic, while minimizing undesirable side effects often associated with t-PA therapies (*i.e.* excessive bleeding).

In another example, a cleavage sequence for a complement protein can be targeted as a predetermined or desired cleavage sequence for selection of a protease using the methods provided herein. A protease selected to have increased substrate specificity against any one or more complement proteins would be a therapeutic candidate for treatment of disorders and diseases associated with inflammation such as, but not limited to, autoimmune diseases, such as rheumatoid arthritis and lupus, cardiac disorders, and other inflammatory disorders such as sepsis and ischemia-reperfusion injury (see *e.g.*, provisional application serial No. 60/729,817). Example 6 to Examples 15 exemplifiy selection of an MT-SP1 protease against an AT3 serpin molecule modified by replacements of its native P4-P2' residues IAGRSL (SEQ ID NO:478) with a cleavage sequence of the C2 complement proteins (i.e. SLGRKI, SEQ ID NO:479). Modification or replacement of amino acid residues by the SLGRKI cleavage sequence, or intermediates thereof such as are described below, can be made in any protease trap polypeptide, such as any serpin polypeptide, for selection of any candidate protease as so desired.

In an additional example, a cleavage sequence can be selected in a VEGFR, such as in the stalk region of a VEGFR, such that the VEGFR is inactivated upon cleavage by a protease having specificity for the cleavage sequence. Examples of cleavage sequences in a VEGFR are described herein and set forth in related published U.S. application serial Nos. US20060024289 and US20060002916. For example, the RSL of a serpin, or analogous sequence in other protease traps such as the "bait" region in alpha-2 macroglobulin, can be modified to have any one or more of amino acid positions P4-P2' replaced with the cleavage sequence of a VEGFR. In

one example, amino acid residues in a native serpin can be modified to contain the P4-P1 positions corresponding to the RRVR (SEQ ID NO:489) cleavage sequence, or the entire P4-P2' sequence RRVRKE (SEQ ID NO:498). A protease selected against such a modified serpin would be a candidate to treat VEGFR-mediated disorders, such as for example, angiogenic disorders.

In some cases, in the methods provided herein, the modifications in any one or more of the P4-P2' positions of a serpin RSL, or analogous sequence in other protease traps, can be made in successive rounds to optimize for selection of proteases with a desired or predetermined substrate specificity. For example, both u-PA and t-PA proteases prefer small amino acids at the P2 position and very different amino acids in the P3 and P4 positions. Thus, modified serpins can be generated that are intermediates for the final target cleavage sequence, where a first intermediate is generated by modification of only the P3 and P4 positions to select for proteases that exhibit specificity at the P3 and P4 positions. The selected protease or proteases can then be used as a template for the generation of a new combinatorial library against a new serpin molecule modified to additionally have the P2 position changed.

Thus, in selection, for example, of a u-PA protease, or variant thereof, that exhibits increased substrate specificity for the VEGFR cleavage sequence RRVR, the first round of selection can be made against an intermediate modified protease trap polypeptide, such as a serpin, where only the P3 and P4 positions are changed as compared to the native sequence at those positions. For example, where the native P4-P1' amino acids in the RSL loop of the serpin PAI-1 are VSARM, a modified intermediate PAI-1 can be made by replacement of only the P4 and P3 VEGFR cleavage sequence, to yield the intermediate serpin molecule containing RRARM (SEQ ID NO:379) in the P4-P1' positions. Subsequent rounds of protease selection can be made against a PAI-1 serpin that has additionally been modified at the P2 position.

Protease traps, including serpins, can be modified using any method known in the art for modification of proteins. Such methods include site-directed mutagenesis, including single or multi-sited directed mutagenesis. Likewise, expression and purification of protease-trap polypeptides, including variant protease-trap polypeptides can be performed using methods standard in the art for expression and purification of polypeptides. Any host cell system can be used for expression,

including, but not limited to, mammalian cells, bacterial cells or insect cells. Further, the protease trap polypeptides can be modified further to include additional sequences that aid in the identification and purification of the protease trap polypeptide. For example, epitope tags, such as but not limited to, His tags or Flag tags, can be added to aid in the affinity purification of the polypeptide. In some examples, protease trap polypeptides are directly biotinylated to aid in capture and/or purification. An exemplary method for biotinylating a protease-trap polypeptide is described in Example 16.

Assays, such as assays for biological function of a serpin molecule or other protease trap are known in the art and can be used to assess the activity of a modified protease trap as an inhibitor in the methods provided herein. Such assays are dependent on the protease trap polypeptide modified for use in the methods herein. Exemplary of such assays for PAI-1 include, for example, active site titration against standard trypsin or titration of standard trypsin such as are exemplified in Example 1. Also exemplary of such assays are protease inhibition assays, which are known in the art, whereby the ability of the protease trap to inhibit the cleavage of a fluorogenic substrate by an active protease is used as a readout for protease trap activity. Exemplary of a protease inhibition assay is a matriptase (MT-SP1) inhibition assay. In one example of such an assay, the protease trap is a serpin. In a specific example, the serpin is AT3 or a variant AT3 protein made according to the methods provided herein, the fluorogenic substrate is RQAR-ACC. Cleavage of the substrate is measured, for example, as exemplified in Example 14A. Thrombin inhibition assays also can be used to assess the activity of AT3, or modified AT3. Similar assays can be designed or are known to one of skill in the art depending on the cognate protease for which a protease trap polypeptide, or variant thereof, normally interacts. Further, it is expected and often is the case that a modified protease trap polypeptide will have reduced activity as compared to a wild-type protease trap polypeptide in normal assays of protease trap activity or function.

D. PROTEASES

In the methods provided herein, candidate proteases are selected for that exhibit an altered substrate specificity, typically for a predetermined or desired substrate. Collections of proteases, mutant protease, or catalytically active portions thereof are contacted with a protease trap polypeptide, such as any provided herein

including, for example, serpins or modified serpins, to select for proteases with altered substrate specificity. The protease collections can be provided on a solid support or in a homogenous mixture such as in solution or suspension. The selected proteases can be isolated as stable complexes with the protease trap polypeptide, and can be identified. Selected proteases display increased catalytic efficiency and reactivity against the desired or predetermined target substrate, and are thereby candidates for use as therapeutics, such as in any disease or disorder for which the target substrate is involved.

1. Candidate Proteases

In the method provided herein, proteases are selected for that have an altered and/or increased specificity for a desired substrate that is involved in a disease or disorder. Generally, proteases are highly specific proteins that hydrolyze target substrates while leaving others intact. For the cleavage of natural substrates, proteases exhibit a high degree of selectivity such that substrate cleavage is favored, whereas non-substrate cleavage is disfavored (Coombs *et al.* (1996) *J. Biol. Chem.*, 271: 4461-4467). Selecting for proteases with an altered specificity and selectivity for a desired target substrate would enable the use of proteases as therapeutics to selectively activate or inactivate proteins to reduce, ameliorate, or prevent a disease or disorder. Target proteases used in the protease trap selection method provided herein can be any known class of protease capable of peptide bond hydrolysis for which the protease trap interacts. Typically, for serpins, such proteases are generally serine or cysteine proteases for which serpins react with to form a covalent intermediate complex. Exemplary of serine and cysteine proteases are any protease set forth in Table 7 below. Typically, a library of modified proteases are used in the methods provided herein to select for a protease variant that exhibits an increased specificity or selectivity for a target protease trap, or variant thereof, such as a serpin, or variant thereof.

Exemplary proteases that can be used, and/or modified to be used, in the selection method provided herein are described, and include truncated polypeptides thereof that include a catalytically active portion. Exemplary candidate proteases are listed in Table 7 and described herein (see *e.g.*, www.merops.sanger.ac.uk). The sequence identifiers (SEQ ID NO) for the nucleotide sequence and encoded amino acid precursor sequence for each of the exemplary candidate proteases is depicted in

the Table. The encoded amino acids corresponding to the signal peptide or propeptide sequence to yield a mature protein also are noted in the Table. In addition, amino acids designating the protease domain (*i.e.* peptidase unit) also are noted, as are the active site residues that make up, for example, the catalytic triad of the respective protease. Since interactions are dynamic, amino acid positions noted are for reference and exemplification. The noted positions reflects a range of loci that vary by 2, 3, 4, 5 or more amino acids. Variations also exist among allelic variants and species variants. Those of skill in the art can identify corresponding sequences by visual comparison or other comparisons including readily available algorithms and software.

Candidate proteases for selection typically are wild-type or modified or variant forms of a wildtype candidate protease, or catalytically active portion thereof, including allelic variant and isoforms of any one protein. A candidate protease can be produced or isolated by any method known in the art including isolation from natural sources, isolation of recombinantly produced proteins in cells, tissues and organisms, and by recombinant methods and by methods including *in silico* steps, synthetic methods and any methods known to those of skill in the art. Modification of a candidate protease for selection can be by any method known to one of skill in the art, such as any method described herein below.

Table 7: Exemplary Candidate Proteases

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
Serine Protease: Chymo-trypsin family	S01.010	granzyme B, human-type	M17016	39	P10144	40	1-18 / 19-20	21-247 (64, 108, 203)
	S01.011	Testisin	NM_006799 (v1) NM_144956 (v2) NM_144957 (v3)	41 43 45	NP_006790 NP_659205 NP_659206	42 44 46	1-19 / 20-41	42-288 (82, 137, 238)
	S01.015	trypstase beta 1 (Homo sapiens) (III)	NM_003294	47	NP_003285	48	1-18 / 19-30	31-274 (74, 121, 224)
	S01.017	kallikrein hk5	NM_012427	49	NP_036559	50	1-22 /	67-292 (108, 153, 245)
	S01.019	Corin	NM_006587	51	NP_00657	52		802-1037

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
					8			(843, 892, 985)
	S01.020	kallikrein 12	NM_019598 (v1) NM_145894 (v2) NM_145895 (v3)	53 55 57	NP_062544 NP_665901 NP_665902	54 56 58	1-17 /	22-248 (843, 892, 985)
	S01.021	DESC1 oritease	AF064819	59	AAF04328	60		191-422 (231, 276, 372)
	S01.028	tryptase gamma 1	NM_012467	61	NP_036599	62	1-19 /	38-272 (78, 125, 222)
	S01.029	kallikrein hK14	NM_022046	63	Q9P0G3	64	1-18 / 19-24	25-249 (67, 111, 204)
	S01.033	hyaluronan-binding serine protease (HGF activator-like protein)	NM_004132	65	NP_004123	66	1-23 /	314-557 (362, 411, 509)
	S01.034	transmembrane protease, serine 4	NM_019894 NM_183247	67 69	NP_063947 NP_899070	68 70		205-436 (245, 290, 387)
	S01.054	tryptase delta 1 (Homo sapiens)	NM_012217	71	Q9BZJ3	72	1-18 / 19-30	31-235 (74, 121, 224)
	S01.074	Marapsin	NM_031948	73	NP_114154	74	1-22 / 23-34	35-279 (75, 124, 229)
	S01.075	Tryptase homologue 2 (Homo sapiens)	BC036846	75	AAN04055	76		37-281 (77, 126, 231)
	S01.076	Tryptase homologue 3 (Homo sapiens)	Putative Only AC005570 (Cosmid 407D8)	77		78		67-304 (107, 213, 259)
	S01.079	transmembrane protease, serine 3	NM_024022 (vA) NM_032401 (vB) NM_032404 (vC) NM_032405 (vD)	79 81 83 85	NP_076927 NP_115777 NP_115780 NP_115781	80 82 84 86		217-451 (257, 304, 401)
	S01.081	kallikrein hK15 (Homo sapiens)	NM_023006 (v1) NM_138563 (v2) NM_138564 (v3) NM_017509 (v4)	87 89 91 93	NP_075382 NP_612630 NP_612631	88 90 92 94	1-16 / 17-21	22-256 (62, 106, 209)

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
					NP_059979			
	S01.085	Mername-AA031 peptidase (deduced from ESTs by MEROPS)	BC035384	95	AAH35384	96		1-241 (56, 101, 195)
	S01.087	membrane-type mosaic serine protease	AB048796	97	BAB39741	98		321-556 (361, 409, 506)
	S01.088	mername-AA038 peptidase	Putative Only AL136097 (RP11-62C3 clone)		CAC12709	99		10-142 (50,101)
	S01.098	mername-AA128 peptidase (deduced from ESTs by MEROPS)	Putative Only BC041609	100	AAH41609	101		33-202 (50,152)
	S01.127	cationic trypsin (Homo sapiens-type 1) (cationic)	NM_002769	102	NP_002760	103	1-15 / 16-23	24-246 (63, 107, 200)
	S01.131	Neutrophils elastase	NM_001972	104	NP_001963	105	1-27 / 28-29	30-249 (70, 117, 202)
	S01.132	mannan-binding lectin-associated serine protease-3	AF284421	106	AAK84071	107	1-19 /	449-710 (497, 553, 664)
	S01.133	cathepsin G	NM_001911	108	NP_001902	109	1-18 / 19-20	21-245 (64, 108, 201)
	S01.134	myeloblastin (proteinase 3)	NM_002777	110	NP_002768	111	1-25 / 26-27	28-250 (71, 118, 203)
	S01.135	granzyme A (CTLA3)	NM_006144	112	NP_006135	113	1-26 / 27-28	29-261 (69, 114, 212)
	S01.139	granzyme M	NM_005317	114	NP_005308	115	1-23 / 24-25	26-256 (66, 111, 207)
	S01.140	chymase (human-type)	NM_001836	116	NP_001827	117	1-19 / 21-21	22-247 (66, 110, 203)
	S01.143	tryptase alpha (1)	NM_003294	118	NP_003285	119	1-18 / 19-30	31-274 (74, 121, 224)
	S01.146	granzyme K	NM_002104	120	NP_002095	121	1-24 / 26-26	27-261 (67, 116, 214)
	S01.147	granzyme H (CTLA1)	NM_033423	122	NP_219491	123	1-18 / 19-20	21-246 (64, 108, 202)
	S01.152	chymotrypsin B	M24400	124	P17538	125	1-18	34-263 (75, 120, 213)

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
	S01.153	pancreatic elastase	NM_001971	126	NP_001962	127	1-8 / 9-18	19-256 (63, 111, 206)
	S01.154	pancreatic endopeptidase E (A)	NM_005747	128	NP_005738	129	1-15 / 16-28	29-270 (73, 123, 217)
	S01.155	pancreatic elastase II (IIA)	M16652	130	AAA52380	131	1-16 / 7-28	29-269 (73, 121, 216)
	S01.156	Enteropeptidase	NM_002772	132	NP_002763	133		785-1019 (825, 876, 971)
	S01.157	chymotrypsin C	NM_007272	134	NP_009203	135	1-16 / 17-29	30-268 (74, 121, 216)
	S01.159	Prostasin	NM_002773	136	NP_002764	137	1-29 / 30-32	45-288 (85, 134, 238)
	S01.160	kallikrein 1	NM_002257	138	NP_002248	139	1-18 / 19-24	25-261 (65, 120, 214)
	S01.161	kallikrein hK2 (Homo sapiens)	NM_005551 (v1) NM_001002231 (v2) NM_001002232 (v3)	140 142 144	NP_005542 NP_001002231 NP_001002232	141 143 145	1-18 / 19-24	25-260 (65, 120, 213)
	S01.162	kallikrein 3	NM_001648 (v1) NM_001030047 (v3) NM_001030048 (v4) NM_001030049 (v5) NM_001030050 (v6)	146 148 150 152 154	NP_001639 (v1) NP_001025218 (v3) NP_001025219 (v4) NP_001025220 (v5) NP_001025221 (v6)	147 149 151 153 155	1-17 / 18-24	25-260 (65, 120, 213)
	S01.174	Mesotrypsin	NM_002771	156	NP_002762	157	1-24 /	24-246 (63, 107, 200)
	S01.205	pancreatic endopeptidase E form B (B)	NM_007352	158	NP_031378	159	1-15 / 16-28	29-270 (73, 123, 217)
	S01.206	pancreatic elastase II form B (Homos sapiens) (IIB)	NM_015849	160	NP_056933	161	1-16 / 17-28	29-269 (73, 121, 216)
	S01.211	coagulation factor XIIa	NM_000505	162	NP_000496	163	1-19 /	373-615 (412, 461, 563)
	S01.212	plasma kallikrein (KLK3)	NM_000892	164	NP_000883	165	1-19 /	391-628 (434, 483, 578)
	S01.213	coagulation factor Xia (HAF)	NM_000128 (v1) NM_019559 (v2)	166 168	NP_000119 (v1) NP_062505 (v2)	167 169	1-18 /	388-625 (431, 480, 575)
	S01.214	coagulation	NM_000133	170	NP_00012	171	1-28 / 29-46	227-461

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
		factor IXa			4			(267, 315, 411)
	S01.215	coagulation factor VIIa	NM_000131 (v1) NM_019616 (v2)	172 174	NP_000122 (v1) NP_062562 (v2)	173 175	1-20 / 21-60	213-454 (253, 302, 404)
	S01.216	coagulation factor Xa	NM_000504	176	NP_000495	177	1-31 / 32-40	235-469 (276, 322, 419)
	S01.217	Thrombin	NM_000506	178	NP_000497	179	1-24 / 25-43	364-620 (406, 462, 568)
	S01.218	protein C (activated)	NM_000312	180	NP_000303	181	1-32 / 33-42	212-452 (253, 299, 402)
	S01.223	Acrosin	NM_001097	182	NP_001088	183	1-19	43-292 (88, 142, 240)
	S01.224	Hepsin	NM_182983 (v1) NM_002151 (v2)	184 186	NP_892028 NP_002142	185 187		163-407 (203, 257, 353)
	S01.228	hepatocyte growth factor activator (HGFA)	NM_001528	188	NP_001519	189	1-35 / 36-372	408-648 (447, 497, 598)
	S01.231	u-plasminogen activator (uPA)	NM_002658	190	NP_002649	191	1-20 /	179-426 (224, 275, 376)
	S01.232	t-plasminogen activator (tPA)	NM_000930 (v1) NM_000931 (v2) NM_033011 (v3)	192 194 196	NP_000921 (v1) NP_000922 (v2) NP_127509 (v3)	193 195 197	1-23 / 24-32 and 33-35	311-562 (357, 406, 513)
	S01.233	Plasmin	NM_000301	198	NP_000292	199	1-19 / 20-97	581-810 (622, 665, 760)
	S01.236	Neurosin	NM_002774 (vA) NM_001012964 (vB) NM_001012965 (vC) NM_001012966 (vD)	200 202 204 206	NP_002765 NP_001012982 NP_001012983 NP_001012984	201 203 205 207	1-16 / 17-21	22-244 (62, 106, 197)
	S01.237	Neurotrypsin	NM_003619	208	NP_003610	209	1-20 /	631-875 (676, 726, 825)
	S01.242	tryptase beta 2 (Homo sapiens) (l)	NM_024164	210	NP_077078	211	1-30 /	31-268
	S01.244	Neuropsin	NM_007196 (v1)	212	NP_009127	213	1-28 / 29-32	33-258 (73, 120,

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
			NM_144505 (v2) NM_144506 (v3) NM_144507 (v4)	214 216 218	(v1) NP_653088 (v2) NP_653089 (v3) NP_653090 (v4)	215 217 219		212)
	S01.246	kallikrein hK10 (Homo sapiens)	NM_002776 (v1) NM_145888 (v2)	220 222	NP_002767 NP_665895	221 223	1-30 /	35-276 (86, 137, 229)
	S01.247	Epitheliasin	NM_005656	224	NP_005647	225		256-491 (296, 345, 441)
	S01.251	Prostase	NM_004917	226	NP_004908	227	1-26 / 27-30	31-254 (71, 116, 207)
	S01.252	Brain serine proteinase 2	NM_022119	228	NP_071402	229	1-32	50-292 (90, 141, 242)
	S01.256	Chymopasin	NM_001907	230	NP_001898	231	1-18 / 19-33	34-264 (75, 121, 214)
	S01.257	kallikrein 11	NM_006853 (v1) NM_144947 (v2)	232 234	NP_006844 (v1) NP_659196 (v2)	233 235	1-50 /51-53	22-250 (62, 110, 203)
	S01.258	anionic trypsin (Homo sapiens) (II) (TRY2, TRY8, TRYP2)	NM_002770	236	NP_002761	237	1-15 / 16-23	24-246 (63, 107, 200)
	S01.291	LOC144757 peptidase (Homo sapiens)	Putative BC048112	238	AAH48112	239		78-319 (122, 171, 268)
	S01.292	Mername-AA169 peptidase	BN000133	240	CAD67985	241	1-19	175-406 (215, 260, 356)
	S01.294	Mername-AA171 peptidase	Putative No DNA			242		
	S01.298	Mername-AA174 peptidase (TRY6)	Putative no DNA seq		AAC80208	243		24-246 (63, 107, 200)
	S01.299	Mername-AA175 peptidase	NM_198464	244	NP_940866	245		68-302 (108, 156, 250)
	S01.300	stratum corneum chymotryptic enzyme (SCCE)	NM_005046 (v1) NM_139277 (v2)	246 248	NP_005037 NP_644806	247 249	1-22 / 23-29	30-250 (70, 112, 205)
	S01.301	trypsin-like enzyme, respiratory	NM_004262	250	NP_004253	251		187-471 (227, 272, 368)

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
		(Transmembrane protease, serine 11D)						
	S01.302	Matripase (MTSP1)	AF118224	252	AAD42765	253		615-855 (656, 711, 805)
	S01.306	kallikrein hK13	NM_015596	254	NP_056411	255	1-16 /	36-263 (76, 124, 218)
	S01.307	kallikrein hK9 (human numbering)	NM_012315	256	NP_036447	257	1-15 /	23-250 (63, 111, 204)
	S01.308	Mername-AA035 peptidase	NM_153609	258	NP_705837	259		49-283 (89, 140, 234)
	S01.309	umbilical vein proteinase	NM_007173	260	NP_009104	261	1-23 /	95-383 (175, 246, 316)
	S01.311	LCLP proteinase (LCLP (N-terminus))	Peptide fragment No DNA		P34168	262		1-26 (0)
	S01.313	Spinesin	NM_030770	263	NP_110397	264		218-455 (258, 308, 405)
	S01.318	Mername-AA178 peptidase	NM_183062	265	NP_898885	266	1-33 /	53-288 (93, 143, 238)
	S01.320	Mername-AA180 peptidase	BN000120	267	CAD66452	268	1-23 /	52-301 (92, 142, 240)
	S01.322	Mername-AA182 peptidase	BN000128	269	CAD67579	270	1-17 /	8-298 (87, 139, 237)
	S01.414	Mername-AA122 peptidase (deduced from ESTs by MEROPS)	Putative AK075142	271	BAC11431	272		1-177 (12, 64, 168)
Cysteine protease: Papain family	C01.032	Cathepsin L	X12451	273	P07711	274	1-17 / 18-113	113-333 (132, 138, 276, 300)
	C01.009	Cathepsin V	U13665	275	O60911	276	1-17 / 18-113	114-334 (132, 138, 277, 301)
	C01.036	Cathepsin K	S93414	277	P43235	278	1-15 / 16-114	115-329 (133, 139, 276, 296)
	C01.034	Cathepsin S	AJ007331	279	P25774	280	1-16 / 17-114	115-331 (133, 139, 278, 298)
	C01.018	Cathepsin F	M14221	281	Q9UBX1	282	1-19 / 20-270	271-484 (289, 295, 431, 451)
	C01.060	Cathepsin B	M15203	283	P07858	284	1-17 / 18-79	80-331 (102, 108, 278, 298)
	C01.001	Papain	M84342	285	P00784	286	1-18 / 19-133	135-342 (158, 292, 308)
	C01.075	Cruzain	Y14734	287	P25779	288	123-467 /	124-334

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
		(Cruzapain)						(147, 284, 304,
Serine Protease: subtilisin family	S08.001	Subtilisin Carlsberg precursor	X03341	290	P00780	289	1-29 / 30-105	*111-370* (137, 168, 325)
	S08.002	Subtilisin (Alkaline mesentericopeptidase)			P07518	291		*6-266* (32, 64, 221)
	S08.003	Subtilisin Savinase (Alkaline protease)			P29600	292		*6-260* (32, 62, 215)
	S08.007	Thermitase			P04072	293		*13-264* (38, 71, 225)
	S08.009	Thermophilic serine proteinase precursor (Ak.1 protease)	L29506	295	Q45670	294	1-24 / 25-121	*134-391* (160, 193, 347)
	S08.020	C5a peptidase precursor	J05229	297	P15926	296	1-31 /	*120-339, 458-560* (130, 193, 512)
	S08.021	fervidolysin	AY035311	299	AAK61552	298		*164-457*
	S08.035	Subtilisin J precursor	M64743	301	P29142	300	1-29 / 30-106	*112-372* (138, 170, 327)
	S08.036	Subtilisin E precursor	K01988	303	P04189	302	1-23 / 24-106	*112-372* (138, 170, 327)
	S08.037	Subtilisin DY			P00781	304		*6-257* (32, 63, 220)
	S08.054	Proteinase K precursor (Endopeptidase K)	X14689	306	P06873	305	1-15 / 16-105	*134-373* (144, 174, 329)
	S08.050	Alkaline serine exoprotease A precursor	M25499	308	P16588	307	1-21 / 22-141	*155-412* (180, 213, 363)
	S08.060	Epidermin leader peptide-processing serine protease epiP precursor	X62386	310	P30199	309	1-23 / 24 -?	*123-451* (149, 194, 402)
	S08.063	Membrane-bound transcription factor site 1 protease precursor (Site-1 protease, Subtilisin/kexin-isozyme 1, SKI-1)	AF078105	312	Q9Z2A8	311	1-14 / 18-186	179-473 (218, 249, 338, 414)
	S08.066	Alkaline proteinase precursor (ALP)	M87516	314	Q03420	313	1-20 / 21-120	121-409 (161, 192, 353)

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
	S08.094	Extracellular serine protease precursor	M13469	316	P09489	315	1-27 /	*50-389* (76, 112, 341)
	S08.090	Tripeptidyl-peptidase II (TPP-II)	AF035251	318	Q9V6K1	317		5-509 (131, 359, 549)
	S08.114	Minor extracellular protease vpr precursor	M76590	320	P29141	319	1-28 / 29-160	*163-365, 487-586* (189, 233, 534)
	S08.116	PIII-type proteinase precursor (Lactocepin)	J04962	322	P15292	321	1-33 / 34-187	*190-379, 584-628* (217, 281, 620)
	S08.048	Furin-like protease 1, isoform 1-CRR precursor	M81431	324	P30430	323	1-? /?-309	*376-646* (372, 413, 587)
	S08.070	Kexin precursor (KEX2 protease) (Kex2-like endoprotease 1, dKLIP-1)	M22870	326	P13134	325	1-19 /20-109 and 110-113	*149-445* (175, 213, 385)
	S08.071	Furin precursor (PACE)	X17094	328	P09958	327	1-24 / 25-107	131-421 (153, 194, 295, 368)
	S08.075	Subtilisin/kexin -like protease PACE4 (Proprotein convertase subtilisin/kexin type 6 precursor)	M80482	330	P29122	329	1-63 / 64-149	182-473 (205, 246, 347, 420)
	S08.079	Calcium-dependent protease precursor (Trypsin)	X56955	332	P23916	331		*254-521* (233, 270, 466)
Cysteine protease: caspase family	C14.001	Caspase-1 precursor (Interleukin-1 beta convertase, IL-1BC)	U14647	334	P43527	333	/ 1-118	120-404 (236, 284)
	C14.002	Cell death protein 3 precursor	L29052	336	P42573	335		235 – 495 (315, 358)
	C14.003	Caspase-3 precursor (Apopain, Cysteine protease)	U13737	338	P42574	337	/ 1-9	10-277 (121, 163)
	C14.004	Caspase-7 precursor (ICE-like apoptotic protease 3, Apoptotic protease Mch-3)	U39613	340	P55210	339	/ 1-23	29-303 (144, 186)
	C14.005	Caspase-6 precursor	U20536	342	P55212	341	/ 1-23	24-292 (121, 163)

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
		(Apoptotic protease Mch-2)						
	C14.006	Caspase-2 precursor (ICH-1 protease, NEDD2 protein)	D28492	344	P29594	343	/ 1-169	170-432 (277, 320)
	C14.007	Caspase-4 precursor (ICH-2 protease, TX protease)	Z48810	346	P49662	345	/ 1-80	93-377 (210, 258)
	C14.008	Caspase-5 precursor (ICH-3 protease, TY protease, ICE(rel)-III)	U28015	348	P51878	347	/ 1-120	134-418 (251, 299)
	C14.009	Caspase-8 precursor (FADD-like ICE, ICE-like apoptotic protease 5)	X98172	350	Q14790	349	/ 1-216	193-479 (317, 360)
	C14.010	Caspase-9 precursor (ICE-LAP6, Apoptotic protease Mch-6	U56390	352	P55211	351		117-416 (237, 287)
	C14.011	Caspase-10 precursor	U60519	354	Q92851	353	/ 1-219	243-514 (358, 401)
	C14.012	Caspase-11 (Caspase-4 precursor)	U59463	356	P70343	355	/ 1-80	89-373 (206, 254)
	C14.013	Caspase-12 precursor	Y13090	358	O08736	357		133-419 (250, 298)
	C14.015	Caspase precursor (insect) (drICE)	Y12261	360	O01382	359	/ 1-28	(169, 211)
	C14.016	Caspase-1 precursor (insect)	AF001464	362	O02002	361	/ 1-33	(154, 196)
	C14.017	Caspase-13 precursor	AF078533	364	O75601	363		(210, 258)
	C14.018	Caspase-14 precursor	AF097874	366	P31944	365		1-242 (89, 132)
	C14.019	Caspase Nc precursor (NEDD2-like caspase DRONC)	AF104357	368	Q9XYF4	367	/1-134	(271, 318)
	C14.026	MALT lymphoma translocation protein 1 paracaspase (paracaspase)	AF130356	370	Q9UDY8	369		337-523 (415, 464)
	C14.971	CASP8 and FADD-like apoptosis	U85059	372	O15519	371		260-433 (315, 363)

Protease Type	Merops Code	Name	Nt. ACC. NO:	Nt. SEQ ID NO:	A.A. ACC. NO:	A.A. SEQ ID NO:	Signal/ propeptide sequence	Peptidase unit (active site residues)
		regulator precursor (c-FLIP)						

a. Classes of Proteases

Proteases (also referred to as proteinases or peptidases) are protein-degrading enzymes that recognize sequences of amino acids or a polypeptide substrate within a target protein. Upon recognition of the substrate sequence of amino acids, proteases catalyze the hydrolysis or cleavage of a peptide bond within a target protein. Such hydrolysis of a target protein, depending on the location of the peptide bond within the context of the full-length sequence of the target sequence, can inactivate, or in some instances activate, a target.

Proteases are classified based on the way they attack the protein, either exo- or endo- proteases. Proteinases or endopeptidases attack inside the protein to produce large peptides. Peptidases or exopeptidases attack ends or fragments of protein to produce small peptides and amino acids. The peptidases are classified on their action pattern: aminopeptidase cleaves amino acids from the amino end: carboxypeptidase cleaves amino acids from the carboxyl end, dipeptidyl peptidase cleaves two amino acids; dipeptidase splits a dipeptide, and tripeptidase cleaves an amino acid from a tripeptide. Most proteases are small from 21,000 to 45,000 Daltons. Many proteases are synthesized and secreted as inactive forms called zymogens and subsequently activated by proteolysis. This changes the architecture of the active site of the enzyme.

Several distinct types of catalytic mechanisms are used by proteases (Barret et al. (1994) *Meth. Enzymol.* 244:18-61; Barret et al. (1994) *Meth. Enzymol* 244:461-486; Barret et al. (1994) *Meth. Enzymol.* 248:105-120; Barret et al. (1994) *Meth. Enzymol.* 248:183-228). Based on their catalytic mechanism, the carboxypeptidases are subdivided into serine-, metallo and cysteine- type carboxypeptidases and the endopeptidases are the serine-, cysteine-, aspartic-, threonine- and

metalloendopeptidases. Serine peptidases have a serine residue involved in the active center, the aspartic have two aspartic acids in the catalytic center, cysteine -type peptidases have a cysteine residue, threonine-type peptidases have a threonine residue, and metallo-peptidases use a metal ion in the catalytic mechanism. Generally, proteases can be divided into classes based on their catalytic activity such that classes of proteases can include serine, cysteine, aspartic, threonine, or metallo-proteases. The catalytic activity of the proteases is required to cleave a target substrate. Hence, modification of a protease to alter the catalytic activity of a protease can affect (*i.e.* modify specificity/ selectivity) the ability of a protease to cleave a particular substrate.

Each protease has a series of amino acids that lines the active site pocket and makes direct contact with the substrate. Crystallographic structures of peptidases show that the active site is commonly located in a groove on the surface of the molecule between adjacent structural domains, and the substrate specificity is dictated by the properties of binding sites arranged along the groove on one or both sides of the catalytic site that is responsible for hydrolysis of the scissile bond. Accordingly, the specificity of a peptidase is described by the ability of each subsite to accommodate a sidechain of a single amino acid residue. The sites are numbered from the catalytic site, S1, S2...Sn towards the N-terminus of the substrate, and S1', S2'...Sn' towards the C-terminus. The residues they accommodate are numbered P1, P2...Pn, and P1', P2'...Pn', respectively. The cleavage of a target protein is catalyzed between P1 and P1' where the amino acid residues from the N to C terminus of the polypeptide substrate are labeled (Pi, ..., P3, P2, P1, P1', P2', P3', ..., Pj) and their corresponding binding recognition pockets on the protease are labeled (Si,..., S3, S2, S1, S1', S2', S3',..., Sj) (Schecter and Berger (1967) *Biochem Biophys Res Commun* 27:157-162). Thus, P2 interacts with S2, P1 with S1, P1' with S1', *etc.* Consequently, the substrate specificity of a protease comes from the S1-S4 positions in the active site, where the protease is in contact with the P1-P4 residues of the peptide substrate sequences. In some cases, there is little (if any) interactions between the S1-S4 pockets of the active site, such that each pocket appears to recognize and bind the corresponding residue on the peptide substrate sequence independent of the other pockets. Thus, the specificity determinants can be changed in one pocket without affecting the specificity of the other pocket. Based upon numerous structures

and modeling of family members, surface residues that contribute to extended substrate specificity and other secondary interactions with a substrate have been defined for many proteases including proteases of the serine, cysteine, aspartic, metallo-, and threonine families (see *e.g.* Wang et al., (2001) Biochemistry 40(34): 10038-46; Hopfner et al., (1999) Structure Fold Des. 7(8):989-96; Friedrich et al. (2002) J Biol Chem. 277(3):2160-8; Waugh et al., (2000) Nat Struct Biol. 7(9):762-5; Cameron *et al.*, (1993) *J Biol Chem.* 268:11711; Cameron *et al.*, (1994) *J Biol Chem.* 269: 11170).

i. Serine Proteases

Serine proteases (SPs), which include secreted enzymes and enzymes sequestered in cytoplasmic storage organelles, have a variety of physiological roles, including in blood coagulation, wound healing, digestion, immune responses and tumor invasion and metastasis. For example, chymotrypsin, trypsin, and elastase function in the digestive tract; Factor 10, Factor 11, Thrombin, and Plasmin are involved in clotting and wound healing; and C1r, C1s, and the C3 convertases play a role in complement activation.

A class of cell surface proteins designated type II transmembrane serine proteases are proteases which are membrane-anchored proteins with extracellular domains. As cell surface proteins, they play a role in intracellular signal transduction and in mediating cell surface proteolytic events. Other serine proteases are membrane bound and function in a similar manner. Others are secreted. Many serine proteases exert their activity upon binding to cell surface receptors, and, hence act at cell surfaces. Cell surface proteolysis is a mechanism for the generation of biologically active proteins that mediate a variety of cellular functions.

Serine proteases, including secreted and transmembrane serine proteases, are involved in processes that include neoplastic development and progression. While the precise role of these proteases has not been fully elaborated, serine proteases and inhibitors thereof are involved in the control of many intra- and extracellular physiological processes, including degradative actions in cancer cell invasion and metastatic spread, and neovascularization of tumors that are involved in tumor progression. Proteases are involved in the degradation and remodeling of extracellular matrix (ECM) and contribute to tissue remodeling, and are necessary for

cancer invasion and metastasis. The activity and/or expression of some proteases have been shown to correlate with tumor progression and development.

Over 20 families (denoted S1-S27) of serine protease have been identified, these being grouped into 6 clans (SA, SB, SC, SE, SF and SG) on the basis of structural similarity and other functional evidence (Rawlings ND et al. (1994) *Meth. Enzymol.* 244: 19-61). There are similarities in the reaction mechanisms of several serine peptidases. Chymotrypsin, subtilisin and carboxypeptidase C clans have a catalytic triad of serine, aspartate and histidine in common: serine acts as a nucleophile, aspartate as an electrophile, and histidine as a base. The geometric orientations of the catalytic residues are similar between families, despite different protein folds. The linear arrangements of the catalytic residues commonly reflect clan relationships. For example the catalytic triad in the chymotrypsin clan (SA) is ordered HDS, but is ordered DHS in the subtilisin clan (SB) and SDH in the carboxypeptidase clan (SC).

Examples of serine proteases of the chymotrypsin superfamily include tissue-type plasminogen activator (tPA), trypsin, trypsin-like protease, chymotrypsin, plasmin, elastase, urokinase (or urinary-type plasminogen activator, u-PA), acrosin, activated protein C, C1 esterase, cathepsin G, chymase, and proteases of the blood coagulation cascade including kallikrein, thrombin, and Factors VIIa, IXa, Xa, XIa, and XIIa (Barret, A.J., In: *Proteinase Inhibitors*, Ed. Barrett, A.J., Et al., Elsevier, Amsterdam, Pages 3-22 (1986); Strassburger, W. *et al.*, (1983) *FEBS Lett.*, 157 :219-223; Dayhoff, M.O., Atlas of Protein Sequence and Structure, Vol 5, National Biomedical Research Foundation, Silver Spring, Md. (1972); and Rosenberg, R.D. *et al.* (1986) *Hosp. Prac.*, 21: 131-137).

The activity of proteases in the serine protease family is dependent on a set of amino acid residues that form their active site. One of the residues is always a serine; hence their designation as serine proteases. For example, chymotrypsin, trypsin, and elastase share a similar structure and their active serine residue is at the same position (Ser-195) in all three. Despite their similarities, they have different substrate specificities; they cleave different peptide bonds during protein digestion. For example, chymotrypsin prefers an aromatic side chain on the residue whose carbonyl carbon is part of the peptide bond to be cleaved. Trypsin prefers a positively charged Lys or Arg residue at this position. Serine proteases differ markedly in their substrate

recognition properties: some are highly specific (*i.e.* the proteases involved in blood coagulation and the immune complement system); some are only partially specific (*i.e.* the mammalian digestive proteases trypsin and chymotrypsin); and others, like subtilisin, a bacterial protease, are completely non-specific. Despite these differences in specificity, the catalytic mechanism of serine proteases is well conserved.

The mechanism of cleavage of a target protein by a serine protease is based on nucleophilic attack of the targeted peptidic bond by a serine. Cysteine, threonine or water molecules associated with aspartate or metals also can play this role. In many cases the nucleophilic property of the group is improved by the presence of a histidine, held in a "proton acceptor state" by an aspartate. Aligned side chains of serine, histidine and aspartate build the catalytic triad common to most serine proteases. For example, the active site residues of chymotrypsin, and serine proteases that are members of the same family as chymotrypsin, such as for example MTSP-1, are Asp102, His57, and Ser195.

The catalytic domains of all serine proteases of the chymotrypsin superfamily have both sequence homology and structural homology. The sequence homology includes the conservation of: 1) the characteristic active site residues (e.g., Ser195, His57, and Asp102 in the case of trypsin); 2) the oxyanion hole (e.g., Gly193, Asp194 in the case of trypsin); and 3) the cysteine residues that form disulfide bridges in the structure (Hartley, B.S., (1974) *Symp. Soc. Gen. Microbiol.*, 24: 152-182). The structural homology includes 1) a common fold characterized by two Greek key structures (Richardson, J. (1981) Adv. Prot. Chem., 34:167-339); 2) a common disposition of catalytic residues; and 3) detailed preservation of the structure within the core of the molecule (Stroud, R.M. (1974) Sci. Am., 231: 24-88).

Throughout the chymotrypsin family of serine proteases, the backbone interaction between the substrate and enzyme is completely conserved, but the side chain interactions vary considerably. The identity of the amino acids that contain the S1-S4 pockets of the active site determines the substrate specificity of that particular pocket. Grafting the amino acids of one serine protease to another of the same fold modifies the specificity of one to the other. Typically, the amino acids of the protease that contain the S1-S4 pockets are those that have side chains within 4 to 5 angstroms of the substrate. The interactions these amino acids have with the protease substrate are generally called "first shell" interactions because they directly contact the

substrate. There, however, can be "second shell" and "third shell" interactions that ultimately position the first shell amino acids. First shell and second shell substrate binding effects are determined primarily by loops between beta-barrel domains. Because these loops are not core elements of the protein, the integrity of the fold is maintained while loop variants with novel substrate specificities can be selected during the course of evolution to fulfill necessary metabolic or regulatory niches at the molecular level. Typically for serine proteases, the following amino acids in the primary sequence are determinants of specificity: 195, 102, 57 (the catalytic triad); 189, 190, 191, 192, and 226 (S1); 57, the loop between 58 and 64, and 99 (S2); 192, 217, 218 (S3); the loop between Cys168 and Cys180, 215, and 97 to 100 (S4); and 41 and 151 (S2'), based on chymotrypsin numbering, where an amino acid in an S1 position affects P1 specificity, an amino acid in an S2 position affects P2 specificity, an amino acid in the S3 position affects P3 specificity, and an amino acid in the S4 position affects P4 specificity. Position 189 in a serine protease is a residue buried at the bottom of the pocket that determines the S1 specificity. Structural determinants for various serine proteases are listed in Table 8 with numbering based on the numbering of mature chymotrypsin, with protease domains for each of the designated proteases aligned with that of the protease domain of chymotrypsin. The number underneath the Cys168-Cys182 and 60's loop column headings indicate the number of amino acids in the loop between the two amino acids and in the loop. The yes/no designation under the Cys191-Cys220 column headings indicates whether the disulfide bridge is present in the protease. These regions are variable within the family of chymotrypsin-like serine proteases and represent structural determinants in themselves. Modification of a protease to alter any one or more of the amino acids in the S1-S4 pocket affect the specificity or selectivity of a protease for a target substrate.

Table 8: The structural determinants for various serine proteases

Residues that Determine Specificity														
	S4					S3		S2			S1			
	171	174	180	215	Cys168 Cys182	192	218	99	57	60's loop	189	190	226	Cys191 Cys220
Granzyme B	Leu	Tyr	Glu	Tyr	14	Arg	Asn	Ile	His	6	Gly	Ser	Arg	No
Granzyme A	Asn	Val	Met	Phe	17	Asn	Leu	Arg	His	7	Asp	Ser	Gly	Yes

Granzyme M	Arg	Ser	Met	Phe	15	Lys	Arg	Leu	His	8	Ala	Pro	Pro	Yes
Cathepsin G	Phe	Ser	Gln	Tyr	13	Lys	Ser	Ile	His	6	Ala	Ala	Glu	No
MT-SP1	Leu	Gln	Met	Trp	13	Gln	Asp	Phe	His	16	Asp	Ser	Gly	Yes
Neutrophil elastase	-	-	-	Tyr	5	Phe	Gly	Leu	His	10	Gly	Val	Asp	Yes
Chymase	Phe	Arg	Gln	Tyr	12	Lys	Ser	Phe	His	6	Ser	Ala	Ala	No
Alpha-tryptase	Tyr	Ile	Met	Trp	22	Lys	Glu	Ile	His	9	Asp	Ser	Gly	Yes
Beta-tryptase(I)	Tyr	Ile	Met	Trp	22	Gln	Glu	Val	His	9	Asp	Ser	Gly	Yes
Beta-tryptase (II)	Tyr	Ile	Met	Trp	22	Lys	Glu	Thr	His	9	Asp	Ser	Gly	Yes
Chymo-trypsin	Trp	Arg	Met	Trp	13	Met	Ser	Val	His	7	Ser	Ser	Gly	Yes
Easter	Tyr	Ser	Gln	Phe	16	Arg	Thr	Gln	His	14	Asp	Ser	Gly	Yes
Collage-nase	Tyr	Ile	-	Phe	12	Asn	Ala	Ile	His	8	Gly	Thr	Asp	Yes
Factor Xa	Ser	Phe	Met	Trp	13	Gln	Glu	Tyr	His	8	Asp	Ala	Gly	Yes
Protein C	Met	asn	Met	Trp	13	Glu	Glu	Thr	His	8	Asp	Ala	Gly	Yes
Plasma kallikrein	Tyr	Gln	Met	Tyr	13	Arg	Pro	Phe	His	11	Asp	Ala	Ala	Yes
Plasmin	Glu	Arg	Glu	Trp	15	Gln	Leu	Thr	His	11	Asp	Ser	Gly	Yes
Trypsin	Tyr	Lys	Met	Trp	13	Gln	Tyr	Leu	His	6	Asp	Ser	Gly	Yes
Thrombin	Thr	Ile	Met	Trp	13	Glu	Glu	Leu	His	16	Asp	Ala	Gly	Yes
tPA	Leu	Thr	Met	Trp	15	Gln	Leu	Tyr	His	11	Asp	Ala	Gly	Yes
uPA	His	Ser	Met	Trp	15	Gln	Arg	His	His	11	Asp	Ser	Gly	yes

(a) Urokinase-type Plasminogen Activator (u-PA)

Urokinase-type plasminogen activator (u-PA, also called urinary plasminogen activator) is an exemplary protease used as a candidate for selection in the methods herein. u-PA is set forth in SEQ ID NO:190 and encodes a precursor amino acid sequence set forth in SEQ ID NO:191. u-PA is found in urine, blood, seminal fluids, and in many cancer tissues. It is involved in a variety of biological process, which are linked to its conversion of plasminogen to plasmin, which itself is a serine protease. Plasmin has roles in a variety of normal and pathological processes including, for example, cell migration and tissue destruction through its cleavage of a variety of molecules including fibrin, fibronectin, proteoglycans, and laminin. u-PA is involved in tissue remodeling during wound healing, inflammatory cell migration, neovascularization and tumor cell invasion. u-PA also cleaves and activates other substrates, including, but not limited to, hepatocyte growth factor/scatter factor (HGF/SF), the latent form of membrane type 1 matrix metalloprotease (MT-SP1), and others.

The mature form of u-PA is a 411 residue protein (corresponding to amino acid residues 21 to 431 in the sequence of amino acids set forth in SEQ ID NO:191, which is the precursor form containing a 20 amino acid signal peptide). u-PA contains three domains: the serine protease domain, the kringle domain and the growth factor domain. In the mature form of human u-PA, amino acids 1-158 represent the N-terminal A chain including a growth factor domain (amino acids 1-49), a kringle domain (amino acids 50-131), and an interdomain linker region (amino acids 132-158). Amino acids 159-411 represent the C-terminal serine protease domain or B chain. u-PA is synthesized and secreted as a single-chain zymogen molecule, which is converted into an active two-chain u-PA by a variety of proteases including, for example, plasmin, kallikrein, cathepsin B, and nerve growth factor-gamma. Cleavage into the two chain form occurs between residues 158 and 159 in a mature u-PA sequence (corresponding to amino acid residues 178 and 179 in SEQ ID NO:191). The two resulting chains are kept together by a disulfide bond, thereby forming the two-chain form of u-PA.

u-PA is regulated by the binding to a high affinity cell surface receptor, uPAR. Binding of u-PA to uPAR increases the rate of plasminogen activation and enhances extracellular matrix degradation and cell invasion. The binary complex formed between uPAR and u-PA interact with membrane-associated plasminogen to form higher order activation complexes that reduce the Km (*i.e.* kinetic rate constant of the approximate affinity for a substrate) for plasminogen activation (Bass *et al.* (2002) *Biochem. Soc, Trans.*, 30: 189-194). In addition, binding of u-PA to uPAR protects the protease from inhibition by the cognate inhibitor, *i.e.* PAI-1. This is because single chain u-PA normally present in plasma is not susceptible to inhibition by PAI-1, and any active u-PA in the plasma will be inhibited by PAI-1. Active u-PA that is receptor bound is fully available for inhibition by PAI-1, however, PAI-1 is unable to access the bound active molecule (Bass *et al.* (2002) *Biochem. Soc, Trans.*, 30: 189-194). As a result, u-PA primarily functions on the cell surface and its functions are correlated with the activation of plasmin-dependent pericellular proteolysis.

The extended substrate specificity of u-PA and t-PA (discussed below) are similar, owing to the fact that both are responsible for cleaving plasminogen into active plasmin. Both u-PA and t-PA have high specificity for cleavage after P1 Arg, and they similarly show a preference for small amino acids at the P2 position. Both

of the P3 and P4 positions are specificity determinants for substrates of u-PA and t-PA, with a particularly prominent role of the P3 position (Ke *et al.* (1997) J. Biol. Chem., 272: 16603-16609). The preference for amino acids at the P3 position are distinct, and is the main determinant for altered substrate discrimination between the two proteases. t-PA has a preference for aromatic amino acids (Phe and Tyr) at the P3 position, while u-PA has a preference for small polar amino acids (Thr and Ser) (see e.g., Ke *et al.* (1997) J. Biol. Chem., 272: 16603-16609; Harris *et al.* (2000) *PNAS*, 97: 7754-7759).

(b) Tissue Plasminogen Activator (t-PA)

A candidate protease for selection against a protease trap in the methods herein also includes the exemplary serine protease tissue plasminogen activator (t-PA), and variants thereof. t-PA is a serine protease that converts plasminogen to plasmin, which is involved in fibrinolysis or the formation of blood clots. Recombinant t-PA is used as a therapeutic in diseases characterized by blood clots, such as for example, stroke. Alternative splicing of the t-PA gene produces three transcripts. The predominant transcript is set forth in SEQ ID NO:192 and encodes a precursor protein set forth in SEQ ID NO:193 containing a 20-23 amino acid signal sequence and a 12-15 amino acid pro-sequence. The other transcripts are set forth in SEQ ID NO:194 and 196, encoding precursor proteins having a sequence of amino acids set forth in SEQ ID NOS: 195 and 197, respectively. The mature sequence of t-PA, lacking the signal sequence and propeptide sequence is 527 amino acids.

t-PA is secreted by the endothelium of blood vessels and circulates in the blood as a single-chain form. Unlike many other serine proteases, the single-chain or "proenzyme" form of t-PA has high catalytic efficiency. The activity of t-PA is increased in the presence of fibrin. In the absence of fibrin, single-chain t-PA is about 8% as active as compared to two-chain t-PA, however in the presence of fibrin the single- and two-chain forms of t-PA display similar activity. (Strandberg *et al.* (1995) *J. Biol. Chem.*, 270: 23444-23449). Thus, activation of single-chain t-PA can be accomplished either by activation cleavage (*i.e.* zymogen cleavage), resulting in a two-chain form, or by binding to the co-factor fibrin. Activation cleavage occurs following cleavage by plasmin, tissue kallikrein, and activated Factor X at amino acid positions Arg^{275}-Ile^{276} (corresponding to Arg^{310}-Ile^{311} in the sequence of amino acids set forth in SEQ ID NO:193) resulting in the generation of the active two-chain form

of t-PA. The two-chain polypeptide contains an A and a B chain that are connected by an interchain disulfide bond.

The mature t-PA contains 16 disulfide bridges and is organized into five distinct domains (Gething *et al.* (1988), *The EMBO J.*, 7: 2731-2740). Residues 4-50 of the mature protein form a finger domain, residues 51-87 form an EGF-like domain, residues 88-175 and 176-263 form two kringle domains that contain three intradomain disulfide bonds each, and residues 277-527 of the mature molecule (corresponding to amino acid residues 311-562 of the precursor sequence set forth in SEQ ID NO:193) make up the serine protease domain.

In contrast to u-PA, which acts as a cellular receptor-bound activator, t-PA functions as a fibrin-dependent circulatory activation enzyme. Likewise, both single- and two-chain forms of t-PA are susceptible to inhibition by their cognate inhibitors, for example, PAI-1, although two-chain t-PA is inhibited by PAI-1 approximately 1.4 times more rapidly than single-chain t-PA (Tachias *et al.* (1997) *J Biol. Chem.*, 272: 14580-5). t-PA can become protected from inhibition by binding to its cellular binding site Annexin-II on endothelial cells. Thus, although both t-PA and u-PA both cleave and activate plasminogen, the action of t-PA in the blood supports t-PA as the primary fibrinolytic activator of plasminogen, while u-PA is the primary cellular activator of plasminogen.

(c) MT-SP1

Membrane-type serine protease MT-SP1 (also called matriptase, TADG-15, suppressor of tumorigenicity 14, ST14) is an exemplary protease for selection in the methods provided herein to select for variants with an altered substrate specificity against a desired or predetermined substrate cleavage sequence. The sequence of MT-SP1 is set forth in SEQ ID NO:252 and encodes an 855 amino acid polypeptide having a sequence of amino acids set forth in SEQ ID NO:253. It is a multidomain proteinase with a C-terminal serine proteinase domain (Friedrich *et al.* (2002) *J Biol Chem* 277(3):2160). A 683 amino acid variant of the protease has been isolated, but this protein appears to be a truncated form or an ectodomain form.

MT-SP1 is highly expressed or active in prostate, breast, and colorectal cancers and it can play a role in the metastasis of breast and prostate cancer. MT-SP1 also is expressed in a variety of epithelial tissues with high levels of activity and/or expression in the human gastrointestinal tract and the prostate. Other species of MT-

SP1 are known. For example, a mouse homolog of MT-SP1 has been identified and is called epithin.

MT-SP1 contains a transmembrane domain, two CUB domains, four LDLR repeats, and a serine protease domain (or peptidase S1 domain; also called the B-chain) between amino acids 615-854 (or 615-855 depending on variations in the literature) in the sequence set forth in SEQ ID NO:253. The amino acid sequence of the protease domain is set forth in SEQ ID NO:505 and encoded by a sequence of nucleic acids set forth in SEQ ID NO:504. MT-SP1 is synthesized as a zymogen, and activated to double chain form by cleavage. In addition, the single chain proteolytic domain alone is catalytically active and functional.

An MT-SP1 variant, termed CB469, having a mutation of C122S corresponding to the wild-type sequence of MT-SP1 set forth in either SEQ ID NO: 253 or 505, based on chymotrypisn numbering, exhibits improved display on phagemid vectors. Such a variant MT-SP1 is set forth in SEQ ID NO:515 (full length MT-SP1) or SEQ ID NO:507 (protease domain) and can be used in the methods described herein below.

MT-SP1 belongs to the peptidase S1 family of serine proteases (also referred to as the chymotrypsin family), which also includes chymotrypsin and trypsin. Generally, chymotrypsin family members share sequence and structural homology with chymotrypsin. MT-SP1 is numbered herein according to the numbering of mature chymotrypsin, with its protease domain aligned with that of the protease domain of chymotrypsin and its residues numbered accordingly. Based on chymotrypsin numbering, active site residues are Asp102, His57, and Ser195 (corresponding to Asp711, His656, and Ser805 in SEQ ID NO:253). The linear amino acid sequence can be aligned with that of chymotrypsin and numbered according to the β sheets of chymotrypsin. Insertions and deletions occur in the loops between the beta sheets, but throughout the structural family, the core sheets are conserved. The serine protease interacts with a substrate in a conserved beta sheet manner. Up to 6 conserved hydrogen bonds can occur between the substrate and enzyme. All serine proteases of the chymotrypsin family have a conserved region at their N-terminus of the protease domain that is necessary for catalytic activity (*i.e.* IIGG, VVGG, or IVGG, where the first amino acid in this quartet is numbered

according to the chymotrypsin numbering and given the designation Ile16. This numbering does not reflect the length of the precursor sequence).

The substrate specificity of MT-SP1 in the protease domain has been mapped using a positional scanning synthetic combinatorial library and substrate phage display (Takeuchi *et al.* (2000) *J Biol Chem* 275: 26333). Cleavage residues in substrates recognized by MT-SP1 contain Arg/Lys at P4 and basic residues or Gln at P3, small residues at P2, Arg or Lys at P1, and Ala at P1'. Effective substrates contain Lys-Arg-Ser-Arg in the P4 to P1 sites, respectively. Generally, the substrate specificity for MT-SP1 reveals a trend whereby if P3 is basic, then P4 tends to be non-basic; and if P4 is basic, then P3 tends to be non-basic. Known substrates for MT-SP1, including, for example, proteinase-activated receptor-2 (PAR-2), single-chain uPA (sc-uPA), the proform of MT-SP1, and hepatocyte growth factor (HGF), conform to the cleavage sequence for MT-SP1 specific substrates.

MT-SP1 can cleave selected synthetic substrates as efficiently as trypsin, but exhibit a more restricted specificity for substrates than trypsin. The catalytic domain of MT-SP1 has the overall structural fold of a (chymo)trypsin-like serine protease, but displays unique properties such as a hydrophobic/acidic S2/S4 sub-sites and an exposed 60 loop. Similarly, MT-SP1 does not indiscriminately cleave peptide substrates at accessible Lys or Arg residues, but requires recognition of additional residues surrounding the scissile peptide bond. This requirement for an extended primary sequence highlights the specificity of MT-SP1 for its substrates. For example, although MT-SP1 cleaves proteinase activated receptor-2 (PAR-2) (displaying a P4 to P1 target sequence of Ser-Lys-Gly-Arg), the enzyme does not activate proteins closely related to this substrate such as PAR-1, PAR-3, and PAR-4 that do not display target sequences matching the extended MT-SP1 specificity near the scissile bond (see Friedrich *et al.* (2002) *J Biol Chem* 277: 2160).

The protease domain of MT-SP1 is composed of a pro-region and a catalytic domain. The catalytically active portion of the polypeptide begins after the autoactivation site at amino acid residue 611 of the mature protein (see, *e.g.*, SEQ ID NO: 253 at RQAR followed by the residues VVGG). The S1 pocket of MT-SP1 and trypsin are similar with good complementarity for Lys as well as Arg P1 residues, thereby accounting for some similarities in substrate cleavage with trypsin. The accommodation of the P1-Lys residues is mediated by Ser^{190} whose side chain

provides an additional hydrogen bond acceptor to stabilize the buried α-ammonium group (see Friedrich *et al.* (2002) *J Biol Chem* 277: 2160). The S2 pocket is shaped to accommodate small to medium-sized hydrophobic side chains of P2 amino acids and generally accepts a broad range of amino acids at the P2 position. Upon substrate binding, the S2 sub-site is not rigid as evidenced by the rotation of the Phe^{99} benzyl group. The substrate amino acids at positions P3 (for either Gln or basic residues) and P4 (for Arg or Lys residues) appears to be mediated by electrostatic interactions in the S3 and S4 pockets with the acidic side chains of Asp-217 and/or Asp-96 which could favorably pre-orient specific basic peptide substrates as they approach the enzyme active site cleft. The side chain of a P3 residue also is able to hydrogen bond the carboxamide group of Gln^{192} or alternatively, the P3 side chain can extend into the S4 sub-site to form a hydrogen bond with Phe^{97} thereby weakening the inter-main chain hydrogen bonds with Gly^{216}. In either conformation, a basic P3 side chain is able to interact favorably with the negative potential of the MT-SP1 S4 pocket. The mutual charge compensation and exclusion from the same S4 site explains the low probability of the simultaneous occurrence of Arg/Lys residues at P3 and P4 in good MT-SP1 substrates. Generally, the amino acid positions of MT-SP1 (based on chymotrypsin numbering) that contribute to extended specificity for substrate binding include: 146 and 151 (S1'); 189, 190, 191, 192, 216, 226 (S1); 57, 58, 59, 60, 61, 62, 63, 64, 99 (S2); 192, 217, 218, 146 (S3); 96, 97, 98, 99, 100, 168, 169, 170, 170A, 171, 172, 173, 174, 175, 176, 178, 179, 180, 215, 217, 224 (S4).

ii. Cysteine Proteases

Cysteine proteases have a catalytic mechanism that involves a cysteine sulfhydryl group. Deprotonation of the cysteine sulfhydryl by an adjacent histidine residue is followed by nucleophilic attack of the cysteine on the peptide carbonyl carbon. A thioester linking the new carboxy-terminus to the cysteine thiol is an intermediate of the reaction (comparable to the acyl-enzyme intermediate of a serine protease). Cysteine proteases include papain, cathepsin, caspases, and calpains.

Papain-like cysteine proteases are a family of thiol dependent endo-peptidases related by structural similarity to papain. They form a two-domain protein with the domains labeled R and L (for right and left) and loops from both domains form a substrate recognition cleft. They have a catalytic triad made up of the amino acids

Cys25, His159, and Asn175. Unlike serine proteases which recognize and proteolyze a target peptide based on a beta-sheet conformation of the substrate, this family of proteases does not have well-defined pockets for substrate recognition. The main substrate recognition occurs at the P2 amino acid (compared to the P1 residue in serine proteases).

The substrate specificity of a number of cysteine proteases (human cathepsin L, V, K, S, F, B, papain, and cruzain) has been determined using a complete diverse positional scanning synthetic combinatorial library (PS-SCL). The complete library contains P1, P2, P3, and P4 tetrapeptide substrates in which one position is held fixed while the other three positions are randomized with equal molar mixtures of the 20 possible amino acids, giving a total diversity of ~160,000 tetrapeptide sequences.

Overall, P1 specificity is almost identical between the cathepsins, with Arg and Lys being strongly favored while small aliphatic amino acids are tolerated. Much of the selectivity is found in the P2 position, where the human cathepsins are strictly selective for hydrophobic amino acids. Interestingly, P2 specificity for hydrophobic residues is divided between aromatic amino acids such as Phe, Tyr, and Trp (cathepsin L, V), and bulky aliphatic amino acids such as Val or Leu (cathepsin K, S, F). Compared to the P2 position, selectivity at the P3 position is significantly less stringent. Several of the proteases, however, have a distinct preference for proline (cathepsin V, S, and papain), leucine (cathepsin B), or arginine (cathepsin S, cruzain). The proteases show broad specificity at the P4 position, as no one amino acid is selected over others.

The S2 pocket is the most selective and best characterized of the protease substrate recognition sites. It is defined by the amino acids at the following spatial positions (papain numbering): 66, 67, 68, 133, 157, 160, and 205. Position 205 plays a role similar to position 189 in the serine proteases - a residue buried at the bottom of the pocket that determines the specificity. The other specificity determinants include the following amino acids (numbering according to papain): 61 and 66 (S3); 19, 20, and 158 (S1). The structural determinant for various cysteine proteases are listed in Table 9. Typically, modification of a cysteine protease, such as for example a papain protease, to alter any one or more of the amino acids in the extended specificity binding pocket or other secondary sites of interaction affect the specificity or

selectivity of a protease for a target substrate including a complement protein target substrate.

Table 9: The structural determinants for various cysteine proteases

Residues that Determine Specificity													
	Active Site Residues			S3		S2					S1		
	25	159	175	61	66	66	133	157	160	205	19	20	158
Cathepsin L	Cys	His	Asn	Glu	Gly	Gly	Ala	Met	Gly	Ala	Gln	Gly	Asp
Cathepsin V	Cys	His	Asn	Gln	Gly	Gly	Ala	Leu	Gly	Ala	Gln	Lys	Asp
Cathepsin K	Cys	His	Asn	Asp	Gly	Gly	Ala	Leu	Ala	Leu	Gln	Gly	Asn
Cathepsin S	Cys	His	Asn	Lys	Gly	Gly	Gly	Val	Gly	Phe	Gln	Gly	Asn
Cathepsin F	Cys	His	Asn	Lys	Gly	Gly	Ala	Ile	Ala	Met	Gln	Gly	Asp
Cathepsin B	Cys	His	Asn	Asp	Gly	Gly	Ala	Gly	Ala	Glu	Gln	Gly	Gly
Papain	Cys	His	Asn	Tyr	Gly	Gly	Val	Val	Ala	Ser	Gln	Gly	Asp
Cruzain	Cys	His	Asn	Ser	Gly	Gly	Ala	Leu	Gly	Glu	Gln	Gly	Asp

E. MODIFIED PROTEASES AND COLLECTIONS FOR SCREENING

Proteases or variants thereof can be used in the methods herein to identify proteases with a desired substrate specificity, most often a substrate specificity that is altered, improved, or optimized. Modified proteases to be used in the method provided herein can be generated by mutating any one or more amino acid residues of a protease using any method commonly known in the art (see also published U.S. Appln. No. 2004/0146938). Proteases for modification and the methods provided herein include, for example, full-length wild-type proteases, known variant forms of proteases, or fragments of proteases that are sufficient for catalytic activity, *e.g.* proteolysis of a substrate. Such modified proteases can be screened individually against a target protease trap, such as a serpin or modified serpin, or they can be screened as a collection, such as for example by using a display library, including a combinatorial library where display of the protease is by, for example, phage display, cell-surface display, bead display, ribosome display, or others. Selection of a protease that exhibits specificity and/or selectivity for a protease trap or modified form thereof, due to the formation of a stable covalent inhibitory complex, can be facilitated by any detection scheme known to one of skill in the art including, but not limited to, affinity labeling and/or purification, ELISA, chromogenic assays, fluorescence-based assays (*e.g.* fluorescence quenching or FRET), among others.

1. Generation of Variant Proteases

Examples of methods to mutate protease sequences include methods that result in random mutagenesis across the entire sequence or methods that result in focused mutagenesis of a select region or domain of the protease sequence. In one example, the number of mutations made to the protease is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20. In a preferred embodiment, the mutation(s) confer increased substrate specificity. In some examples, the activity of the protease variant is increased by at least 10-fold, 100-fold, or 1000-fold over the activity of the wild-type protease. In related aspects, the increase in activity is in substrate specificity.

a. Random Mutagenesis

Random mutagenesis methods include, for example, use of E.coli XL1red, UV irradiation, chemical modification such as by deamination, alkylation, or base analog mutagens, or PCR methods such as DNA shuffling, cassette mutagenesis, site-directed random mutagenesis, or error prone PCR (see *e.g.* U.S. Application No.: 2006-0115874). Such examples include, but are not limited to, chemical modification by hydroxylamine (Ruan, H., *et al.* (1997) *Gene* 188:35–39), the use of dNTP analogs (Zaccolo, M., *et al.* (1996) *J. Mol. Biol.* 255:589–603), or the use of commercially available random mutagenesis kits such as, for example, GeneMorph PCR-based random mutagenesis kits (Stratagene) or Diversify random mutagenesis kits (Clontech). The Diversify random mutagenesis kit allows the selection of a desired mutation rate for a given DNA sequence (from 2 to 8 mutations/1000 base pairs) by varying the amounts of manganese (Mn2+) and dGTP in the reaction mixture. Raising manganese levels initially increases the mutation rate, with a further mutation rate increase provided by increased concentration of dGTP. Even higher rates of mutation can be achieved by performing additional rounds of PCR.

b. Focused Mutagenesis

Focused mutation can be achieved by making one or more mutations in a pre-determined region of a gene sequence, for example, in regions of the protease domain that mediate catalytic activity. In one example, any one or more amino acids of a protease are mutated using any standard single or multiple site-directed mutagenesis kit such as for example QuikChange (Stratagene). In another example, any one or more amino acids of a protease are mutated by saturation mutagenesis (Zheng *et al.* (2004) *Nucl. Acids. Res.*, 32:115), such as for example, mutagenesis of active site

residues. In this example, residues that form the S1-S4 pocket of a protease (where the protease is in contact with the P1-P4 residues of the peptide substrate) and/or that have been shown to be important determinants of specificity are mutated to every possible amino acid, either alone or in combination. In some cases, there is little (if any) interaction between the S1-S4 pockets of the active site, such that each pocket appears to recognize and bind the corresponding residue on the peptide substrate sequence independent of the other pockets. Thus, the specificity determinants generally can be changed in one pocket without affecting the specificity of the other pockets. In one exemplary embodiment, a saturation mutagenesis technique is used in which the residue(s) lining the pocket are mutated to each of the 20 possible amino acids (see for example the Kunkle method, Current Protocols in Molecular Biology, John Wiley and Sons, Inc., Media Pa.). In such a technique, a degenerate mutagenic oligonucleotide primer can be synthesized which contains randomization of nucleotides at the desired codon(s) encoding the selected amino acid(s). Exemplary randomization schemes include NNS- or NNK-randomization, where N represents any nucleotide, S represents guanine or cytosine and K represents guanine or thymine. The degenerate mutagenic primer is annealed to the single stranded DNA template and DNA polymerase is added to synthesize the complementary strand of the template. After ligation, the double stranded DNA template is transformed into *E.coli* for amplification.

Amino acids that form the extended substrate binding pocket of exemplary proteases are described herein. Generally, the substrate specificity of a protease is known such as for example by molecular modeling based on three-dimensional structures of the complex of a protease and substrate (see for example, Wang *et al.*, (2001) *Biochemistry* 40(34):10038; Hopfner *et al., Structure Fold Des.* 1999 7(8):989; Friedrich *et al.*, (2002) *J Biol Chem* 277(3):2160; Waugh *et al.*, (2000) *Nat Struct Biol.* 7(9):762). For example, focused mutations of MT-SP1 can be in any one or more residues (based on chymotrypsin numbering) that contribute to substrate specificity including 195, 102, 157 (the catalytic triad); 189, 190, 191, 192, 216 and 226 (S1); 57, 58, 59, 60, 61, 62, 63, 64, 99 (S2); 146, 192, 217, 218 (S3); 96, 97, 98, 99, 100, 168, 169, 170, 170A, 171, 172, 173, 174, 175, 176, 178, 179, 180, 215, 217, 224 (S4). In another example, mutation of amino acid residues in a papain family protease can be in any one or more residues that affect P2 specificity (standard papain

numbering) including 66-68, 133, 157, 160, and/or 215. In addition, residues that do not directly contact the protease substrate, but do affect the position and/or conformation of contact residues (such as for example those listed above) also can be mutated to alter the specificity of a protease scaffold.

In another example, focused amino acids for mutagenesis can be selected by sequence comparison of homologous proteases with similar substrate specificities. Consensus amino acid residues can be identified by alignment of the amino sequences of the homologous proteins, for example, alignment of regions of the protease that are involved in substrate binding. Typically, proteases with similar substrate specificities share consensus amino acids, for example, amino acids in the substrate binding pocket can be identical or similar between the compared proteases. Additionally, the amino acid sequences of proteases with differing substrate specificities can be compared to identify amino acids that can be involved in substrate recognition. These methods can be combined with methods, such as three-dimensional modeling, to identify target residues for mutagenesis.

In an additional example, focused mutagenesis can be restricted to amino acids that are identified as hot spots in the initial rounds of protease screening. For example, following selection of proteases from randomly mutagenized combinatorial libraries, several "hot spot" positions are typically observed and selected over and over again in the screening methods. Most often, since random mutagenesis broadly mutates a polypeptide sequence but with only a few mutations at each site, focused mutagenesis is used as a second strategy to specifically target hot spot positions for further mutagenesis. Focused mutagenesis of hot spot positions allows for a more diverse and deep mutagenesis at particular specified positions, as opposed to the more shallow mutagenesis that occurs following random mutagenesis of a polypeptide sequence. For example, saturation mutagenesis can be used to mutate "hot spots" such as by using oligos containing NNt/g or NNt/c at these positions. In one example, using the methods provided herein, the following hot spots have been identified in u-PA as contributing to increased substrate specificity: 73, 80, 30, and 155, based on chymotrypsin numbering. Mutation of these positions can be achieved, such as for example, by using saturation mutagenesis of a wild-type or template protease sequence at one or more of these sites to create collections of protease mutants to be used in subsequent screenings.

2. Chimeric Forms of Variant Proteases

Variant proteases provided herein can include chimeric or fusion proteins. In one example, a protease fusion protein comprises at least one catalytically-active portion of a protease protein. In another example, a protease fusion protein comprises at least two or more catalytically-active portions of a protease. Within the fusion protein, the non-protease polypeptide can be fused to the N-terminus or C-terminus of the protease polypeptide. In one embodiment, the fusion protein can include a flexible peptide linker or spacer, that separates the protease from a non-protease polypeptide. In another embodiment, the fusion protein can include a tag or detectable polypeptide. Exemplary tags and detectable proteins are known in the art and include for example, but are not limited to, a histidine tag, a hemagglutinin tag, a myc tag or a fluorescent protein. In yet another embodiment, the fusion protein is a GST-protease fusion protein in which the protease sequences are fused to the N-terminus of the GST (glutathione S-transferase) sequences. Such fusion proteins can facilitate the purification of recombinant protease polypeptides. In another embodiment, the fusion protein is a Fc fusion in which the protease sequences are fused to the N-terminus of the Fc domain from immunoglobulin G. Such fusion proteins can have better pharmacodynamic properties *in vivo*. In another embodiment, the fusion protein is a protease protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of protease can be increased through use of a heterologous signal sequence.

A protease chimeric or fusion protein can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, *e.g.*, by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (see,

e.g., Ausubel et al. (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A protease-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the protease protein.

3. Combinatorial Libraries and Other Libraries

The source of compounds for the screening assays, can be collections such as libraries, including, but not limited to, combinatorial libraries. Methods for synthesizing combinatorial libraries and characteristics of such combinatorial libraries are known in the art (See generally, *Combinatorial Libraries: Synthesis, Screening and Application Potential* (Cortese Ed.) Walter de Gruyter, Inc., 1995; Tietze and Lieb, *Curr. Opin. Chem. Biol.*, 2(3):363-71 (1998); Lam, *Anticancer Drug Des.*, 12(3):145-67 (1997); Blaney and Martin, *Curr. Opin. Chem. Biol.*, 1(1):54-9 (1997); and Schultz and Schultz, *Biotechnol. Prog.*, 12(6):729-43 (1996)).

Methods and strategies for generating diverse libraries, including protease or enzyme libraries, including positional scanning synthetic combinatorial libraries (PSSCL), have been developed using molecular biology methods and/or simultaneous chemical synthesis methodologies (see, *e.g.* Georgiou, et al. (1997) *Nat. Biotechnol.* 15:29-34; Kim *et al.* (2000) *Appl Environ Microbiol.* 66: 788 793; MacBeath, G.P. et al. (1998) *Science* 279:1958-1961; Soumillion, P.L. *et al.* (1994) *Appl. Biochem. Biotechnol.* 47:175-189, Wang, C. I. *et al.* (1996). *Methods Enzymol.* 267:52-68, U.S. Patents 6,867,010, 6,168,919, U.S. Patent Application No. 2006-0024289). The resulting combinatorial libraries potentially contain millions of compounds that can be screened to identify compounds that exhibit a selected activity.

In one example, the components of the collection or library of proteases can be displayed on a genetic package, including, but not limited to any replicable vector, such as a phage, virus, or bacterium, that can display a polypeptide moiety. The plurality of displayed polypeptides is displayed by a genetic package in such a way as to allow the polypeptide, such as a protease or catalytically active portion thereof, to bind and/or interact with a target polypeptide. Exemplary genetic packages include, but are not limited to, bacteriophages (see, *e.g.*, Clackson et 25 a/. (1991) Making Antibody Fragments Using Phage Display Libraries, *Nature*, 352:624-628; Glaser et al. (1992) Antibody Engineering by Condon-Based Mutagenesis in a Filamentous

Phage Vector System, *J. Immunol.*, 149:3903 3913; Hoogenboom *et al.* (1991) Multi-Subunit Proteins on the Surface of Filamentous Phage: Methodologies for Displaying Antibody (Fate) Heavy and 30 Light Chains, *Nucleic Acids Res.*, 19:4133-41370), baculoviruses (see, *e.g.*, Boublik et a/. (1995) Eukaryotic Virus Display: Engineering the Major Surface Glycoproteins of the Autographa California Nuclear Polyhedrosis Virus (ACNPV) for the Presentation of Foreign Proteins on the Virus Surface, *Bio/Technology*, 13:1079-1084), bacteria and other suitable vectors for displaying a protein, such as a phage-displayed protease. For example bacteriophages of interest include, but are not limited to, T4 phage, M13 phage and HI phage. Genetic packages are optionally amplified such as in a bacterial host. Any of these genetic packages as well as any others known to those of skill in the art, are used in the methods provided herein to display a protease or catalytically active portion thereof.

a. Phage Display Libraries

Libraries of variant proteases, or catalytically active portions thereof, for screening can be expressed on the surfaces bacteriophages, such as, but not limited to, M13, fd, f1, T7, and λ phages (see, e.g., Santini (1998) *J. Mol. Biol.* 282:125-135; Rosenberg *et al.* (1996) *Innovations* 6:1-6; Houshmand *et al.* (1999) *Anal Biochem* 268:363-370, Zanghi *et al.* (2005) *Nuc. Acid Res.* 33(18)e160:1-8). The variant proteases can be fused to a bacteriophage coat protein with covalent, non-covalent, or non-peptide bonds. (See, *e.g.*, U.S. Pat. No. 5,223,409, Crameri *et al.* (1993) *Gene* 137:69 and WO 01/05950). Nucleic acids encoding the variant proteases can be fused to nucleic acids encoding the coat protein to produce a protease-coat protein fusion protein, where the variant protein is expressed on the surface of the bacteriophage. For example, nucleic acid encoding the variant protease can be fused to nucleic acids encoding the C-terminal domain of filamentous phase M13 Gene III (gIIIp; SEQ ID NO:512). In some examples, a mutant protease exhibiting improved display on the phage is used as a template to generate mutant phage display libraries as described herein. For example, as described in Example 8, a mutant MT-SP1 having the mutation of serine to cysteine at position corresponding to position 122 of wild-type MT-SP1, based on chymotrypsin numbering exhibits improved phage display. Hence, such a mutant can be used as the template from which to generate diversity in the library.

Additionally, the fusion protein can include a flexible peptide linker or spacer, a tag or detectable polypeptide, a protease site, or additional amino acid modifications to improve the expression and/or utility of the fusion protein. For example, addition of a protease site can allow for efficient recovery of desired bacteriophages following a selection procedure. Exemplary tags and detectable proteins are known in the art and include for example, but not limited to, a histidine tag, a hemagglutinin tag, a myc tag or a fluorescent protein. In another example, the nucleic acid encoding the protease-coat protein fusion can be fused to a leader sequence in order to improve the expression of the polypeptide. Exemplary of leader sequences include, but are not limited to, STII or OmpA. Phage display is described, for example, in Ladner *et al.*, U.S. Pat. No. 5,223,409; Rodi *et al.* (2002) *Curr. Opin. Chem. Biol.* 6:92-96; Smith (1985) *Science* 228:1315-1317; WO 92/18619; WO 91/17271; WO 92/20791; WO 92/15679; WO 93/01288; WO 92/01047; WO 92/09690; WO 90/02809; de Haard *et al.* (1999) *J. Biol. Chem* 274:18218-30; Hoogenboom *et al.* (1998) Immunotechnology 4:1-20; Hoogenboom e*t al.* (2000) Immunol Today 2:371-8; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum Antibod Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J Mol Biol* 226:889-896; Clackson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *PNAS* 89:3576-3580; Garrard *et al.* (1991) *Bio/Technology* 9:1373-1377; Rebar *et al.* (1996) *Methods Enzymol.* 267:129-49; Hoogenboom *et al.* (1991) *Nuc Acid Res* 19:4133-4137; and Barbas *et al.* (1991) *PNAS* 88:7978-7982.

Nucleic acids suitable for phage display, *e.g.*, phage vectors, are known in the art (see, *e.g.*, Andris-Widhopf *et al.* (2000) *J Immunol Methods*, 28: 159-81; Armstrong *et al.* (1996) Academic Press, Kay *et al.*, Ed. pp.35-53; Corey *et al.* (1993) *Gene* 128(1):129-34; Cwirla *et al.* (1990) *Proc Natl Acad Sci USA* 87(16):6378-82; Fowlkes *et al.* (1992) *Biotechniques* 13(3):422-8; Hoogenboom *et al.* (1991) *Nuc Acid Res* 19(15):4133-7; McCafferty *et al.* (1990) *Nature* 348(6301):552-4; McConnell *et al.* (1994) *Gene* 151(1-2):115-8; Scott and Smith (1990) *Science* 249(4967):386-90).

A library of nucleic acids encoding the protease-coat protein fusion proteins, typically protease variants generated as described above, can be incorporated into the genome of the bacteriophage, or alternatively inserted into in a phagemid vector. In a phagemid system, the nucleic acid encoding the display protein is provided on a

phagemid vector, typically of length less than 6000 nucleotides. The phagemid vector includes a phage origin of replication so that the plasmid is incorporated into bacteriophage particles when bacterial cells bearing the plasmid are infected with helper phage, *e.g.* M13K01 or M13VCS. Phagemids, however, lack a sufficient set of phage genes in order to produce stable phage particles after infection. These phage genes can be provided by a helper phage. Typically, the helper phage provides an intact copy of the gene III coat protein and other phage genes required for phage replication and assembly. Because the helper phage has a defective origin of replication, the helper phage genome is not efficiently incorporated into phage particles relative to the plasmid that has a wild type origin. See, *e.g.*, U.S. Pat. No. 5,821,047. The phagemid genome contains a selectable marker gene, *e.g.* Amp.sup.R or Kan.sup.R (for ampicillin or kanamycin resistance, respectively) for the selection of cells that are infected by a member of the library.

In another example of phage display, vectors can be used that carry nucleic acids encoding a set of phage genes sufficient to produce an infectious phage particle when expressed, a phage packaging signal, and an autonomous replication sequence. For example, the vector can be a phage genome that has been modified to include a sequence encoding the display protein. Phage display vectors can further include a site into which a foreign nucleic acid sequence can be inserted, such as a multiple cloning site containing restriction enzyme digestion sites. Foreign nucleic acid sequences, *e.g.*, that encode display proteins in phage vectors, can be linked to a ribosomal binding site, a signal sequence (*e.g.*, a M13 signal sequence), and a transcriptional terminator sequence.

Vectors can be constructed by standard cloning techniques to contain sequence encoding a polypeptide that includes a protease and a portion of a phage coat protein, and which is operably linked to a regulatable promoter. In some examples, a phage display vector includes two nucleic acid sequences that encode the same region of a phage coat protein. For example, the vector includes one sequence that encodes such a region in a position operably linked to the sequence encoding the display protein, and another sequence which encodes such a region in the context of the functional phage gene (*e.g.*, a wild-type phage gene) that encodes the coat protein. Expression of both the wild-type and fusion coat proteins can aid in the production of mature phage by lowering the amount of fusion protein made per phage particle. Such

methods are particularly useful in situations where the fusion protein is less tolerated by the phage.

Phage display systems typically utilize filamentous phage, such as M13, fd, and f1. In some examples using filamentous phage, the display protein is fused to a phage coat protein anchor domain. The fusion protein can be co-expressed with another polypeptide having the same anchor domain, *e.g.*, a wild-type or endogenous copy of the coat protein. Phage coat proteins that can be used for protein display include (i) minor coat proteins of filamentous phage, such as gene III protein (gIIIp), and (ii) major coat proteins of filamentous phage such as gene VIII protein (gVIIIp). Fusions to other phage coat proteins such as gene VI protein, gene VII protein, or gene IX protein also can be used (see, *e.g.*, WO 00/71694).

Portions (*e.g.*, domains or fragments) of these proteins also can be used. Useful portions include domains that are stably incorporated into the phage particle, *e.g.*, so that the fusion protein remains in the particle throughout a selection procedure. In one example, the anchor domain of gIIIp is used (see, e.g., U.S. Pat. No. 5,658,727 and Examples below). In another example, gVIIIp is used (see, e.g., U.S. Pat. No. 5,223,409), which can be a mature, full-length gVIIIp fused to the display protein. The filamentous phage display systems typically use protein fusions to attach the heterologous amino acid sequence to a phage coat protein or anchor domain. For example, the phage can include a gene that encodes a signal sequence, the heterologous amino acid sequence, and the anchor domain, *e.g.*, a gIIIp anchor domain.

Valency of the expressed fusion protein can be controlled by choice of phage coat protein. For example, gIIIp proteins typically are incorporated into the phage coat at three to five copies per virion. Fusion of gIIIp to variant proteases thus produces a low-valency. In comparison, gVIII proteins typically are incorporated into the phage coat at 2700 copies per virion (Marvin (1998) *Curr. Opin. Struct. Biol.* 8:150-158). Due to the high-valency of gVIIIp, peptides greater than ten residues are generally not well tolerated by the phage. Phagemid systems can be used to increase the tolerance of the phage to larger peptides, by providing wild-type copies of the coat proteins to decrease the valency of the fusion protein. Additionally, mutants of gVIIIp can be used which are optimized for expression of larger peptides. In one such

example, a mutant gVIIp was obtained in a mutagenesis screen for gVIIIp with improved surface display properties (Sidhu *et al.* (2000) *J. Mol. Biol.* 296:487-495).

Regulatable promoters also can be used to control the valency of the display protein. Regulated expression can be used to produce phage that have a low valency of the display protein. Many regulatable (*e.g.*, inducible and/or repressible) promoter sequences are known. Such sequences include regulatable promoters whose activity can be altered or regulated by the intervention of user, *e.g.*, by manipulation of an environmental parameter, such as, for example, temperature or by addition of stimulatory molecule or removal of a repressor molecule. For example, an exogenous chemical compound can be added to regulate transcription of some promoters. Regulatable promoters can contain binding sites for one or more transcriptional activator or repressor protein. Synthetic promoters that include transcription factor binding sites can be constructed and also can be used as regulatable promoters. Exemplary regulatable promoters include promoters responsive to an environmental parameter, e.g., thermal changes, hormones, metals, metabolites, antibiotics, or chemical agents. Regulatable promoters appropriate for use in *E. coli* include promoters which contain transcription factor binding sites from the *lac, tac, trp, trc*, and *tet* operator sequences, or operons, the alkaline phosphatase promoter (*pho*), an arabinose promoter such as an araBAD promoter, the rhamnose promoter, the promoters themselves, or functional fragments thereof (see, *e.g.*, Elvin *et al.* (1990) *Gene* 37: 123-126; Tabor and Richardson, (1998) *Proc. Natl. Acad. Sci. U.S.A.* 1074-1078; Chang *et al.* (1986) *Gene* 44: 121-125; Lutz and Bujard, (1997) *Nucl. Acids. Res.* 25: 1203-1210; D. V Goeddel *et al.* (1979) *Proc. Nat. Acad. Sci. U.S.A.*, 76:106-110; J. D. Windass *et al.* (1982) *Nucl. Acids. Res.*, 10:6639-57; R. Crowl *et al.* (1985) *Gene*, 38:31-38; Brosius (1984) *Gene* 27: 161-172; Amanna and Brosius, (1985) *Gene* 40: 183-190; Guzman *et al.* (1992) *J. Bacteriol.*, 174: 7716-7728; Haldimann *et al.* (1998) *J. Bacteriol.*, 180: 1277-1286).

The *lac* promoter, for example, can be induced by lactose or structurally related molecules such as isopropyl-beta-D-thiogalactoside (IPTG) and is repressed by glucose. Some inducible promoters are induced by a process of derepression, *e.g.*, inactivation of a repressor molecule.

A regulatable promoter sequence also can be indirectly regulated. Examples of promoters that can be engineered for indirect regulation include: the phage lambda

P_R, P_L, phage T7, SP6, and T5 promoters. For example, the regulatory sequence is repressed or activated by a factor whose expression is regulated, *e.g.*, by an environmental parameter. One example of such a promoter is a T7 promoter. The expression of the T7 RNA polymerase can be regulated by an environmentally-responsive promoter such as the *lac* promoter. For example, the cell can include a heterologous nucleic acid that includes a sequence encoding the T7 RNA polymerase and a regulatory sequence (*e.g.*, the *lac* promoter) that is regulated by an environmental parameter. The activity of the T7 RNA polymerase also can be regulated by the presence of a natural inhibitor of RNA polymerase, such as T7 lysozyme.

In another configuration, the lambda P_L can be engineered to be regulated by an environmental parameter. For example, the cell can include a nucleic acid sequence that encodes a temperature sensitive variant of the lambda repressor. Raising cells to the non-permissive temperature releases the P_L promoter from repression.

The regulatory properties of a promoter or transcriptional regulatory sequence can be easily tested by operably linking the promoter or sequence to a sequence encoding a reporter protein (or any detectable protein). This promoter-report fusion sequence is introduced into a bacterial cell, typically in a plasmid or vector, and the abundance of the reporter protein is evaluated under a variety of environmental conditions. A useful promoter or sequence is one that is selectively activated or repressed in certain conditions.

In some embodiments, non-regulatable promoters are used. For example, a promoter can be selected that produces an appropriate amount of transcription under the relevant conditions. An example of a non-regulatable promoter is the gIII promoter.

b. Cell Surface Display Libraries

Libraries of variant proteases for screening can be expressed on the surfaces of cells, for example, prokaryotic or eukaryotic cells. Exemplary cells for cell surface expression include, but are not limited to, bacteria, yeast, insect cells, avian cells, plant cells, and mammalian cells (Chen and Georgiou (2002) *Biotechnol Bioeng* 79: 496-503). In one example, the bacterial cells for expression are *Escherichia coli*.

Variant proteases can be expressed as a fusion protein with a protein that is expressed on the surface of the cell, such as a membrane protein or cell surface-

associated protein. For example, a variant protease can be expressed in *E. coli* as a fusion protein with an *E. coli* outer membrane protein (*e.g.* OmpA), a genetically engineered hybrid molecule of the major *E. coli* lipoprotein (Lpp) and the outer membrane protein OmpA or a cell surface-associated protein (*e.g.* pili and flagellar subunits). Generally, when bacterial outer membrane proteins are used for display of heterologous peptides or proteins, it is achieved through genetic insertion into permissive sites of the carrier proteins. Expression of a heterologous peptide or protein is dependent on the structural properties of the inserted protein domain, since the peptide or protein is more constrained when inserted into a permissive site as compared to fusion at the N- or C-terminus of a protein. Modifications to the fusion protein can be done to improve the expression of the fusion protein, such as the insertion of flexible peptide linker or spacer sequences or modification of the bacterial protein (*e.g* by mutation, insertion, or deletion, in the amino acid sequence). Enzymes, such as β-lacatamase and the Cex exoglucanase of *Cellulomonas fimi*, have been successfully expressed as Lpp-OmpA fusion proteins on the surface of *E. coli* (Francisco J.A. and Georgiou G. *Ann N Y Acad Sci.* 745:372–382 (1994) and Georgiou G. *et al. Protein Eng.* 9:239–247 (1996)). Other peptides of 15-514 amino acids have been displayed in the second, third, and fourth outer loops on the surface of OmpA (Samuelson et al. *J. Biotechnol.* 96: 129-154 (2002)). Thus, outer membrane proteins can carry and display heterologous gene products on the outer surface of bacteria.

In another example, variant proteases can be fused to autotransporter domains of proteins such as the *N. gonorrhoeae* IgA1 protease, *Serratia marcescens* serine protease, the *Shigella flexneri* VirG protein, and the *E. coli* adhesin AIDA-I (Klauser *et al. EMBO J.* 1991–1999 (1990); Shikata S, *et al. J Biochem.* 114:723–731 (1993); Suzuki T *et al. J Biol Chem.* 270:30874–30880 (1995); and Maurer J *et al. J Bacteriol.* 179:794–804 (1997)). Other autotransporter proteins include those present in gram-negative species (*e.g.* E. coli, *Salmonella* serovar *Typhimurium, and S. flexneri*). Enzymes, such as β-lactamase, have been successful expressed on the surface of *E. coli* using this system (Lattemann CT *et al. J Bacteriol.* 182(13): 3726–3733 (2000)).

Bacteria can be recombinantly engineered to express a fusion protein, such a membrane fusion protein. Nucleic acids encoding the variant proteases can be fused

to nucleic acids encoding a cell surface protein, such as, but not limited to, a bacterial OmpA protein. The nucleic acids encoding the variant proteases can be inserted into a permissible site in the membrane protein, such as an extracellular loop of the membrane protein. Additionally, a nucleic acid encoding the fusion protein can be fused to a nucleic acid encoding a tag or detectable protein. Such tags and detectable proteins are known in the art and include for example, but are not limited to, a histidine tag, a hemagglutinin tag, a myc tag or a fluorescent protein. The nucleic acids encoding the fusion proteins can be operably linked to a promoter for expression in the bacteria. For example a nucleic acid can be inserted in a vector or plasmid, which can carry a promoter for expression of the fusion protein and optionally, additional genes for selection, such as for antibiotic resistance. The bacteria can be transformed with such plasmids, such as by electroporation or chemical transformation. Such techniques are known to one of ordinary skill in the art.

Proteins in the outer membrane or periplasmic space are usually synthesized in the cytoplasm as premature proteins, which are cleaved at a signal sequence to produce the mature protein that is exported outside the cytoplasm. Exemplary signal sequences used for secretory production of recombinant proteins for *E. coli* are known. The N-terminal amino acid sequence, without the Met extension, can be obtained after cleavage by the signal peptidase when a gene of interest is correctly fused to a signal sequence. Thus, a mature protein can be produced without changing the amino acid sequence of the protein of interest (Choi and Lee. *Appl. Microbiol. Biotechnol.* 64: 625-635 (2004)).

Other cell surface display systems are known in the art and include, but are not limited to ice nucleation protein (Inp)-based bacterial surface display system (Lebeault J M (1998) *Nat Biotechnol.* 16: 576 80), yeast display (e.g. fusions with the yeast Aga2p cell wall protein; see U.S. Pat. No. 6,423,538), insect cell display (*e.g.* baculovirus display; see Ernst et al. (1998) Nucleic Acids Research, Vol 26, Issue 7 1718-1723), mammalian cell display, and other eukaryotic display systems (see *e.g.* 5,789,208 and WO 03/029456).

c. Other Display Libraries

It also is possible to use other display formats to screen libraries of variant proteases, *e.g.*, libraries whose variation is designed as described herein. Exemplary other display formats include nucleic acid-protein fusions, ribozyme display (see e.g.

Hanes and Pluckthun (1997) *Proc. Natl. Acad. Sci. U.S.A.* 13:4937-4942), bead display (Lam, K. S. *et al.* Nature (1991) 354, 82-84; , K. S. *et al.* (1991) *Nature*, 354, 82-84; Houghten, R. A. *et al.* (1991) *Nature*, 354, 84-86; Furka, A. *et al.* (1991) *Int. J. Peptide Protein Res.* 37, 487-493; Lam, K. S., *et al.* (1997) *Chem. Rev.*, 97, 411-448; U.S. Published Patent Application 2004-0235054) and protein arrays (see *e.g.* Cahill (2001*) J. Immunol. Meth.* 250:81-91, WO 01/40803, WO 99/51773, and US2002-0192673-A1)

In specific other cases, it can be advantageous to instead attach the proteases, variant proteases, or catalytically active portions or phage libraries or cells expressing variant proteases to a solid support. For example, in some examples, cells expressing variant proteases can be naturally adsorbed to a bead, such that a population of beads contains a single cell per bead (Freeman *et al.* Biotechnol. Bioeng. (2004) 86:196-200). Following immobilization to a glass support, microcolonies can be grown and screened with a chromogenic or fluorogenic substrate. In another example, variant proteases or phage libraries or cells expressing variant proteases can be arrayed into titer plates and immobilized.

F. METHODS OF CONTACTING, ISOLATING, AND IDENTIFYING SELECTED PROTEASES

After a plurality of collections or libraries displaying proteases or catalytically active portions thereof have been chosen and prepared, the libraries are used to contact a target protease trap polypeptide with the protease components. The target substrates, including, for example, a protease trap polypeptide such as a serpin mutated in its RSL loop to have a desired cleavage sequence, are contacted with the displayed protease libraries for selection of a protease with altered substrate specificity. The protease and protease trap polypeptide can be contacted in suspension, solution, or via a solid support. The components are contacted for a sufficient time, temperature, or concentration for interaction to occur and for the subsequent cleavage reaction and formation of a stable intermediate complex of the selected protease and protease trap polypeptide. The stringency by which the reaction is maintained can be modulated by changing one or more parameters from among the temperature of the reaction, concentration of the protease trap polypeptide inhibitor, concentration of a competitor (if included), concentration of the collection of proteases in the mixture, and length of time of the incubation.

The selected proteases that form covalent complexes with the protease trap polypeptide are captured and isolated. To facilitate capture, protease trap polypeptides for screening against can be provided in solution, in suspension, or attached to a solid support, as appropriate for the assay method. For example, the protease trap polypeptide can be attached to a solid support, such as for example, one or more beads or particles, microspheres, a surface of a tube or plate, a filter membrane, and other solid supports known in the art. Exemplary solid support systems include, but are not limited to, a flat surface constructed, for example, of glass, silicon, metal, nylon, cellulose, plastic or a composite, including multiwell plates or membranes; or can be in the form of a bead such as a silica gel, a controlled pore glass, a magnetic (Dynabead) or cellulose bead. Such methods can be adapted for use in suspension or in the form of a column. Target protease trap polypeptides can be attached directly or indirectly to a solid support, such as a polyacrylamide bead. Covalent or non-covalent methods can be used for attachment. Covalent methods of attachment of target compounds include chemical crosslinking methods. Reactive reagents can create covalent bonds between functional groups on the target molecule and the support. Examples of functional groups that can be chemically reacted are amino, thiol, and carboxyl groups. N-ethylmaleimide, iodoacetamide, N-hydrosuccinimide, and glutaraldehyde are examples of reagents that react with functional groups. In other examples, target substrates can be indirectly attached to a solid support by methods such as, but not limited to, immunoaffinity or ligand-receptor interactions (*e.g.* biotin-streptavidin or glutathione S-transferase-glutathione). For example, a protease-trap polypeptide can be coated to an ELISA plate, or other similar addressable array. In one example, the wells of the plate can be coated with an affinity capture agent, which binds to and captures the protease-trap polypeptide. Example 9 exemplifies a method whereby biotinylated anti-His antibody is coated onto a streptavidin containing plate to facilitate capture of a protease-trap polypeptide containing a His-tag.

Attachment of the protease trap polypeptide to a solid support can be performed either before, during, or subsequent to their contact with variant proteases or phage libraries or cells expressing variant proteases. For example, target substrates can be pre-absorbed to a solid support, such as a chromatography column, prior to

incubation with the variant protease. In other examples, the attachment of a solid support is performed after the target substrate is bound to the variant protease.

In such an example, the solid support containing the complexed substrate-protease pair can be washed to remove any unbound protease. The complex can be recovered from the solid support by any method known to one of skill in the art, such as for example, by treatment with dilute acid, followed by neutralization (Fu *et al.* (1997) *J Biol. Chem.* 272:25678-25684) or with triethylamine (Chiswell *et al.* (1992) Trends Biotechnol. 10:80-84). This step can be optimized to ensure reproducible and quantitative recovery of the display source from the solid substrate. For example, the binding of the display source to the target substrate attached to the solid support can be monitored independently using methods well known to those of skill in the art, such as by using an antibody directed against the phage, such as against M13 phage (*e.g.*, New England Biolabs, MA) and a standard ELISA (see *e.g.*, Ausubel *et al.* (1987) Current Protocols in Molecular Biology, John Wiley & Sons, New York).

Another method of capturing and isolating a substrate-protease complex is from solution. Typically, in such a method, a protease trap polypeptide or variant thereof is contacted with a collection of proteases such as, for example, in a small volume of an appropriate binding buffer (*i.e.* 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500 or more microliters) where each protease trap polypeptide is associated with a predetermined marker, tag, or other detectable moiety for identification and isolation thereof. The detectable moiety can be any moiety that facilitates the detection and isolation of substrate-protease complex. For example, the moiety can be an epitope tag for which an antibody specific for the tag exists (*i.e.* myc-tag, His-tag, or others). The antibody can be bound to a solid support, such as a bead, to facilitate capture of the stable complex. Other similar strategies can be used and include, for example, labeling of the target substrate with biotin and capture using streptavidin attached to a solid support such as magnetic beads or a microtiter plate or labeling with polyhistidine (*e.g.*, His 6-tag) and capture using a metal chelating agent such as, but not limited to, nickel sulphate ($NiSO_4$), cobalt chloride ($CoCl_2$), copper sulphate ($CuSO_4$), or zinc chloride ($ZnCl_2$). The capturing agents can be coupled to large beads, such as for example, sepharose beads, whereby isolation of the bound beads can be easily achieved by centrifugation. Alternatively, capturing agents can be coupled to smaller beads, such as for example, magnetic beads (*i.e.* Miltenyi Biotec),

that can be easily isolated using a magnetic column. In addition, the moiety can be a fluorescent moiety. For example, in some display systems, such as for example, cell surface display systems, a fluorescent label can facilitate isolation of the selected complex by fluorescence activated cell sorting (FACS; see *e.g.*, Levin et al. (2006) Molecular BioSystems, 2: 49-57).

In some instances, one or more distinct protease trap polypeptides are contacted with a collection of proteases, where each of the protease trap polypeptides are associated with different detection moieties so as to individually isolate one or more than one protease trap polypeptide-protease complex. The ability to include in a single reaction 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more distinct protease trap polypeptides, each with a different desired RSL cleavage sequence, permits the detection and isolation of tens of hundreds or thousands of covalent complexes simultaneously.

The selected proteases, captured as covalent complexes with the protease trap polypeptide, can be separated from uncomplexed proteases from the collection of proteases. The selected proteasescan then be amplified to facilitate identification of the selected protease. After removal of any uncomplexed proteases to the protease trap polypeptide, the source of material to which the protease is displayed (*i.e.* phage, cells, beads, *etc*...) is amplified and expressed in an appropriate host cell. For example, where the protease is displayed on phage, generally, the protease-phage in complex with a protease trap polypeptide is incubated with a host cell to allow phage adsorption, followed by addition of a small volume of nutrient broth and agitation of the culture to facilitate phage probe DNA replication in the multiplying host. In some examples, this is done in the presence of helper phage in order to ensure that the host cells are infected by the phage. After this incubation, the media is supplemented with an antibiotic and/or an inducer. The phage protease genome also can contain a gene encoding resistance to the antibiotic to allow for selective growth of those bacterial cells that maintain the phage protease DNA. Typically, for amplification of phage as a source of phage supernatant containing selected proteases, rescue of the phage is required by the use of helper phage. In some examples, it is possible to assay for the presence of a selected protease without a rescue step. For example, following incubation of the captured complex containing the selected or identified protease with a host cell, for example, bacteria, and growth in the presence of a selective agent, the periplasm or cell culture medium can be directly sampled as a source of the selected

protease, for example, to measure protease activity. Such a procedure is described in Example 17.

Additionally, the amplification of the display source, such as in a bacterial host, can be optimized in a variety of ways. For example, the amount of bacteria added to the assay material, such as in microwells, can be in vast excess of the phage source recovered from the binding step thereby ensuring quantitative transduction of the phage genome. The efficiency of transduction optionally can be measured when phage are selected. The amplification step amplifies the genome of the display source, such as phage genomes, allowing over-expression of the associated signature polypeptide and identification thereof, such as by DNA sequencing.

A panning approach can be used whereby proteases or catalytically active portions thereof that interact with a target protein, such as a protease trap polypeptide or RSL variant thereof, are quickly selected. Panning is carried out, for example, by incubating a library of phage-displayed polypeptides, such as phage-displayed proteases, with a surface-bound or soluble target protein, washing away the unbound phage, and eluting the specifically and covalently-bound phage. The eluted phage is then amplified, such as via infection of a host, and taken through additional cycles of panning and amplification to successively enrich the pool of phage for those with the highest affinities for the target polypeptide. After several rounds, individual clones are identified, such as by DNA sequencing, and their activity can be measured, such as by any method set forth in Section G below.

Once the selected protease is identified, it can be purified from the display source and tested for activity. Generally, such methods include general biochemical and recombinant DNA techniques and are routine to those of skill in the art. In one method, polyethylene glycol (PEG) precipitation can be used to remove potentially contaminating protease activity in the purified selected phage supernatants. In such an example, following phage rescue in the presence of helper phage, phage supernatant containing the selected protease can be precipated in the presence of PEG. One of skill in the art is able to determine the percentage of PEG required for the particular precipitation application. Generally, for precipitation of protease supernatants, 20% PEG is used.

In some examples, the supernatant, either from the rescued phage supernatant, or from the bacterial cell periplasm or cell medium (without phage rescue) can be

assayed for protease activity as described herein. Alternatively or additionally, the selected protease can be purified from the supernatant or other source. For example, DNA encoding the selected protease domain can be isolated from the display source to enable purification of the selected protein. For example, following infection of *E.coli* host cells with selected phage as set forth above, the individual clones can be picked and grown up for plasmid purification using any method known to one of skill in the art, and if necessary can be prepared in large quantities, such as for example, using the Midi Plasmid Purification Kit (Qiagen). The purified plasmid can used for DNA sequencing to identify the sequence of the variant protease, or can be used to transfect into any cell for expression, such as but not limited to, a mammalian expression system. If necessary, one or two-step PCR can be performed to amplify the selected sequence, which can be subcloned into an expression vector of choice. The PCR primers can be designed to facilitate subcloning, such as by including the addition of restriction enzyme sites. Example 4 exemplifies a two step PCR procedure to accomplish amplification and purification of the full-length u-PA gene, where the selected protease phage contained only the protease domain of the u-PA gene. Following transfection into the appropriate cells for expression such as is described in detail below, conditioned medium containing the protease polypeptide, or catalytically active portion thereof can be tested in activity assays or can be used for further purification. In addition, if necessary, the protease can be processed accordingly to yield an active protease, such as by cleavage of a single chain form, into a two chain form. Such manipulations are known to one of skill in the art. For example, single chain u-PA can be made active the cleavage of plasmin such as is described herein.

1. Iterative Screening

In the methods provided herein, iterative screening is employed to optimize the modification of the proteases. Thus, in methods of iterative screening, a protease can be evolved by performing the panning reactions a plurality of times under various parameters, such as for example, by using different protease trap polypeptides or competitors. In such methods of iterative screening, the protease collection can be kept constant in successive rounds of screening. Alternatively, a new protease collection can be generated containing only the selected proteases identified in the

preceding rounds and/or by creating a new collection of mutant proteases that have been further mutated as compared to a template protease identified in the first round.

In one example, a first round screening of the protease library can identify variant proteases containing one or more mutations which alter the specificity of the protease. A second round library synthesis can then be performed in which the amino acid positions of the one or mutations are held constant, and focused or random mutagenesis is carried out on the remainder of the protein or desired region or residue. After an additional round of screening, the selected protease can be subjected to additional rounds of library synthesis and screening. For example, 2, 3, 4, 5, or more rounds of library synthesis and screening can be performed. In some examples, the specificity of the variant protease toward the altered substrate is further optimized with each round of selection.

In another method of iterative screening, a first round screening of a protease collection can be against an intermediate protease trap polypeptide to identify variant proteases containing one or more mutations which alter the specificity of the protease to the intermediate substrate. The selected protease complexes can be isolated, grown up, and amplified in the appropriate host cells and used as the protease collection in a second round of screening against a protease trap polypeptide containing the complete cleavage sequence of a target polypeptide. For example, such an approach can be used to select for proteases having substrate specificity for a VEGFR cleavage sequence where the one or more rounds of panning are against a RRARM intermediate cleavage sequence, and subsequent rounds of panning are performed against a protease trap polypeptide containing the VEGFR2 cleavage sequence RRVR.

In an additional example of iterative screening, two or more protease trap polypeptides containing different substrate recognition or cleavage sequences for two or more different polypeptides are used in the methods in alternative rounds of panning. Such a method is useful to select for proteases that are optimized to have selectivity for two different substrates. The selected variants typically have narrow specificity, but high activity towards two or more substrate recognition sequences. In such methods, a first round screening of a protease collection against a first protease trap polypeptide, that has been modified to select for a protease with a first predetermined substrate specificity, can identify variant proteases containing one or

more mutations which alter the specificity of the protease. The selected proteases can be isolated, grown up, and amplified in the appropriate host cells and used as the protease collection in a second round of screening against a second protease trap polypeptide that has been modified to select for a protease with a second predetermined substrate specificity. The first and second protease trap polypeptide used in the methods can be the same or different, but each is differently modified in its reactive site to mimic a substrate recognition site (*i.e.* cleavage sequence) of different target substrates. In some examples, the stringency in the selection can be enhanced in the presence of competitors, such as for example, narrow or broad competitors as described herein.

2. Exemplary Selected Proteases

Provided herein are variant u-PA and MT-SP1 polypeptides identified in the methods provided herein as having an altered and/or improved substrate specificity. Such variant u-PA and MT-SP1 polypeptides were identified as having an increased specificity for a selected or desired cleavage sequence of a target protein. Exemplary of such target proteins include, but are not limited to, a cleavage sequence in a VEGFR or a complement protein, for example, complement protein C2. Any modified serpin can be used in the selection methods herein to identify variant proteases. Exemplary of such modified serpins are PAI-1 or AT3 modified in their RSL to contain cleavage sequences for a target protein, for example, a VEGFR or C2, as described herein above. The resulting selected modified proteases exhibit altered, typically improved, substrate specificity for the cleavage sequence in the target protein as compared to the template or starting protease, which does not contain the selected modifications. As described below, specificity is typically increased and is generally at least 2-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 times or more when compared to the specificity of a wild-type or template protease for the target substrate selected against versus a non-target substrate.

a. Variant u-PA polypeptides

For example, variant u-PA polypeptides provided herein were selected for to have an increased reactivity for a mutant serpin polypeptide modified in its RSL sequence by replacement of the native P4-P1' reactive site amino acids with those of a desired or selected target protein. In one example, variant u-PA polypeptides were

identified against selection of a modified PAI-1 polypeptide. Examples of modified PAI-1 polypeptide molecules used in the u-PA selection methods provided herein include, for example, PAI-1 modified in its native P4-P1' residues VSARM (SEQ ID NO:378) with amino acid residues for an intermediate VEGFR-2 cleavage sequence RRARM (SEQ ID NO:379), where the desired cleavage sequence in the P4-P1 positions is the VEGFR-2 cleavage sequence RRVR (SEQ ID NO:489), or with amino acid residues for the optimal t-PA cleavage sequence PFGRS (SEQ ID NO:389).

Using the methods provided herein, the following positions were identified as contributing to substrate specificity of a u-PA polypeptide: 21, 24, 30, 38, 39, 61(A), 72, 73, 75, 80, 82, 84, 89, 92, 132, 133, 137, 138, 155, 156, 158, 159, 160, 187, and 217, based on chymotrypsin numbering. Amino acid replacement or replacements can be at any one or more positions corresponding to any of the following positions F21, I24, F30, V38, T39, Y61(A), R72, L73, S75, E80, K82, E84, I89, K92, F132, G133, E137, I138, L155, K156, T158, V159, V160, K187, and R217 of a u-PA polypeptide, such as a u-PA polypeptide set forth in SEQ ID NO:433 or catalytically active portion thereof, based on chymotrypsin numbering. A modified u-PA polypeptide provided herein that exhibits increased substrate specificity can contain one or more amino acid modifications corresponding to any one or more modification of F21V, I24L, F30I, F30V, F30L, F30T, F30G, F30M, V38D, T39A, Y61(A)H, R72G, L73A, L73P, S75P, E80G, K82E, E84K, I89V, K92E, F132L, G133D, E137G, I138T, L155P, L155V, L155M, K156Y, T158A, V159A, V160A, K187E, and R217C of a u-PA polypeptide, such as a u-PA polypeptide set forth in SEQ ID NO:433 or catalytically active portion thereof, based on chymotrypsin numbering.

In one example, a modified u-PA polypeptide provided herein having increased substrate specificity for a VEGFR-2 cleavage sequence contains one or more amino acid modifications corresponding to any one or more modifications of V38D, F30I, F30T, F30L, F30V, F30G, F30M, R72G, L73A, L73P, S75P, I89V, F132L, G133D, E137G, I138T, L155P, L155V, L155M, V160A, and R217C, based on chymotrypsin numbering. Exemplary of such polypeptides are those u-PA polypeptides containing one or more amino acid modifications corresponding to any of F30I; L73A/I89V; L73P; R217C; L155P; S75P/I89V/I138T; E137G; R72G/L155P; G133D; V160A; V38D; F132L/V160A; L73A/I89V/F30T;

L73A/I89V/F30L; L73A/I89V/F30V; L73A/I89V/F30G; L73A/I89V/L155V; L73A/I89V/F30M; L73A/I89V/L155M; L73A/I89V/F30L/L155M; and L73A/I89V/F30G/L155M in a u-PA polypeptide, such as a u-PA polypeptide having an amino acid sequence set forth in SEQ ID NO:433 or a catalytically active fragment thereof. Exemplary of such sequences are those set forth in any of SEQ ID NOS: 434-459, or fragments thereof of contiguous amino acids containing the mutation and having catalytic activity. In particular, modified u-PA polypeptides having the following amino acid modifications are provided: L73A/I89V; L155P; R72G/L155P; F132L/V160A; L73A/I89V/F30T; L73A/I89V/L155V; L73A/I89V/L155M; and L73A/I89V/F30L/L155M, based on chymotrypsin numbering.

In another example, a modified u-PA polypeptide provided herein having increased specificity for a cleavage sequence recognized by t-PA contains one or more amino acid modifications corresponding to any one or more modifications of F21V, I24L, F30V, F30L, T39A, Y61(A)H, E80G, K82E, E84K, I89V, K92E, K156T, T158A, V159A, and K187E, based on chymotrypsin numbering. Exemplary of such polypeptides are those u-PA polypeptides containing one or more amino acid modifications corresponding to any of F21V; I24L; F30V; F30L; F30V/Y61(A)H; F30V/K82E; F30V/K156T; F30V/K82E/V159A; F30V/K82E/T39A/V159A; F30V/K82E/T158A/V159A; F30V/Y61(A)H/K92E; F30V/K82E/V159A/E80G/I89V/K187E; and F30V/K82E/V159A/E80G/E84K/I89V/K187E, in a u-PA polypeptide, such as a u-PA polypeptide having an amino acid sequence set forth in SEQ ID NO:433 or a catalytically active fragment thereof. Exemplary of such sequences are those set forth in any of SEQ ID NOS:460-472, or fragments thereof of contiguous amino acids containing the mutation and having catalytic activity.

Also provided herein are variant proteases of the chymotrypsin family having the corresponding mutation as compared to the variant u-PA polypeptides provided herein, based on chymotrypsin numbering. For example, based on chymotrypsin numbering, modification of position F30 in u-PA corresponds to modification of position Q30 in t-PA, Q30 in trypsin, and Q30 in chymotrypsin (Bode *et al.* (1997) *Current Opinion in Structural Biology*, 7: 865-872). One of skill in the art could determine corresponding mutations in any other chymotrypsin family member, including but not limited to modification of any protease set forth in Table 7 and

having a sequence of amino acids set forth in any of SEQ ID NOS: 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 242, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 262, 264, 266, 268, 270, 272, or catalytically active fragments thereof.

b. Variant MT-SP1 polypeptides

In another example, variant MT-SP1 polypeptides provided herein were selected for to have an increased reactivity for a mutant serpin polypeptide modified in its RSL sequence by replacement of the native P4-P2' reactive site amino acids with those of a desired or selected target protein. In one example, variant MT-SP1 polypeptides were identified against selection of a modified AT3 polypeptide. Examples of modified AT3 polypeptide molecules used in the MT-SP1 selection methods provided herein include, for example, AT3 modified in its native P4-P2' residues IAGRSL (SEQ ID NO:478) with amino acid residues for a complement protein C2 cleavage sequence SLGRKI (SEQ ID NO:479).

Using the methods provided herein, the following positions were identified as contributing to substrate specificity of an MT-SP1 polypeptide: 23, 41, 52,60(g), 65, 71, 93, 95, 97, 98, 99, 126, 129, 131, 136, 143, 144, 154, 164, 166, 171, 173, 175, 184(a), 192, 201, 209, 217, 221(a), 230, 234, and 244 , based on chymotrypsin numbering. Amino acid replacement or replacements can be at any one or more positions corresponding to any of the following positions D23, I41, L52, Y60(g), T65, H71, F93, N95, F97, I98, F99, A126, V129, P131, I136, H143, T144, I154, N164, T166, L171, P173, Q175, F184(a), Q192, S201, Q209, D217, Q221(a), R230, F234, and V244 of an MT-SP1 polypeptide, such as full-length MT-SP1 polypeptide set forth in SEQ ID NO:253 or 515 or catalytically active portion thereof set forth in SEQ ID NO:505 or 507, based on chymotrypsin numbering. A modified MT-SP1 polypeptide provided herein that exhibits increased substrate specificity can contain one or more amino acid modifications corresponding to any one or more modification of D23E, I41F, I41T, L52M, Y60(g)s, T56K, H71R, F93L, N95K, F97Y, F97L, T98P, F99L, A126T, V129D, P131S, I136T, I136V, H143R, T144I, I154V, N164D,

T166A, L171F, P173S, Q175R, F184(a)L, Q192H, S201I, Q209L, D217V, Q221(a)L, R230W, F234L, and V244G of an MT-SP1 polypeptide, such as full-length MT-SP1 polypeptide set forth in SEQ ID NO:253 or 515 or catalytically active portion thereof set forth in SEQ ID NO:505 or 507, based on chymotrypsin numbering. In particular, a modified MT-SP1 polypeptide contains one or more amino acid modifications corresponding to any one or more modification of I41F, F97Y, L171F, Q175R, D217V and V244G, for example, any one or more of I41F, F97Y, L171F and V244G.

Typically, such a modified MT-SP1 polypeptide exhibits increased substrate specificity for complement protein C2. Exemplary of such polypeptides are those MT-SP1 polypeptides containing one or more amino acid modifications corresponding to any of I136T/N164D/T166A/F184(A)L/D217V; I41F; I41F/ A126T/V244G; D23E/I41F/T98P /T144I; I41F/ L171F/V244G; H143R/Q175R; I41F/ L171F; R230W; I41F /I154V/V244G; I141F/L52M/ V129D/Q221(A)L; F99L; F97Y/ I136V/Q192H/S201I; H71R/ P131S/D217V; D217V; T65K/F93L/F97Y/ D217V; I41T/ P173S/Q209L; F97L/ F234L; Q175R; N95K; and Y60(G)S in an MT-SP1 polypeptide, such as an MT-SP1 polypeptide having an amino acid sequence set forth in SEQ ID NO:253 or a catalytically active fragment thereof set forth in SEQ ID NO:505. Exemplary of such sequences are those set forth in any of SEQ ID NOS: 589-609, or fragments thereof of contiguous amino acids containing the mutation and having catalytic activity such as, for example, any set forth in any of SEQ ID NOS: 568-588. In some examples, the variant MT-SP1 polypeptides provided herein additionally contain a modification corresponding to C122S in an MT-SP1 polypeptide such as an MT-SP1 polypeptide having an amino acid sequence set forth in SEQ ID NO:253 or a catalytically active fragment thereof set forth in SEQ ID NO:505. Exemplary of such variant MT-SP1 polypeptides are set forth in any of SEQ ID NOS: 537-557, or fragments thereof of contiguous amino acids containing the mutation and having catalytic activity such as, for example, any set forth in any of SEQ ID NOS: 516-536.

In particular, modified u-PA polypeptides having the following amino acid modifications are provided: L73A/I89V; L155P; R72G/L155P; F132L/V160A; L73A/I89V/F30T; L73A/I89V/L155V; L73A/I89V/L155M; and L73A/I89V/F30L/L155M, based on chymotrypsin numbering.

G. METHODS OF ASSESSING PROTEASE ACTIVITY AND SPECIFICITY

Proteases selected in the methods provided herein can be tested to determine if, following selection, the proteases retain catalytic efficiency and exhibit the desired substrate specificity. Activity assessment can be performed using supernatant from the amplified display source or from purified protein. For example, as discussed above, phage supernatant can be assayed following rescue of phage with helper phage and phage amplification. Alternatively, protease activity can be assayed directly from the cell medium or periplasm of infected bacteria. Protease activity of the purified selected protease also can be determined.

Catalytic efficiency and/or substrate specificity can be assessed by assaying for substrate cleavage using known substrates of the protease. For example, cleavage of plasminogen can be asseesed in the case where t-PA or u-Pa are used in the selection method herein. In another example, a peptide substrate recognized by the protease can be used. For example, RQAR (SEQ ID NO:513), which is the auto-activation site of MT-SP1, can be used to assess the activity of selected MT-SP1 proteases. In one embodiment, a fluorogenically tagged tetrapeptide of the peptide substrate can be used, for example, an ACC- or AMC- tetrapeptide. In addition, a fluorogenic peptide substrates designed based on the cleavage sequence of a desired target substrate for which the protease was selected against can be used to assess activity.

In some examples, the selected protease can be assessed for its activity against a known peptide substrate in the presence or absence of the variant protease trap polypeptide used in the selection method. Typically, such an activity assessment is performed in order to further select for those proteases that are inhibited in the presence of protease trap polypeptide containing the desired cleavage sequence of the target substrate, and thereby optimize for selected proteases having improved selectivity for the target substrate. Comparisons of inhibition can be made against the wild-type or template protease and/or with all other proteases identified in the selection method.

Kinetic analysis of cleavage of native substrates of a selected protease can be compared to analysis of cleavage of desired target substrates to assess specificity of the selected protease for the target sequence. In addition, second order rate constants

of inhibition (k*i*) can be assessed to monitor the efficiency and reactivity of a selected protease for a substrate, such as for example, the protease trap polypeptide, or variant thereof, used in the selection method. Example 5 exemplifies various assays used to assess the catalytic efficiency and reactivity of mutant u-PA polypeptides identified in the methods provided herein. Example 10 and Example 12 exemplify various assays used to assess the catalytic efficiency of selected MT-SP1 phage supernatants. Example 14 exemplifies various assays used to assess the catalytic efficiency and reactivity of selected purified variant MT-SP1 proteases.

In one example, selected proteases, such as for example selected u-PA or MT-SP1 proteases, that are selected to match the desired specificity profile of the mutated protease trap polypepide, can be assayed using individual fluorogenic peptide substrates corresponding to the desired cleavage sequence. For example, a method of assaying for a modified protease that can cleave any one or more of the desired cleavage sequences of a target substrate includes: (a) contacting a peptide fluorogenic sample (containing a desired target cleavage sequence) with a protease, in such a manner whereby a fluorogenic moiety is released from a peptide substrate sequence upon action of the protease, thereby producing a fluorescent moiety; and (b) observing whether the sample undergoes a detectable change in fluorescence, the detectable change being an indication of the presence of the enzymatically active protease in the sample. In such an example, the desired cleavage sequence for which the protease was selected against is made into a fluorogenic peptide by methods known in the art. In one embodiment, the individual peptide cleavage sequences can be attached to a fluorogenically tagged substrate, such as for example an ACC or AMC fluorogenic leaving group, and the release of the fluorogenic moiety can be determined as a measure of specificity of a protease for a peptide cleavage sequence. The rate of increase in fluorescence of the target cleavage sequence can be measured such as by using a fluorescence spectrophotometer. The rate of increase in fluorescence can be measured over time. Michaelis-Menton kinetic constants can be determined by the standard kinetic methods. The kinetic constants k_{cat}, K_m and k_{cat}/K_m can be calculated by graphing the inverse of the substrate concentration versus the inverse of the velocity of substrate cleavage, and fitting to the Lineweaver-Burk equation ($1/velocity=(K_m/V_{max})(1/[S]) + 1/V_{max}$; where $V_{max}=[ET]k_{cat}$). The second order rate constant or specificity constant (k_{cat}/K_m) is a measure of how well a

substrate is cut by a particular protease. For example, an ACC- or AMC- tetrapeptide such as Ac-RRAR-AMC, Ac-SLGR-AMC, Ac-SLGR-ACC, Ac-RQAR-ACC, can be made and incubated with a protease selected in the methods provided herein and activity of the protease can be assessed by assaying for release of the fluorogenic moiety. The choice of the tetrapeptide depends on the desired cleavage sequence to by assayed for and can be empirically determined.

Assaying for a protease in a solution simply requires adding a quantity of the stock solution to a protease to a fluorogenic protease indicator peptide and measuring the subsequent increase in fluorescence or decrease in excitation band in the absorption spectrum. The solution and the fluorogenic indicator also can be combined and assayed in a "digestion buffer" that optimizes activity of the protease. Buffers suitable for assaying protease activity are well known to those of skill in the art. In general, a buffer is selected with a PH which corresponds to the PH optimum of the particular protease. For example, a buffer particularly suitable for assaying elastase activity contains 50mM sodium phosphate, 1 mM EDTA at pH 8.9. The measurement is most easily made in a fluorometer, an instrument that provides an "excitation" light source for the fluorophore and then measures the light subsequently emitted at a particular wavelength. Comparison with a control indicator solution lacking the protease provides a measure of the protease activity. The activity level can be precisely quantified by generating a standard curve for the protease/indicator combination in which the rate of change in fluorescence produced by protease solutions of known activity is determined.

While detection of fluorogenic compounds can be accomplished using a fluorometer, detection can be accomplished by a variety of other methods well known to those of skill in the art. Thus, for example, when the fluorophores emit in the visible wavelengths, detection can be simply by visual inspection of fluorescence in response to excitation by a light source. Detection also can be by means of an image analysis system utilizing a video camera interfaced to a digitizer or other image acquisition system. Detection also can be by visualization through a filter, as under a fluorescence microscope. The microscope can provide a signal that is simply visualized by the operator. Alternatively, the signal can be recorded on photographic film or using a video analysis system. The signal also can simply be quantified in real time using either an image analysis system or a photometer.

Thus, for example, a basic assay for protease activity of a sample involves suspending or dissolving the sample in a buffer (at the pH optima of the particular protease being assayed) adding to the buffer a fluorogenic protease peptide indicator, and monitoring the resulting change in fluorescence using a spectrofluorometer as shown in *e.g.*, Harris *et al.*, (1998) *J Biol Chem* 273:27364. The spectrofluorometer is set to excite the fluorophore at the excitation wavelength of the fluorophore. The fluorogenic protease indicator is a substrate sequence of a protease that changes in fluorescence due to a protease cleaving the indicator.

Selected proteases also can be assayed to ascertain that they will cleave the desired sequence when presented in the context of the full-length protein. In one example, a purified target protein, *i.e.* VEGFR2 or complement protein C2, can be incubated in the presence or absence of a selected protease and the cleavage event can be monitored by SDS-PAGE followed by Coomassie Brilliant Blue staining for protein and analysis of cleavage products using densitometry. The specificity constant of cleavage of a full length protein by a protease can be determined by using gel densitometry to assess changes in densitometry over time of a full-length target substrate band incubated in the presence of a protease. In addition, the activity of the target protein also can be assayed using methods well known in the art for assaying the activity of a desired target protein, to verify that its function has been destroyed by the cleavage event.

In specific embodiments, comparison of the specificities of a selected protease, typically a modified protease, can be used to determine if the selected protease exhibits altered, for example, increased, specificity compared to the wild-type or template protease. The specificity of a protease for a target substrate can be measured by observing how many disparate sequences a modified protease cleaves at a given activity compared to a wild-type or template protease. If the modified protease cleaves fewer target substrates than the wildtype protease, the modified protease has greater specificity than the wild-type protease for those target substrates. The specificity of a protease for a target substrate can be determined from the specificity constant of cleavage of a target substrate compared to a non-target substrate (*i.e.* a native wildtype substrate sequence of a protease). A ratio of the specificity constants of a modified protease for a target substrate versus a non-target substrate can be made to determine a ratio of the efficiency of cleavage of the

protease. Comparison of the ratio of the efficiency of cleavage between a modified protease and a wild-type or template protease can be used to assess the fold change in specificity for a target substrate. Specificity can be at least 2-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 times or more when compared to the specificity of a wild-type or template protease for a target substrate versus a non-target substrate.

H. METHODS OF PRODUCING NUCLEIC ACIDS ENCODING PROTEASE TRAP POLYPEPTIDES (*i.e.* SERPINS) OR VARIANTS THEREOF OR PROTEASES/MODIFIED PROTEASES

Polypeptides set forth herein, including protease trap polypeptides or protease polypeptides or catalytically active portions thereof, including modified u-PA polypeptides or modified MT-SP1 polypeptides, can be obtained by methods well known in the art for protein purification and recombinant protein expression. Any method known to those of skill in the art for identification of nucleic acids that encode desired genes can be used. Any method available in the art can be used to obtain a full length (*i.e.*, encompassing the entire coding region) cDNA or genomic DNA clone encoding a desired protease trap polypeptide or protease protein, such as from a cell or tissue source. Modified polypeptides, such as variant protease trap polypeptides or selected variant proteases, can be engineered as described herein from a wildtype polypeptide, such as by site-directed mutagenesis.

Polypeptides can be cloned or isolated using any available methods known in the art for cloning and isolating nucleic acid molecules. Such methods include PCR amplification of nucleic acids and screening of libraries, including nucleic acid hybridization screening, antibody-based screening and activity-based screening.

Methods for amplification of nucleic acids can be used to isolate nucleic acid molecules encoding a desired polypeptide, including for example, polymerase chain reaction (PCR) methods. A nucleic acid containing material can be used as a starting material from which a desired polypeptide-encoding nucleic acid molecule can be isolated. For example, DNA and mRNA preparations, cell extracts, tissue extracts, fluid samples (*e.g.* blood, serum, saliva), samples from healthy and/or diseased subjects can be used in amplification methods. Nucleic acid libraries also can be used as a source of starting material. Primers can be designed to amplify a desired

polypeptide. For example, primers can be designed based on expressed sequences from which a desired polypeptide is generated. Primers can be designed based on back-translation of a polypeptide amino acid sequence. Nucleic acid molecules generated by amplification can be sequenced and confirmed to encode a desired polypeptide.

Additional nucleotide sequences can be joined to a polypeptide-encoding nucleic acid molecule, including linker sequences containing restriction endonuclease sites for the purpose of cloning the synthetic gene into a vector, for example, a protein expression vector or a vector designed for the amplification of the core protein coding DNA sequences. Furthermore, additional nucleotide sequences specifying functional DNA elements can be operatively linked to a polypeptide-encoding nucleic acid molecule. Examples of such sequences include, but are not limited to, promoter sequences designed to facilitate intracellular protein expression, and secretion sequences designed to facilitate protein secretion. Additional nucleotide residues sequences such as sequences of bases specifying protein binding regions also can be linked to protease-encoding nucleic acid molecules. Such regions include, but are not limited to, sequences of residues that facilitate or encode proteins that facilitate uptake of a protease into specific target cells, or otherwise alter pharmacokinetics of a product of a synthetic gene.

In addition, tags or other moieties can be added, for example, to aid in detection or affinity purification of the polypeptide. For example, additional nucleotide residues sequences such as sequences of bases specifying an epitope tag or other detectable marker also can be linked to protease-encoding nucleic acid molecules or to a serpin-encoding nucleic acid molecule, or variants thereof. Exemplary of such sequences and nucleic acid sequences encoding a His tag (e.g., 6xHis, HHHHH; SEQ ID NO:496) or Flag Tag (DYKDDDDK; SEQ ID NO:495).

The identified and isolated nucleic acids can then be inserted into an appropriate cloning vector. A large number of vector-host systems known in the art can be used. Possible vectors include, but are not limited to, plasmids or modified viruses, but the vector system must be compatible with the host cell used. Such vectors include, but are not limited to, bacteriophages such as lambda derivatives, or plasmids such as pCMV4, pBR322 or pUC plasmid derivatives or the Bluescript vector (Stratagene, La Jolla, CA). The insertion into a cloning vector can, for

example, be accomplished by ligating the DNA fragment into a cloning vector which has complementary cohesive termini. Insertion can be effected using TOPO cloning vectors (INVITROGEN, Carlsbad, CA). If the complementary restriction sites used to fragment the DNA are not present in the cloning vector, the ends of the DNA molecules can be enzymatically modified. Alternatively, any site desired can be produced by ligating nucleotide sequences (linkers) onto the DNA termini; these ligated linkers can contain specific chemically synthesized oligonucleotides encoding restriction endonuclease recognition sequences. In an alternative method, the cleaved vector and protein gene can be modified by homopolymeric tailing. Recombinant molecules can be introduced into host cells via, for example, transformation, transfection, infection, electroporation and sonoporation, so that many copies of the gene sequence are generated.

In specific embodiments, transformation of host cells with recombinant DNA molecules that incorporate the isolated protein gene, cDNA, or synthesized DNA sequence enables generation of multiple copies of the gene. Thus, the gene can be obtained in large quantities by growing transformants, isolating the recombinant DNA molecules from the transformants and, when necessary, retrieving the inserted gene from the isolated recombinant DNA.

1. Vectors and cells

For recombinant expression of one or more of the desired proteins, such as any described herein, the nucleic acid containing all or a portion of the nucleotide sequence encoding the protein can be inserted into an appropriate expression vector, *i.e.*, a vector that contains the necessary elements for the transcription and translation of the inserted protein coding sequence. The necessary transcriptional and translational signals also can be supplied by the native promoter for protease genes, and/or their flanking regions.

Also provided are vectors that contain a nucleic acid encoding the protease or modified protease. Cells containing the vectors also are provided. The cells include eukaryotic and prokaryotic cells, and the vectors are any suitable for use therein.

Prokaryotic and eukaryotic cells, including endothelial cells, containing the vectors are provided. Such cells include bacterial cells, yeast cells, fungal cells, Archea, plant cells, insect cells and animal cells. The cells are used to produce a protein thereof by growing the above-described cells under conditions whereby the

encoded protein is expressed by the cell, and recovering the expressed protein. For purposes herein, for example, the protease can be secreted into the medium.

In one embodiment, vectors containing a sequence of nucleotides that encodes a polypeptide that has protease activity, such as encoding any of the u-PA variant polypeptide provided herein, and contains all or a portion of the protease domain, or multiple copies thereof, are provided. Also provided are vectors that contain a sequence of nucleotides that encodes the protease domain and additional portions of a protease protein up to and including a full length protease protein, as well as multiple copies thereof. The vectors can be selected for expression of the modified protease protein or protease domain thereof in the cell or such that the protease protein is expressed as a secreted protein. When the protease domain is expressed, the nucleic acid is linked to a nucleic acid encoding a secretion signal, such as the *Saccharomyces cerevisiae* " mating factor signal sequence or a portion thereof, or the native signal sequence.

A variety of host-vector systems can be used to express the protein coding sequence. These include but are not limited to mammalian cell systems infected with virus (*e.g.* vaccinia virus, adenovirus and other viruses); insect cell systems infected with virus (*e.g.* baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system used, any one of a number of suitable transcription and translation elements can be used.

Any methods known to those of skill in the art for the insertion of DNA fragments into a vector can be used to construct expression vectors containing a chimeric gene containing appropriate transcriptional/translational control signals and protein coding sequences. These methods can include *in vitro* recombinant DNA and synthetic techniques and *in vivo* recombinants (genetic recombination). Expression of nucleic acid sequences encoding protein, or domains, derivatives, fragments or homologs thereof, can be regulated by a second nucleic acid sequence so that the genes or fragments thereof are expressed in a host transformed with the recombinant DNA molecule(s). For example, expression of the proteins can be controlled by any promoter/enhancer known in the art. In a specific embodiment, the promoter is not native to the genes for a desired protein. Promoters which can be used include but are

not limited to the SV40 early promoter (Bernoist and Chambon, *Nature 290*:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al. Cell 22*:787-797 (1980)), the herpes thymidine kinase promoter (Wagner *et al.*, *Proc. Natl. Acad. Sci. USA 78*:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster *et al.*, *Nature 296*:39-42 (1982)); prokaryotic expression vectors such as the β-lactamase promoter (Jay *et al.*, (1981) *Proc. Natl. Acad. Sci. USA 78*:5543) or the *tac* promoter (DeBoer *et al.*, *Proc. Natl. Acad. Sci. USA 80*:21-25 (1983)); see also "Useful Proteins from Recombinant Bacteria": in Scientific American *242*:79-94 (1980)); plant expression vectors containing the nopaline synthetase promoter (Herrar-Estrella *et al.*, *Nature 303*:209-213 (1984)) or the cauliflower mosaic virus 35S RNA promoter (Garder *et al.*, *Nucleic Acids Res. 9*:2871 (1981)), and the promoter of the photosynthetic enzyme ribulose bisphosphate carboxylase (Herrera-Estrella *et al.*, *Nature 310*:115-120 (1984)); promoter elements from yeast and other fungi such as the Gal4 promoter, the alcohol dehydrogenase promoter, the phosphoglycerol kinase promoter, the alkaline phosphatase promoter, and the following animal transcriptional control regions that exhibit tissue specificity and have been used in transgenic animals: elastase I gene control region which is active in pancreatic acinar cells (Swift *et al.*, *Cell 38*:639-646 (1984); Ornitz *et al.*, *Cold Spring Harbor Symp. Quant. Biol. 50*:399-409 (1986); MacDonald, *Hepatology 7*:425-515 (1987)); insulin gene control region which is active in pancreatic beta cells (Hanahan *et al.*, *Nature 315*:115-122 (1985)), immunoglobulin gene control region which is active in lymphoid cells (Grosschedl *et al.*, *Cell 38*:647-658 (1984); Adams *et al.*, *Nature 318*:533-538 (1985); Alexander *et al.*, *Mol. Cell Biol. 7*:1436-1444 (1987)), mouse mammary tumor virus control region which is active in testicular, breast, lymphoid and mast cells (Leder *et al.*, *Cell 45*:485-495 (1986)), albumin gene control region which is active in liver (Pinckert *et al.*, *Genes and Devel. 1*:268-276 (1987)), alpha-fetoprotein gene control region which is active in liver (Krumlauf *et al.*, *Mol. Cell. Biol. 5*:1639-1648 (1985); Hammer *et al.*, *Science 235*:53-58 1987)), alpha-1 antitrypsin gene control region which is active in liver (Kelsey *et al.*, *Genes and Devel. 1*:161-171 (1987)), beta globin gene control region which is active in myeloid cells (Mogram *et al.*, *Nature 315*:338-340 (1985); Kollias *et al.*, *Cell 46*:89-94 (1986)), myelin basic protein gene control region which

is active in oligodendrocyte cells of the brain (Readhead *et al.*, *Cell 48*:703-712 (1987)), myosin light chain-2 gene control region which is active in skeletal muscle (Sani, *Nature 314*:283-286 (1985)), and gonadotrophic releasing hormone gene control region which is active in gonadotrophs of the hypothalamus (Mason *et al.*, *Science 234*:1372-1378 (1986)).

In a specific embodiment, a vector is used that contains a promoter operably linked to nucleic acids encoding a desired protein, or a domain, fragment, derivative or homolog, thereof, one or more origins of replication, and optionally, one or more selectable markers (*e.g.*, an antibiotic resistance gene). For example, vectors and systems for expression of the protease domains of the protease proteins include the well known *Pichia* vectors (available, for example, from Invitrogen, San Diego, CA), particularly those designed for secretion of the encoded proteins. Exemplary plasmid vectors for transformation of *E.coli* cells, include, for example, the pQE expression vectors (available from Qiagen, Valencia, CA; see also literature published by Qiagen describing the system). pQE vectors have a phage T5 promoter (recognized by *E. coli* RNA polymerase) and a double lac operator repression module to provide tightly regulated, high-level expression of recombinant proteins in *E. coli,* a synthetic ribosomal binding site (RBS II) for efficient translation, a 6XHis tag coding sequence, t_0 and T1 transcriptional terminators, ColE1 origin of replication, and a beta-lactamase gene for conferring ampicillin resistance. The pQE vectors enable placement of a 6xHis tag at either the N- or C-terminus of the recombinant protein. Such plasmids include pQE 32, pQE 30, and pQE 31 which provide multiple cloning sites for all three reading frames and provide for the expression of N-terminally 6xHis-tagged proteins. Other exemplary plasmid vectors for transformation of *E. coli* cells, include, for example, the pET expression vectors (see, U.S patent 4,952,496; available from NOVAGEN, Madison, WI; see, also literature published by Novagen describing the system). Such plasmids include pET 11a, which contains the T7lac promoter, T7 terminator, the inducible *E. coli* lac operator, and the lac repressor gene; pET 12a-c, which contains the T7 promoter, T7 terminator, and the *E. coli* ompT secretion signal; and pET 15b and pET19b (NOVAGEN, Madison, WI), which contain a His-Tag™ leader sequence for use in purification with a His column and a thrombin cleavage site that permits cleavage following purification over the column, the T7-lac promoter region and the T7 terminator.

2. Expression

Proteins, such as any set forth herein including any protease trap polypeptides or variants thereof, or selected proteases or catalytically active portions thereof, can be produced by any method known to those of skill in the art including *in vivo* and *in vitro* methods. Desired proteins can be expressed in any organism suitable to produce the required amounts and forms of the proteins, such as for example, needed for administration and treatment. Expression hosts include prokaryotic and eukaryotic organisms such as *E.coli*, yeast, plants, insect cells, mammalian cells, including human cell lines and transgenic animals. Expression hosts can differ in their protein production levels as well as the types of post-translational modifications that are present on the expressed proteins. The choice of expression host can be made based on these and other factors, such as regulatory and safety considerations, production costs and the need and methods for purification.

Many expression vectors are available and known to those of skill in the art and can be used for expression of proteins. The choice of expression vector will be influenced by the choice of host expression system. In general, expression vectors can include transcriptional promoters and optionally enhancers, translational signals, and transcriptional and translational termination signals. Expression vectors that are used for stable transformation typically have a selectable marker which allows selection and maintenance of the transformed cells. In some cases, an origin of replication can be used to amplify the copy number of the vector.

Proteins, such as for example any variant protease provided herein or any protease trap polypeptide or variant thereof, also can be utilized or expressed as protein fusions. For example, a protease fusion can be generated to add additional functionality to a protease. Examples of protease fusion proteins include, but are not limited to, fusions of a signal sequence, a tag such as for localization, *e.g.* a his_6 tag or a myc tag, or a tag for purification, for example, a GST fusion, and a sequence for directing protein secretion and/or membrane association.

In one embodiment, a protease can be expressed in an active form. In another embodiment, a protease is expressed in an inactive, zymogen form. **a. Prokaryotic Cells**

Prokaryotes, especially *E.coli*, provide a system for producing large amounts of proteins. Transformation of *E.coli* is simple and rapid technique well known to

those of skill in the art. Expression vectors for *E.coli* can contain inducible promoters, such promoters are useful for inducing high levels of protein expression and for expressing proteins that exhibit some toxicity to the host cells. Examples of inducible promoters include the lac promoter, the trp promoter, the hybrid tac promoter, the T7 and SP6 RNA promoters and the temperature regulated λPL promoter.

Proteins, such as any provided herein, can be expressed in the cytoplasmic environment of *E.coli*. The cytoplasm is a reducing environment and for some molecules, this can result in the formation of insoluble inclusion bodies. Reducing agents such as dithiothreotol and β-mercaptoethanol and denaturants, such as guanidine-HCl and urea can be used to resolubilize the proteins. An alternative approach is the expression of proteins in the periplasmic space of bacteria which provides an oxidizing environment and chaperonin-like and disulfide isomerases and can lead to the production of soluble protein. Typically, a leader sequence is fused to the protein to be expressed which directs the protein to the periplasm. The leader is then removed by signal peptidases inside the periplasm. Examples of periplasmic-targeting leader sequences include the pelB leader from the pectate lyase gene and the leader derived from the alkaline phosphatase gene. In some cases, periplasmic expression allows leakage of the expressed protein into the culture medium. The secretion of proteins allows quick and simple purification from the culture supernatant. Proteins that are not secreted can be obtained from the periplasm by osmotic lysis. Similar to cytoplasmic expression, in some cases proteins can become insoluble and denaturants and reducing agents can be used to facilitate solubilization and refolding. Temperature of induction and growth also can influence expression levels and solubility, typically temperatures between 25°C and 37°C are used. Typically, bacteria produce aglycosylated proteins. Thus, if proteins require glycosylation for function, glycosylation can be added *in vitro* after purification from host cells.

b. Yeast Cells

Yeasts such as *Saccharomyces cerevisae, Schizosaccharomyces pombe, Yarrowia lipolytica, Kluyveromyces lactis* and *Pichia pastoris* are well known yeast expression hosts that can be used for production of proteins, such as any described herein. Yeast can be transformed with episomal replicating vectors or by stable

chromosomal integration by homologous recombination. Typically, inducible promoters are used to regulate gene expression. Examples of such promoters include GAL1, GAL7 and GAL5 and metallothionein promoters, such as CUP1, AOX1 or other *Pichia* or other yeast promoter. Expression vectors often include a selectable marker such as LEU2, TRP1, HIS3 and URA3 for selection and maintenance of the transformed DNA. Proteins expressed in yeast are often soluble. Co-expression with chaperonins such as Bip and protein disulfide isomerase can improve expression levels and solubility. Additionally, proteins expressed in yeast can be directed for secretion using secretion signal peptide fusions such as the yeast mating type alpha-factor secretion signal from Saccharomyces cerevisae and fusions with yeast cell surface proteins such as the Aga2p mating adhesion receptor or the *Arxula adeninivorans* glucoamylase. A protease cleavage site such as for the Kex-2 protease, can be engineered to remove the fused sequences from the expressed polypeptides as they exit the secretion pathway. Yeast also is capable of glycosylation at Asn-X-Ser/Thr motifs.

c. Insect Cells

Insect cells, particularly using baculovirus expression, are useful for expressing polypeptides such as modified proteases or modified protease trap polypeptides. Insect cells express high levels of protein and are capable of most of the post-translational modifications used by higher eukaryotes. Baculovirus have a restrictive host range which improves the safety and reduces regulatory concerns of eukaryotic expression. Typical expression vectors use a promoter for high level expression such as the polyhedrin promoter of baculovirus. Commonly used baculovirus systems include the baculoviruses such as *Autographa californica* nuclear polyhedrosis virus (AcNPV), and the *bombyx mori* nuclear polyhedrosis virus (BmNPV) and an insect cell line such as Sf9 derived from *Spodoptera frugiperda, Pseudaletia unipuncta* (A7S) and *Danaus plexippus* (DpN1). For high-level expression, the nucleotide sequence of the molecule to be expressed is fused immediately downstream of the polyhedrin initiation codon of the virus. Mammalian secretion signals are accurately processed in insect cells and can be used to secrete the expressed protein into the culture medium. In addition, the cell lines *Pseudaletia unip*uncta (A7S) and *Danaus plexippus* (DpN1) produce proteins with glycosylation patterns similar to mammalian cell systems.

An alternative expression system in insect cells is the use of stably transformed cells. Cell lines such as the Schnieder 2 (S2) and Kc cells (*Drosophila melanogaster*) and C7 cells (*Aedes albo*pictus) can be used for expression. The *Drosophila* metallothionein promoter can be used to induce high levels of expression in the presence of heavy metal induction with cadmium or copper. Expression vectors are typically maintained by the use of selectable markers such as neomycin and hygromycin.

d. Mammalian Cells

Mammalian expression systems can be used to express proteins including modified proteases or catalytically active portions thereof, or protease trap polypeptides or variants thereof. Expression constructs can be transferred to mammalian cells by viral infection such as adenovirus or by direct DNA transfer such as liposomes, calcium phosphate, DEAE-dextran and by physical means such as electroporation and microinjection. Expression vectors for mammalian cells typically include an mRNA cap site, a TATA box, a translational initiation sequence (Kozak consensus sequence) and polyadenylation elements. Such vectors often include transcriptional promoter-enhancers for high-level expression, for example the SV40 promoter-enhancer, the human cytomegalovirus (CMV) promoter and the long terminal repeat of Rous sarcoma virus (RSV). These promoter-enhancers are active in many cell types. Tissue and cell-type promoters and enhancer regions also can be used for expression. Exemplary promoter/enhancer regions include, but are not limited to, those from genes such as elastase I, insulin, immunoglobulin, mouse mammary tumor virus, albumin, alpha fetoprotein, alpha 1 antitrypsin, beta globin, myelin basic protein, myosin light chain 2, and gonadotropic releasing hormone gene control. Selectable markers can be used to select for and maintain cells with the expression construct. Examples of selectable marker genes include, but are not limited to, hygromycin B phosphotransferase, adenosine deaminase, xanthine-guanine phosphoribosyl transferase, aminoglycoside phosphotransferase, dihydrofolate reductase and thymidine kinase. Fusion with cell surface signaling molecules such as TCR-ζ and $Fc_{\varepsilon}RI$-γ can direct expression of the proteins in an active state on the cell surface.

Many cell lines are available for mammalian expression including mouse, rat human, monkey, chicken and hamster cells. Exemplary cell lines include but are not

limited to CHO, Balb/3T3, HeLa, MT2, mouse NS0 (nonsecreting) and other myeloma cell lines, hybridoma and heterohybridoma cell lines, lymphocytes, fibroblasts, Sp2/0, COS, NIH3T3, HEK293, 293S, 2B8, and HKB cells. Cell lines also are available adapted to serum-free media which facilitates purification of secreted proteins from the cell culture media. One such example is the serum free EBNA-1 cell line (Pham *et al.*, (2003) *Biotechnol. Bioeng. 84*:332-42.)

e. Plants

Transgenic plant cells and plants can be used to express proteins such as any described herein. Expression constructs are typically transferred to plants using direct DNA transfer such as microprojectile bombardment and PEG-mediated transfer into protoplasts, and with agrobacterium-mediated transformation. Expression vectors can include promoter and enhancer sequences, transcriptional termination elements and translational control elements. Expression vectors and transformation techniques are usually divided between dicot hosts, such as *Arabidopsis* and tobacco, and monocot hosts, such as corn and rice. Examples of plant promoters used for expression include the cauliflower mosaic virus promoter, the nopaline syntase promoter, the ribose bisphosphate carboxylase promoter and the ubiquitin and UBQ3 promoters. Selectable markers such as hygromycin, phosphomannose isomerase and neomycin phosphotransferase are often used to facilitate selection and maintenance of transformed cells. Transformed plant cells can be maintained in culture as cells, aggregates (callus tissue) or regenerated into whole plants. Transgenic plant cells also can include algae engineered to produce proteases or modified proteases (see for example, Mayfield *et al.* (2003) *PNAS 100*:438-442). Because plants have different glycosylation patterns than mammalian cells, this can influence the choice of protein produced in these hosts.

3. Purification Techniques

Method for purification of polypeptides, including protease polypeptides or other proteins, from host cells will depend on the chosen host cells and expression systems. For secreted molecules, proteins are generally purified from the culture media after removing the cells. For intracellular expression, cells can be lysed and the proteins purified from the extract. When transgenic organisms such as transgenic plants and animals are used for expression, tissues or organs can be used as starting material to make a lysed cell extract. Additionally, transgenic animal production can

include the production of polypeptides in milk or eggs, which can be collected, and if necessary, the proteins can be extracted and further purified using standard methods in the art.

In one example, proteases can be expressed and purified to be in an inactive form (zymogen form) or alternatively the expressed protease can be purified into an active form, such as a two-chain form, by autocatalysis to remove the proregion. Typically, the autoactivation occurs during the purification process, such as by incubating at room temperature for 24-72 hours. The rate and degree of activation is dependent on protein concentration and the specific modified protease, such that for example, a more dilute sample can need to be incubated at room temperature for a longer period of time. Activation can be monitored by SDS-PAGE (*e.g.*, a 3 kilodalton shift) and by enzyme activity (cleavage of a fluorogenic substrate). Typically, a protease is allowed to achieve >75% activation before purification.

Proteins, such as proteases or protease-trap polypeptides, can be purified using standard protein purification techniques known in the art including but not limited to, SDS-PAGE, size fraction and size exclusion chromatography, ammonium sulfate precipitation and ionic exchange chromatography, such as anion exchange. Affinity purification techniques also can be utilized to improve the efficiency and purity of the preparations. For example, antibodies, receptors and other molecules that bind proteases or protease trap polypeptides can be used in affinity purification. Expression constructs also can be engineered to add an affinity tag to a protein such as a myc epitope, GST fusion or His_6 and affinity purified with myc antibody, glutathione resin and Ni-resin, respectively. Purity can be assessed by any method known in the art including gel electrophoresis and staining and spectrophotometric techniques.

4. Fusion Proteins

Fusion proteins containing a variant protease provided herein and one or more other polypeptides also are provided. Pharmaceutical compositions containing such fusion proteins formulated for administration by a suitable route are provided. Fusion proteins are formed by linking in any order the modified protease and another polypeptide, such as an antibody or fragment thereof, growth factor, receptor, ligand and other such agent for the purposes of facilitating the purification of a protease,

altering the pharmacodynamic properties of a protease by directing the protease to a targeted cell or tissue, and/or increasing the expression or secretion of a protease. Within a protease fusion protein, the protease polypeptide can correspond to all or a catalytically active portion thereof of a protease protein. In some embodiments, the protease or catalytically active portion thereof is a modified protease. Fusion proteins provided herein retain substantially all of their specificity and/or selectivity for any one or more of the desired target substrates. Generally, protease fusion polypeptides retain at least about 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90% or 95% substrate specificity and/or selectivity compared with a non-fusion protease, including 96%, 97%, 98%, 99% or greater substrate specificity compared with a non-fusion protease.

Linkage of a protease polypeptide and another polypeptide can be effected directly or indirectly via a linker. In one example, linkage can be by chemical linkage, such as via heterobifunctional agents or thiol linkages or other such linkages. Fusion of a protease to another polypeptide can be to the N- or C- terminus of the protease polypeptide. Non-limiting examples of polypeptides that can be used in fusion proteins with a protease provided herein include, for example, a GST (glutathione S-transferase) polypeptide, Fc domain from an immunoglobulin, or a heterologous signal sequence. The fusion proteins can contain additional components, such as *E. coli* maltose binding protein (MBP) that aid in uptake of the protein by cells (*see*, International PCT application No. WO 01/32711).

A protease fusion protein can be produced by standard recombinant techniques. For example, DNA fragments coding for the different polypeptide sequences can be ligated together in-frame in accordance with conventional techniques, *e.g.*, by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, *e.g.*, Ausubel *et al.* (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially

available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A protease-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the protease protein.

5. Nucleotide Sequences

Nucleic acid molecules encoding modified proteases are provided herein. Nucleic acid molecules include allelic variants or splice variants of any encoded protease, or catalytically active portion thereof. In one embodiment, nucleic acid molecules provided herein have at least 50, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, or 99% sequence identity or hybridize under conditions of medium or high stringency along at least 70% of a full-length of any nucleic acid encoded wild-type protease, or catalytically active portion thereof. In another embodiment, a nucleic acid molecule can include those with degenerate codon sequences of any of the proteases or catalytically active portions thereof such as those provided herein.

Nucleic acid molecules, or fusion proteins containing a catalytically active portion of a nucleic acid molecule, operably-linked to a promoter, such as an inducible promoter for expression in mammalian cells also are provided. Such promoters include, but are not limited to, CMV and SV40 promoters; adenovirus promoters, such as the E2 gene promoter, which is responsive to the HPV E7 oncoprotein; a PV promoter, such as the PBV p89 promoter that is responsive to the PV E2 protein; and other promoters that are activated by the HIV or PV or oncogenes.

Modified proteases provided herein, also can be delivered to the cells in gene transfer vectors. The transfer vectors also can encode additional other therapeutic agent(s) for treatment of the disease or disorder, such as coagulation disorders or cancer, for which the protease is administered. Transfer vectors encoding a protease can be used systemically, by administering the nucleic acid to a subject. For example, the transfer vector can be a viral vector, such as an adenovirus vector. Vectors encoding a protease also can be incorporated into stem cells and such stem cells administered to a subject such as by transplanting or engrafting the stem cells at sites for therapy. For example, mesenchymal stem cells (MSCs) can be engineered to express a protease and such MSCs engrafted at a tumor site for therapy.

I. PREPARATION, FORMULATION AND ADMINISTRATION OF SELECTED PROTEASE POLYPEPTIDES

1. Compositions and Delivery

Compositions of selected proteases, such as for example selected mutant u-PA polypeptides, can be formulated for administration by any route known to those of skill in the art including intramuscular, intravenous, intradermal, intraperitoneal injection, subcutaneous, epidural, nasal, oral, rectal, topical, inhalational, buccal (*e.g.*, sublingual), and transdermal administration or any route. Selected proteases can be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and can be administered with other biologically active agents, either sequentially, intermittently or in the same composition. Administration can be local, topical or systemic depending upon the locus of treatment. Local administration to an area in need of treatment can be achieved by, for example, but not limited to, local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant. Administration also can include controlled release systems including controlled release formulations and device controlled release, such as by means of a pump. The most suitable route in any given case depends on a variety of factors, such as the nature of the disease, the progress of the disease, the severity of the disease the particular composition which is used.

Various delivery systems are known and can be used to administer selected proteases, such as but not limited to, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor mediated endocytosis, and delivery of nucleic acid molecules encoding selected proteases such as retrovirus delivery systems.

Pharmaceutical compositions containing selected proteases can be prepared. Generally, pharmaceutically acceptable compositions are prepared in view of approvals for a regulatory agency or other agency prepared in accordance with generally recognized pharmacopeia for use in animals and in humans. Pharmaceutical compositions can include carriers such as a diluent, adjuvant, excipient, or vehicle with which an isoform is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, and sesame oil. Water is a typical carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions also can be employed as

liquid carriers, particularly for injectable solutions. Compositions can contain along with an active ingredient: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acaciagelatin, glucose, molasses, polvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, and ethanol. A composition, if desired, also can contain minor amounts of wetting or emulsifying agents, or pH buffering agents, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, and sustained release formulations. A composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and other such agents. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the compound, generally in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

Formulations are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. Pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit dosage forms or multiple dosage forms. Each unit dose contains a predetermined quantity of therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit dose forms include ampoules and syringes and individually packaged tablets or

capsules. Unit dose forms can be administered in fractions or multiples thereof. A multiple dose form is a plurality of identical unit dosage forms packaged in a single container to be administered in segregated unit dose form. Examples of multiple dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit doses that are not segregated in packaging.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier can be prepared. For oral administration, pharmaceutical compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinized maize starch, polyvinyl pyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets can be coated by methods well-known in the art.

Pharmaceutical preparation also can be in liquid form, for example, solutions, syrups or suspensions, or can be presented as a drug product for reconstitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid).

Formulations suitable for rectal administration can be provided as unit dose suppositories. These can be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin or to the eye include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Exemplary carriers include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The topical formulations also can contain 0.05 to 15, 20, 25 percent by weight of thickeners selected from among hydroxypropyl methyl cellulose, methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, poly (alkylene glycols),

poly/hydroxyalkyl, (meth)acrylates or poly(meth)acrylamides. A topical formulation is often applied by instillation or as an ointment into the conjunctival sac. It also can be used for irrigation or lubrication of the eye, facial sinuses, and external auditory meatus. It also can be injected into the anterior eye chamber and other places. A topical formulation in the liquid state also can be present in a hydrophilic three-dimensional polymer matrix in the form of a strip or contact lens, from which the active components are released.

For administration by inhalation, the compounds for use herein can be delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin, for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Formulations suitable for buccal (sublingual) administration include, for example, lozenges containing the active compound in a flavored base, usually sucrose and acacia or tragacanth; and pastilles containing the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions of selected proteases can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampules or in multi-dose containers, with an added preservative. The compositions can be suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for reconstitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water or other solvents, before use.

Formulations suitable for transdermal administration are provided. They can be provided in any suitable format, such as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches contain the active compound in optionally buffered aqueous solution of, for example, 0.1 to 0.2M concentration with respect to the active compound. Formulations suitable for transdermal administration also can be delivered by

iontophoresis (see, *e.g.*, *Pharmaceutical Research 3(6)*, 318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound.

Pharmaceutical compositions also can be administered by controlled release formulations and/or delivery devices (see, *e.g.*, in U.S. Patent Nos. 3,536,809; 3,598,123; 3,630,200; 3,845,770; 3,847,770; 3,916,899; 4,008,719; 4,687,610; 4,769,027; 5,059,595; 5,073,543; 5,120,548; 5,354,566; 5,591,767; 5,639,476; 5,674,533 and 5,733,566).

In certain embodiments, liposomes and/or nanoparticles also can be employed with selected protease administration. Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)). MLVs generally have diameters of from 25 nm to 4 μm. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 angstroms containing an aqueous solution in the core.

Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios, the liposomes form. Physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

Liposomes interact with cells via different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. Varying the liposome formulation can alter which mechanism is operative, although more than one can

operate at the same time. Nanocapsules can generally entrap compounds in a stable and reproducible way. To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use herein, and such particles can be easily made.

Administration methods can be employed to decrease the exposure of selected proteases to degradative processes, such as proteolytic degradation and immunological intervention via antigenic and immunogenic responses. Examples of such methods include local administration at the site of treatment. Pegylation of therapeutics has been reported to increase resistance to proteolysis, increase plasma half-life, and decrease antigenicity and immunogenicity. Examples of pegylation methodologies are known in the art (see for example, Lu and Felix, *Int. J. Peptide Protein Res., 43*: 127-138, 1994; Lu and Felix, *Peptide Res., 6:* 142-6, 1993; Felix *et al., Int. J. Peptide Res., 46* : 253-64, 1995; Benhar *et al., J. Biol. Chem., 269*: 13398-404, 1994; Brumeanu *et al., J Immunol., 154*: 3088-95, 1995; see also, Caliceti *et al.* (2003) *Adv. Drug Deliv. Rev. 55(10)*:1261-77 and Molineux (2003) *Pharmacotherapy 23 (8 Pt 2)*:3S-8S). Pegylation also can be used in the delivery of nucleic acid molecules *in vivo*. For example, pegylation of adenovirus can increase stability and gene transfer (see, e.g., Cheng *et al.* (2003) *Pharm. Res. 20(9)*: 1444-51).

Desirable blood levels can be maintained by a continuous infusion of the active agent as ascertained by plasma levels. It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust therapy to lower dosage due to toxicity, or bone marrow, liver or kidney dysfunctions. Conversely, the attending physician would also know how to and when to adjust treatment to higher levels if the clinical response is not adequate (precluding toxic side effects).

Pharmaceutical compositions can be administered, for example, by oral, pulmonary, parental (intramuscular, intraperitoneal, intravenous (IV) or subcutaneous injection), inhalation (via a fine powder formulation), transdermal, nasal, vaginal, rectal, or sublingual routes of administration and can be formulated in dosage forms appropriate for each route of administration (see, *e.g.*, International PCT application Nos. WO 93/25221 and WO 94/17784; and European Patent Application 613,683).

A selected protease is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. Therapeutically effective concentration can be determined empirically by testing the compounds in known *in vitro* and *in vivo* systems, such as the assays provided herein.

The concentration of a selected protease in the composition depends on absorption, inactivation and excretion rates of the complex, the physicochemical characteristics of the complex, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. The amount of a selected protease to be administered for the treatment of a disease or condition, for example cancer or angiogenesis treatment can be determined by standard clinical techniques. In addition, *in vitro* assays and animal models can be employed to help identify optimal dosage ranges. The precise dosage, which can be determined empirically, can depend on the route of administration and the seriousness of the disease.

A selected protease can be administered at once, or can be divided into a number of smaller doses to be administered at intervals of time. Selected proteases can be administered in one or more doses over the course of a treatment time for example over several hours, days, weeks, or months. In some cases, continuous administration is useful. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and can be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values also can vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or use of compositions and combinations containing them. The compositions can be administered hourly, daily, weekly, monthly, yearly or once. The mode of administration of the composition containing the polypeptides as well as compositions containing nucleic acids for gene therapy, includes, but is not limited to intralesional, intraperitoneal, intramuscular and intravenous administration. Also included are infusion, intrathecal, subcutaneous, liposome-mediated, depot-mediated

administration. Also included, are nasal, ocular, oral, topical, local and otic delivery. Dosages can be empirically determined and depend upon the indication, mode of administration and the subject. Exemplary dosages include from 0.1, 1, 10, 100, 200 and more mg/day/kg weight of the subject.

2. *In vivo* Expression of Selected Proteases and Gene Therapy

Selected proteases can be delivered to cells and tissues by expression of nucleic acid molecules. Selected proteases can be administered as nucleic acid molecules encoding a selected protease, including *ex vivo* techniques and direct *in vivo* expression.

a. Delivery of Nucleic Acids

Nucleic acids can be delivered to cells and tissues by any method known to those of skill in the art.

i. Vectors – Episomal and Integrating

Methods for administering selected proteases by expression of encoding nucleic acid molecules include administration of recombinant vectors. The vector can be designed to remain episomal, such as by inclusion of an origin of replication or can be designed to integrate into a chromosome in the cell. Recombinant vectors can include viral vectors and non-viral vectors. Non-limiting viral vectors include, for example, adenoviral vector, herpes virus vectors, retroviral vectors, and any other viral vector known to one of skill in the art. Non-limiting non-viral vectors include artificial chromosomes or liposomes or other non-viral vector. Selected proteases also can be used in *ex vivo* gene expression therapy using viral and non-viral vectors. For example, cells can be engineered to express a selected protease, such as by integrating a selected protease encoding-nucleic acid into a genomic location, either operatively linked to regulatory sequences or such that it is placed operatively linked to regulatory sequences in a genomic location. Such cells then can be administered locally or systemically to a subject, such as a patient in need of treatment.

A selected protease can be expressed by a virus, which is administered to a subject in need of treatment. Virus vectors suitable for gene therapy include adenovirus, adeno-associated virus, retroviruses, lentiviruses and others noted above. For example, adenovirus expression technology is well-known in the art and adenovirus production and administration methods also are well known. Adenovirus serotypes are available, for example, from the American Type Culture Collection

(ATCC, Rockville, MD). Adenovirus can be used *ex vivo*, for example, cells are isolated from a patient in need of treatment, and transduced with a selected protease-expressing adenovirus vector. After a suitable culturing period, the transduced cells are administered to a subject, locally and/or systemically. Alternatively, selected protease-expressing adenovirus particles are isolated and formulated in a pharmaceutically-acceptable carrier for delivery of a therapeutically effective amount to prevent, treat or ameliorate a disease or condition of a subject. Typically, adenovirus particles are delivered at a dose ranging from 1 particle to 1014 particles per kilogram subject weight, generally between 106 or 108 particles to 1012 particles per kilogram subject weight. In some situations it is desirable to provide a nucleic acid source with an agent that targets cells, such as an antibody specific for a cell surface membrane protein or a target cell, or a ligand for a receptor on a target cell.

ii. Artificial Chromosomes and Other Non-viral Vector Delivery Methods

The nucleic acid molecules can be introduced into artificial chromosomes and other non-viral vectors. Artificial chromosomes (see, *e.g.*, U.S. Patent No. 6,077,697 and PCT International PCT application No. WO 02/097059) can be engineered to encode and express the isoform.

iii. Liposomes and Other Encapsulated Forms and Administration of Cells Containing Nucleic Acids

The nucleic acids can be encapsulated in a vehicle, such as a liposome, or introduced into cells, such as a bacterial cell, particularly an attenuated bacterium or introduced into a viral vector. For example, when liposomes are employed, proteins that bind to a cell surface membrane protein associated with endocytosis can be used for targeting and/or to facilitate uptake, *e.g.* capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, and proteins that target intracellular localization and enhance intracellular half-life.

b. *In vitro* and *Ex vivo* Delivery

For *ex vivo* and *in vivo* methods, nucleic acid molecules encoding the selected protease is introduced into cells that are from a suitable donor or the subject to be treated. Cells into which a nucleic acid can be introduced for purposes of therapy

include, for example, any desired, available cell type appropriate for the disease or condition to be treated, including but not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, *e.g.*, such as stem cells obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, and other sources thereof.

For *ex vivo* treatment, cells from a donor compatible with the subject to be treated, or cells from the subject to be treated, are removed, the nucleic acid is introduced into these isolated cells and the modified cells are administered to the subject. Treatment includes direct administration, such as or, for example, encapsulated within porous membranes, which are implanted into the patient (see, e.g. U.S. Pat. Nos. 4,892,538 and 5,283,187). Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes and cationic lipids (e.g., DOTMA, DOPE and DC-Chol) electroporation, microinjection, cell fusion, DEAE-dextran, and calcium phosphate precipitation methods. Methods of DNA delivery can be used to express selected proteases *in vivo*. Such methods include liposome delivery of nucleic acids and naked DNA delivery, including local and systemic delivery such as using electroporation, ultrasound and calcium-phosphate delivery. Other techniques include microinjection, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer and spheroplast fusion.

In vivo expression of a selected protease can be linked to expression of additional molecules. For example, expression of a selected protease can be linked with expression of a cytotoxic product such as in an engineered virus or expressed in a cytotoxic virus. Such viruses can be targeted to a particular cell type that is a target for a therapeutic effect. The expressed selected protease can be used to enhance the cytotoxicity of the virus.

In vivo expression of a selected protease can include operatively linking a selected protease encoding nucleic acid molecule to specific regulatory sequences such as a cell-specific or tissue-specific promoter. Selected proteases also can be expressed from vectors that specifically infect and/or replicate in target cell types

and/or tissues. Inducible promoters can be used to selectively regulate selected protease expression.

c. Systemic, Local and Topical Delivery

Nucleic acid molecules, as naked nucleic acids or in vectors, artificial chromosomes, liposomes and other vehicles can be administered to the subject by systemic administration, topical, local and other routes of administration. When systemic and *in vivo*, the nucleic acid molecule or vehicle containing the nucleic acid molecule can be targeted to a cell.

Administration also can be direct, such as by administration of a vector or cells that typically targets a cell or tissue. For example, tumor cells and proliferating cells can be targeted cells for *in vivo* expression of selected proteases. Cells used for *in vivo* expression of an isoform also include cells autologous to the patient. Such cells can be removed from a patient, nucleic acids for expression of a selected protease introduced, and then administered to a patient such as by injection or engraftment.

2. Combination Therapies

Any of the selected protease polypeptides, and nucleic acid molecules encoding selected protease polypeptides described herein can be administered in combination with, prior to, intermittently with, or subsequent to, other therapeutic agents or procedures including, but not limited to, other biologics, small molecule compounds and surgery. For any disease or condition, including all those exemplified above, for which other agents and treatments are available, selected protease polypeptides for such diseases and conditions can be used in combination therewith. For example, selected protease polypeptides provided herein for the treatment of a proliferative disease for example, cancer, can be administered in combination with, prior to, intermittently with, or subsequent to, other anti-cancer therapeutic agents, for example chemotherapeutic agents, radionuclides, radiation therapy, cytokines, growth factors, photosensitizing agents, toxins, anti-metabolites, signaling modulators, anti-cancer antibiotics, anti-cancer antibodies, angiogenesis inhibitors, or a combination thereof. In a specific example, selected protease polypeptides provided herein for the treatment of thrombotic diseases can be administered in combination with, prior to, intermittently with, or subsequent to, other anticoagulant agents including, but not limited to, platelet inhibitors, vasodilators, fibrolytic activators, or other

anticoagulants. Exemplary anticoagulants include heparin, coumarin, hirudin, aspirin, naproxen, meclofenamic acid, ibuprofen, indomethacin, phenylbutazare, ticlopidine, streptokinase, urokinase, and tissue plasminogen activator.

3. Articles of Manufacture and Kits

Pharmaceutical compounds of selected protease polypeptides for nucleic acids encoding selected protease polypeptides, or a derivative or a biologically active portion thereof can be packaged as articles of manufacture containing packaging material, a pharmaceutical composition which is effective for treating the disease or disorder, and a label that indicates that selected protease polypeptide or nucleic acid molecule is to be used for treating the disease or disorder.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, for example, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252, each of which is incorporated herein in its entirety. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any target-mediated disease or disorder.

Selected protease polypeptides and nucleic acid molecules also can be provided as kits. Kits can include a pharmaceutical composition described herein and an item for administration. For example a selected protease can be supplied with a device for administration, such as a syringe, an inhaler, a dosage cup, a dropper, or an applicator. The kit can, optionally, include instructions for application including dosages, dosing regimens and instructions for modes of administration. Kits also can include a pharmaceutical composition described herein and an item for diagnosis. For example, such kits can include an item for measuring the concentration, amount or activity of the selected protease in a subject.

J. EXEMPLARY METHODS OF TREATMENT WITH SELECTED PROTEASE POLYPEPTIDES

The selected protease polypeptides provided herein that cleave particular targets and nucleic acid molecules that encode the selected proteases provided herein

can be used for treatment of any disease or condition associated with a protein containing the target sequence or for which a protease that cleaves the target sequence is employed. For example, selected uPA polypeptides engineered to cleave tPA target substrates, such as plasminogen, can be used for treatment of any disease or condition associated with the tPA target substrate or for which tPA polypeptides are employed. Exemplary diseases associated with a tPA target substrate include thrombolytic diseases where treatment with a selected protease provided herein can promote cleavage of plasminogen to its active protease form plasmin, and induce dissolution of a blot clot.

Selected protease polypeptides have therapeutic activity alone or in combination with other agents. The selected protease polypeptides provided herein are designed to exhibit improved properties over competing binding proteins. Such properties, for example, can improve the therapeutic effectiveness of the polypeptides. This section provides exemplary uses of and administration methods. These described therapies are exemplary and do not limit the applications of selected protease polypeptides.

The selected protease polypeptides provided herein can be used in various therapeutic as well as diagnostic methods that are associated with a protein containing the target sequence. Such methods include, but are not limited to, methods of treatment of physiological and medical conditions described and listed below. Selected protease polypeptides provided herein can exhibit improvement of *in vivo* activities and therapeutic effects compared to competing binding proteins or a protease that cleaves the particular target, including lower dosage to achieve the same effect, a more sustained therapeutic effect and other improvements in administration and treatment. Examples of therapeutic improvements using selected protease polypeptides include, but are not limited to, better target tissue penetration (*e.g.* tumor penetration), higher effectiveness, lower dosages, fewer and/or less frequent administrations, decreased side effects and increased therapeutic effects. Notably, because the selected proteases can cleave and inactivate high numbers of the target substrate, the selected proteases offer substantial therapeutic amplification.

In particular, selected protease polypeptides, are intended for use in therapeutic methods in which a protease that cleaves the particular target has been used for treatment. Such methods include, but are not limited to, methods of

treatment of diseases and disorders, such as, but not limited to, blood coagulation disorders, including thrombolytic disorders and disseminated intravascular coagulation, cardiovascular diseases, neurological disorders, proliferative diseases, such as cancer, inflammatory diseases, autoimmune diseases, viral infection, bacterial infection, respiratory diseases, gastrointestinal disorders, and metabolic diseases.

Treatment of diseases and conditions with selected protease polypeptides can be effected by any suitable route of administration using suitable formulations as described herein including, but not limited to, intramuscular, intravenous, intradermal, intraperitoneal injection, subcutaneous, epidural, nasal oral, rectal, topical, inhalational, buccal (e.g., sublingual), and transdermal administration. If necessary, a particular dosage and duration and treatment protocol can be empirically determined or extrapolated. For example, exemplary doses of wild-type protease polypeptides that cleave similar sequences can be used as a starting point to determine appropriate dosages. For example, a dosage of a recombinant tPA polypeptide can be used as a guideline for determining dosages of selected uPA polypeptides that cleave tPA targets.

Dosage levels and regimens can be determined based upon known dosages and regimens, and, if necessary can be extrapolated based upon the changes in properties of the selected protease polypeptides and/or can be determined empirically based on a variety of factors. Factors such as the level of activity and half-life of the selected protease polypeptides in comparison to other similar proteases can be used in making such determinations. Particular dosages and regimens can be empirically determined. Other such factors include body weight of the individual, general health, age, the activity of the specific compound employed, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, and the patient's disposition to the disease and the judgment of the treating physician. The active ingredient, the selected protease polypeptide, typically is combined with a pharmaceutically effective carrier. The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form or multi-dosage form can vary depending upon the host treated and the particular mode of administration.

The effect of the selected protease polypeptides on the treatment of a disease or amelioration of symptoms of a disease can be monitored using any diagnostic test

known in the art for the particular disease to be treated. Upon improvement of a patient's condition, a maintenance dose of a compound or compositions can be administered, if necessary; and the dosage, the dosage form, or frequency of administration, or a combination thereof can be modified. In some cases, a subject can require intermittent treatment on a long-term basis upon any recurrence of disease symptoms or based upon scheduled dosages. In other cases, additional administrations can be required in response to acute events such as hemorrhage, trauma, or surgical procedures.

In some examples, variants of the selected protease proteins that function as either protease agonists (i.e., mimetics) or as protease antagonists are employed. Variants of the selected protease polypeptide can be generated by mutagenesis (e.g., discrete point mutation or truncation of the protease protein). An agonist of the selected protease polypeptide can retain substantially the same, or a subset of, the biological activities of the naturally occurring form of the selected protease polypeptide. An antagonist of the selected protease polypeptide can inhibit one or more of the activities of the naturally occurring form of the selected protease polypeptide by, for example, cleaving the same target protein as the selected protease polypeptide. Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the selected protease polypeptide has fewer side effects in a subject relative to treatment with the naturally occurring form of the selected protease polypeptide.

The following are some exemplary diseases or conditions for which selected proteases can be used as a treatment agent alone or in combination with other agents. Exemplary targets for selection of proteases are for illustrative purposes and not intended to limit the scope of possible targets for use in the methods provided herein.

1. Exemplary Methods of Treatment for Selected uPA Polypeptides That Cleave tPA Targets

Selected uPA polypeptides that cleave tPA target sequences are useful in therapeutic applications for use in ameliorating thrombotic disorders including both acute and chronic conditions. Acute conditions include among others both heart attack and stroke while chronic situations include those of arterial and deep vein thrombosis and restenosis. The selected uPA polypeptides can be used as

thrombolytic therapeutic agents for ameliorating the symptoms of such conditions. Therapeutic compositions include the polypeptides, cDNA molecules alone or part of a viral vector delivery system or other vector-based gene expression delivery system, presented in a liposome delivery system and the like. A composition for use as a thrombolytic therapeutic agent generally is a physiologically effective amount of the selected uPA polypeptides in a pharmaceutically suitable excipient. Depending on the mode of administration and the condition to be treated, the thrombolytic therapeutic agents are administered in single or multiple doses. One skilled in the art will appreciate that variations in dosage depend on the condition to be treated.

Selected uPA polypeptides provided herein that inhibit or antagonize blood coagulation can be used in anticoagulant methods of treatment for ischemic disorders, such as a peripheral vascular disorder, a pulmonary embolus, a venous thrombosis, deep vein thrombosis (DVT), superficial thrombophlebitis (SVT), arterial thrombosis, a myocardial infarction, a transient ischemic attack, unstable angina, a reversible ischemic neurological deficit, an adjunct thrombolytic activity, excessive clotting conditions, reperfusion injury, sickle cell anemia or stroke disorder. In patients with an increased risk of excessive clotting, such as DVT or SVT, during surgery, protease inactive selected uPA polypeptides provided herein can be administered to prevent excessive clotting in surgeries, such as, but not limited to heart surgery, angioplasty, lung surgery, abdominal surgery, spinal surgery, brain surgery, vascular surgery, or organ transplant surgery, including transplantation of heart, lung, pancreas, or liver. In some cases treatment is performed with selected uPA polypeptides alone. In some cases, selected uPA polypeptides are administered in conjunction with additional anticoagulation factors as required by the condition or disease to be treated.

tPA is the only therapy for acute thromboembolic stroke, which is approved by the Food and Drug Administration (FDA). tPA and variants thereof are commercially available and have been approved for administration to humans for a variety of conditions. For example alteplase (Activase®, Genentech, South San Francisco, Calif.) is recombinant human tPA. Reteplase (Retavase®, Rapilysin®; Boehringer Mannheim, Roche Centoror) is a recombinant non-glycosylated form of human tPA in which the molecule has been genetically engineered to contain 355 of the 527 amino acids of the original protein. Tenecteplase (TNKase®, Genentech) is a 527 amino acid glycoprotein derivative of human tPA that differs from naturally

occurring human tPA by having three amino acid substitutions. These substitutions decrease plasma clearance, increase fibrin binding (and thereby increase fibrin specificity), and increase resistance to plasminogen activator inhibitor-1 (PAI-1). Anistreplase (Eminase®, SmithKline Beecham) is yet another commercially available human tPA. Selected uPA polypeptides provided herein with specificity toward tPA targets can be similarly modified and prescribed for any therapy that is treatable with tPA.

a. Thrombotic Diseases and Conditions

Thrombotic diseases are characterized by hypercoagulation, or the deregulation of hemostasis in favor of development of blot clots. Exemplary thrombotic diseases and conditions include arterial thrombosis, venous thrombosis, venous thromboembolism, pulmonary embolism, deep vein thrombosis, stroke, ischemic stroke, myocardial infarction, unstable angina, atrial fibrillation, renal damage, percutaneous translumenal coronary angioplasty, disseminated intravascular coagulation, sepsis, artificial organs, shunts or prostheses, and other acquired thrombotic diseases, as discussed below. Typical therapies for thrombotic diseases involve anticoagulant therapies, including inhibition of the coagulation cascade.

The selected uPA polypeptides provided herein and the nucleic acids encoding the selected uPA polypeptides provided herein can be used in anticoagulant therapies for thrombotic diseases and conditions, including treatment of conditions involving intravascular coagulation. The selected uPA polypeptides provided herein the can inhibit blood coagulation can be used, for example, to control, dissolve, or prevent formation of thromboses. In a particular embodiment, the selected uPA polypeptides herein, and nucleic acids encoding selected uPA polypeptides can be used for treatment of an arterial thrombotic disorder. In another embodiment, the selected uPA polypeptides herein, and nucleic acids encoding modified selected uPA polypeptides can be used for treatment of a venous thrombotic disorder, such as deep vein thrombosis. In a particular embodiment, the selected uPA polypeptides herein, and nucleic acids encoding selected uPA polypeptides can be used for treatment of an ischemic disorder, such as stroke. Examples of therapeutic improvements using selected uPA polypeptides include for example, but are not limited to, lower dosages, fewer and/or less frequent administrations, decreased side effects, and increased therapeutic effects. Selected uPA polypeptides can be tested for therapeutic

effectiveness, for example, by using animal models. For example mouse models of ischemic stroke, or any other known disease model for a thrombotic disease or condition, can be treated with selected uPA polypeptides (Dodds, *Ann NY Acad Sci* 516: 631-635 (1987)). Progression of disease symptoms and phenotypes is monitored to assess the effects of the selected uPA polypeptides. Selected uPA polypeptides also can be administered to animal models as well as subjects such as in clinical trials to assess *in vivo* effectiveness in comparison to placebo controls.

i. Arterial Thrombosis

Arterial thrombi form as a result of a rupture in the arterial vessel wall. Most often the rupture occurs in patients with vascular disease, such as atherosclerosis. The arterial thrombi usually form in regions of disturbed blood flow and at sites of rupture due to an atherosclerotic plaque, which exposes the thrombogenic subendothelium to platelets and coagulation proteins, which in turn activate the coagulation cascade. Plaque rupture also can produce further narrowing of the blood vessel due to hemorrhage into the plaque. Nonocclusive thrombi can become incorporated into the vessel wall and can accelerate the growth of atherosclerotic plaques. Formation arterial thrombi can result in ischemia either by obstructing flow or by embolism into the distal microcirculation. Anticoagulants and drugs that suppress platelet function and the coagulation cascade can be effective in the prevention and treatment of arterial thrombosis. Such classes of drugs are effective in the treatment of arterial thrombosis. Arterial thrombosis can lead to conditions of unstable angina and acute myocardial infarction. Selected uPA polypeptides provided herein that inhibit coagulation can be used in the treatment and/or prevention of arterial thrombosis and conditions, such as unstable angina and acute myocardial infarction.

ii. Venous Thrombosis and Thromboembolism

Venous thrombosis is a condition in which a blood clot forms in a vein due to imbalances in the signals for clot formation versus clot dissolution, especially in instances of low blood flow through the venous system. Results of thrombus formation can include damage to the vein and valves of the vein, though the vessel wall typically remains intact. The clots can often embolize, or break off, and travel through the blood stream where they can lodge into organ areas such as the lungs (pulmonary embolism), brain (ischemic stroke, transient ischemic attack), heart (heart attack/myocardial infarction, unstable angina), skin (purpura fulminans), and adrenal

gland. In some instances the blockage of blood flow can lead to death. Patients with a tendency to have recurrent venous thromboembolism are characterized as having thrombophilia. Risk factors for developing thromboembolic disease include trauma, immobilization, malignant disease, heart failure, obesity, high levels of estrogens, leg paralysis, myocardial infarction, varicose veins, cancers, dehydration, smoking, oral contraceptives, and pregnancy. Genetic studies of families with thrombophilia have shown inheritable high levels coagulation factors, including FVIII, FIX, and FXI (Lavigne *et al. J. Thromb. Haemost.* 1:2134-2130 (2003)).

Deep vein thrombosis (DVT) refers the formation of venous blot clot in the deep leg veins. The three main factors that contribute to DVT are injury to the vein lining, increased tendency for the blood to clot and slowing of blood flow. Collectively, these factor are called Virchow's triad. Veins can become injured during trauma or surgery, or as a result of disease condition, such as Buerger's disease or DIC, or another clot. Other contributing factors to development of DVT are similar to that of more general thromboembolic diseases as discussed above. The clot that forms in DVT causes only minor inflammation, thus, allowing it to break loose into the blood stream more easily. Often the thrombus can break off as a result of minor contraction of the leg muscles. Once the thrombus becomes an embolus it can become lodged into vessels of the lungs where is can cause a pulmonary infarction. Patients with high levels of active FIX in their bloodstream are at an increased risk of developing deep vein thrombosis (Weltermann et al. J. Thromb. Haemost. 1(1): 16-18 (2003)).

Thromboembolic disease can be hereditary, wherein the disease is caused by hereditary abnormalities in clotting factors, thus leading to the imbalance in hemostasis. Several congenital deficiencies include antithrombin III, protein C, protein S, or plasminogen. Other factors include resistance to activated protein C (also termed APC resistance or Factor V leiden effect, in which a mutation in factor V makes it resistant to degradation by protein C), mutation in prothrombin, dysfibrinogemia (mutations confer resistance to fibrinolysis), and hyperhomocysteinemia. Development of thromboembolic disease in younger patients is most often due to the congenital defects described above and is called Juvenile Thrombophilia.

Treatments for venous thromboembolic disease and DVT typically involve anticoagulant therapy, in which oral doses of heparin and warfarin are administered. Heparin is usually infused into patients to control acute events, followed by longer term oral anticoagulant therapy with warfarin to control future episodes. Other therapies include direct thrombin inhibitors, inhibitors of platelet function, such as aspirin and dextran, and therapies to counteract venous stasis, including compression stockings and pneumatic compression devices. Selected uPA polypeptides provided herein that inhibit blood coagulation can be used in anticoagulant therapies for thromboembolic disease and/or DVT. In some embodiments, selected uPA polypeptides provided herein that inhibit blood coagulation can be used in prevention therapies thromboembolic disease and/or DVT in patients exhibiting risk factors for thromboembolic disease and/or DVT.

(a) Ischemic stroke

Ischemic stroke occurs when the blood flow to the brain is interrupted, wherein the sudden loss of circulation to an area of the brain results in a corresponding loss of neurologic function. In contrast to a hemorrhagic stroke, which is characterized by intracerebral bleeding, an ischemic stroke is usually caused by thrombosis or embolism. Ischemic strokes account for approximately 80% of all strokes. In addition to the causes and risk factors for development a thromboembolism as discussed above, processes that cause dissection of the cerebral arteries (*e.g.*, trauma, thoracic aortic dissection, arteritis) can cause thrombotic stroke. Other causes include hypoperfusion distal to a stenotic or occluded artery or hypoperfusion of a vulnerable watershed region between 2 cerebral arterial territories. Treatments for ischemic stroke involve anticoagulant therapy for the prevention and treatment of the condition. Selected uPA polypeptides provided herein that inhibit coagulation can be used in the treatment and/or prevention or reduction of risk of ischemic stroke.

iii. Acquired Coagulation Disorders

Acquired coagulation disorders are the result of conditions or diseases, such as vitamin K deficiency, liver disease, disseminated intravascular coagulation (DIC), or development of circulation anticoagulants. The defects in blood coagulation are the result of secondary deficiencies in clotting factors caused by the condition or disease. For example, production of coagulation factors from the liver is often impaired when the liver is in a diseased state. Along with decreased synthesis of coagulation factors,

fibrinolysis becomes increased and thrombocytopenia (deficiency in platelets) is increased. Decreased production of coagulation factors by the liver also can result from fulminant hepatitis or acute fatty liver of pregnancy. Such conditions promote intravascular clotting which consumes available coagulation factors. Selected uPA polypeptides provided herein can be used in the treatment of acquired coagulation disorders in order to alleviate deficiencies in blood clotting factors.

(a) Disseminated Intravascular Coagulation (DIC)

Disseminated intravascular coagulation (DIC) is a disorder characterized by a widespread and ongoing activation of coagulation. In DIC, there is a loss of balance between thrombin activation of coagulation and plasmin degradation of blot clots. Vascular or microvascular fibrin deposition as a result can compromise the blood supply to various organs, which can contribute to organ failure. In sub-acute or chronic DIC, patients present with a hypercoagulatory phenotype, with thromboses from excess thrombin formation, and the symptoms and signs of venous thrombosis can be present. In contrast to acute DIC, sub-acute or chronic DIC is treated by methods of alleviating the hyperthrombosis, including heparin, anti-thrombin III and activated protein C treatment. The selected uPA polypeptides provided herein and the nucleic acids encoding the selected uPA polypeptides provided herein can be used in therapies for sub-acute or chronic DIC. In one embodiment, the sub-acute or chronic DIC polypeptides herein, and nucleic acids encoding the selected uPA polypeptides can be used in combination with other anticoagulation therapies. Selected uPA polypeptides can be tested for therapeutic effectiveness, for example, by using animal models. Progression of disease symptoms and phenotypes is monitored to assess the effects of the selected uPA polypeptides. Selected uPA polypeptides also can be administered to animal models as well as subjects such as in clinical trials to assess *in vivo* effectiveness in comparison to placebo controls.

(b) Bacterial Infection and Periodontitis

Systemic infection with microorganisms, such as bacteria, is commonly associated with DIC. The upregulation of coagulation pathways can be mediated in part by cell membrane components of the microorganism (lipopolysaccharide or endotoxin) or bacterial exotoxins (e.g. staphylococcal alpha toxin) that cause

inflammatory responses leading to elevated levels of cytokines. The cytokines, in turn, can influence induction of coagulation.

Bacterial pathogens, such as *Porphyrus gingivalis*, are well-known as causative agents for adult periodontitis. The *Porphyrus gingivalis* bacterium produces arginine-specific cysteine proteinases that function as virulence factors (Grenier *et al. J. Clin. Microbiol.* 25:738-740 (1987), Smalley *et al. Oral Microbiol. Immunol.* 4:178-181 (1989), Marsh, *et al. FEMS Microbiol.* 59:181-185 (1989), and Potempa *et al. J. Biol. Chem.* 273:21648-21657 (1998). *Porphyrus gingivalis* generated two proteinases that are referred to as 50 kDa and 95 kDa gingipains R (RgpB and HRgpA, respectively). The protease can proteolytically cleave and hence activate coagulation factors. During bacterial infection release of the gingipains R into the blood stream can thus lead to uncontrolled activation of the coagulation cascade leading to overproduction of thrombin and increase the possibility of inducing disseminated intravascular coagulation (DIC). The large increases in thrombin concentrations can furthermore contribute alveolar bone resorption by osteoclasts at sites of periodontitis.

The selected uPA polypeptides provided herein that inhibit blood coagulation, and nucleic acids encoding selected uPA polypeptides can be used in treatment of periodontitis. Selected uPA polypeptides can be tested for therapeutic effectiveness for airway responsiveness in periodontitis models. Such models are available in animals, such as nonhuman primates, dogs, mice, rats, hamsters, and guinea pigs (Weinberg and Bral, *J. of Periodontology* 26(6), 335-340). Selected uPA polypeptides also can be administered to animal models as well as subjects such as in clinical trials to assess *in vivo* effectiveness in comparison to placebo controls.

b. Other tPA Target-associated Conditions

The selected uPA polypeptides provided herein also can be used in treatment of neurological conditions for which tPA had been implicated. tPA is thought to regulate physiological processes that include tissue remodeling and plasticity due to the ability of tPA to hydrolyze extracellular matrix proteins and other substrates (Gravanis and Tsirska (2004) *Glia* 49:177-183). Patients who have experienced events such as stroke or injury (e.g., due to accident or surgery) often suffer from neurological damage that can be treatable with selected uPA polypeptides provided herein. The selected uPA polypeptides provided herein can be useful for treating

subjects suffering from a variety of neurological diseases and conditions including, but not limited to, neurodegenerative diseases such as multiple sclerosis, amyotrophic lateral sclerosis, subacute sclerosing panencephalitis, Parkinson's disease, Huntington's disease, muscular dystrophy, and conditions caused by nutrient deprivation or toxins (e.g., neurotoxins, drugs of abuse). Additionally, selected uPA polypeptides can be useful for providing cognitive enhancement and/or for treating cognitive decline, e.g., "benign senescent forgetfulness", "age-associated memory impairment", "age-associated cognitive decline", etc. (Petersen et al., *J Immunological Meth.* 257:107-116 (2001)), and Alzheimer's disease.

Selected uPA polypeptides can be tested using any of a variety of animal models for injury to the nervous system. Models that can be used include, but are not limited to, rodent, rabbit, cat, dog, or primate models for thromboembolic stroke (Krueger and Busch, *Invest. Radiol.* 37:600-8 (2002); Gupta and Briyal, *Indian J Physiol. Pharmacol.* 48:379-94 (2004)), models for spinal cord injury (Webb et al., *Vet. Rec.* 155:225-30 (2004)), etc. The methods and compositions also can be tested in humans. A variety of different methods, including standardized tests and scoring systems, are available for assessing recovery of motor, sensory, behavioral, and/or cognitive function in animals and humans. Any suitable method can be used. In one example, the American Spinal Injury Association score, which has become the principal instrument for measuring the recovery of sensory function in humans, could be used. See, e.g., Martinez-Arizala, *J Rehabil. Res. Dev.* 40:35-9 (2003), Thomas and Noga, *J Rehabil. Res. Dev.* 40:25-33 (2003), Kesslak and Keirstead, *J Spinal Cord Med.* 26:323-8 (2003) for examples of various scoring systems and methods. Preferred dose ranges for use in humans can be established by testing the agent(s) in tissue culture systems and in animal models taking into account the efficacy of the agent(s) and also any observed toxicity.

c. Diagnostic Methods

Selected uPA polypeptides provided herein can be used in diagnostic methods including, but not limited to, diagnostic assays to detect fibrin and fibrin degradation products that have altered activities. The assays are thus indicated in thrombotic conditions. Other diagnostic applications, include kits containing antibodies against the selected uPA polypeptides and are familiar to one of ordinary skill in the art.

2. Exemplary Methods of Treatment for Selected Protease Polypeptides That Cleave VEGF or VEGFR Targets

Vascular endothelial growth factor (VEGF) is a cytokine that binds and signals through a specific cell surface receptor (VEGFR) to regulate angiogenesis, the process in which new blood vessels are generated from existing vasculature. Pathological angiogenesis describes the increased vascularization associated with disease and includes events such as the growth of solid tumors (McMahon, (2000) *Oncologist.* 5 Suppl 1:3-10), macular degeneration and diabetes. In cancer, solid tumors require an ever-increasing blood supply for growth and metastasis. Hypoxia or oncogenic mutation increases the levels of VEGF and VEGF-R mRNA in the tumor and surrounding stromal cells leading to the extension of existing vessels and formation of a new vascular network. In wet macular degeneration, abnormal blood vessel growth forms beneath the macula. These vessels leak blood and fluid into the macula damaging photoreceptor cells. In diabetes, a lack of blood to the eyes also can lead to blindness. VEGF stimulation of capillary growth around the eye leads to disordered vessels which do not function properly.

Three tyrosine kinase family receptors of VEGF have been identified (VEGF-R-1/Flt-1, VEGF-R-2/Flk-1/KDR, VEGF-R-3/Flt-4). KDR (the mouse homolog is Flk-1) is a high affinity receptor of VEGF with a Kd of 400-800 pM (Waltenberger, (1994) *J Biol Chem.* 269(43):26988-95) expressed exclusively on endothelial cells. VEGF and KDR association has been identified as a key endothelial cell-specific signaling pathway required for pathological angiogenesis (Kim, (1993) *Nature.* 362 (6423):841-4; Millauer, (1994) *Nature.* 367 (6463):576-9; Yoshiji, (1999) *Hepatology.* 30(5): 1179-86). Dimerization of the receptor upon ligand binding causes autophosphorylation of the cytoplasmic domains, and recruitment of binding partners that propagate signaling throughout the cytoplasm and into the nucleus to change the cell growth programs. Treatment of tumors with a soluble VEGF-R2 inhibits tumor growth (Lin, (1998) *Cell Growth Differ.* 9(1):49-58), and chemical inhibition of phosphorylation causes tumor cells to become apoptotic (Shaheen, (1999) *Cancer Res.* 59(21):5412-6).

Signaling by vascular endothelial growth factor (VEGF) and its receptors is implicated in pathological angiogenesis and the rapid development of tumor vasculature in cancer. Drugs that block this signaling pathway prevent the growth and

maintenance of tumor blood supply, and lead to the systematic death of the tumor. The recent success of the anti-VEGF antibody AVASTIN™ in patients with metastatic colon cancer has validated VEGF as a target for anti-angiogenic therapy of cancer. Despite these encouraging results, tumor progression has still occurred despite anti-VEGF treatment. The mechanisms of antibody affecting VEGF function and how the antibody impedes tumor growth are unknown. Knock down experiments show that blocking VEGF function blocks angiogenesis. Thus the inhibition of angiogenic signaling through VEGFR-2 represents an underdeveloped therapeutic area ideal for the development of engineered proteases with novel targeting.

Therapies targeting the VEGF receptors and Flk-1/KDR specifically have inhibited pathological angiogenesis and shown reduction of tumor size in multiple mouse models of human and mouse solid tumors (Prewett, (1999) *Cancer Res.* 59(20):5209-18; Fong, (1999) *Neoplasia* 1(1):31-41. Erratum in: (1999) *Neoplasia* 1(2):183) alone and in combination with cytotoxic therapies (Klement, (2000) *J Clin Invest.* 105(8):R15-24). Studies with small molecule inhibitors and antibodies validate the VEGF receptor family as a potent anti-angiogenesis target but more effective therapeutics are still needed.

VEGFR is composed of an extracellular region of seven immunoglobin (Ig)-like domains, a transmembrane region, and two cytoplasmic tyrosine kinase domains. The first three Ig-like domains have been shown to regulate ligand binding, while domains 4 through 7 have a role in inhibiting correct dimerization and signaling in the absence of ligand. As a target for selective proteolysis by engineered proteases, it has the following promising target characteristics: a labile region of amino acids accessible to proteolysis; high sequence identity between the human, rat and mouse species; down regulation of signaling upon cleavage; and proteolytic generation of soluble receptors able to non-productively bind ligand. Several regions of VEGF-R2 are available for specific proteolysis including the stalk region before the transmembrane region and unstructured loop between Ig-like domains. In one example, serine-like proteases provided herein can be engineered to cleave specific target receptors between their transmembrane and cytokine or growth factor binding domains (*e.g.* VEGFR). The stalk regions that function to tether protein receptors to the surface of a cell or loop regions are thereby disconnected from the globular domains in a polypeptide chain.

a. Angiogenesis, Cancer, and Other Cell Cycle Dependent Diseases or Conditions

Exemplary selected proteases provided herein cleave a VEGF or VEGFR which are responsible for modulation of angiogenesis. Where the cell surface molecule is a VEGFR signaling in tumor angiogenesis, cleavage prevents the spread of cancer. For example, cleavage of a cell surface domain from a VEGFR molecule can inactivate its ability to transmit extracellular signals, especially cell proliferation signals. Without angiogenesis to feed the tumor, cancer cells often cannot proliferate. In one embodiment, a selected protease provided herein is therefore used to treat cancer. Also, cleavage of VEGFR can be used to modulate angiogenesis in other pathologies, such as macular degeneration, inflammation and diabetes. In one embodiment, cleaving a target VEGF or VEGFR protein involved in cell cycle progression inactivates the ability of the protein to allow the cell cycle to go forward. Without the progression of the cell cycle, cancer cells can not proliferate. Therefore, the selected proteases provided herein which cleave VEGF or VEGFR are used to treat cancer and other cell cycle dependent pathologies.

Selected proteases provided herein also can cleave soluble proteins that are responsible for tumorigenicity. Cleaving VEGF polypeptide prevents signaling through the VEGF receptor and decreases angiogenesis, thus decreasing disease in which angiogenesis plays a role, such as cancer, macular degeneration, inflammation and diabetes. Further, VEGF signaling is responsible for the modulation of the cell cycle in certain cell types. Therefore, the selected proteases provided herein which cleave VEGF are useful in the treatment of cancer and other cell cycle dependent pathologies.

b. Combination Therapies with Selected Proteases That Cleave VEGF or VEGFR

In one embodiment, treatment of a pathology, such as a cancer, involves administration to a subject in need thereof therapeutically effective amounts of a protease that specifically cleaves and inactivates the signaling of the VEGF/VEGFR-2 complex, such as in combination with at least one anti-cancer agent. Antiangiogenic therapy has proven successful against both solid cancers and hematological malignancies. (See, e.g., Ribatti et al. (2003) *J Hematother Stem Cell Res.* 12(1), 11-22). Therefore, compositions provided herein as antiangiogenic therapy can facilitate

the treatment of both hematological and sold tissue malignancies. Compositions and methods of treatment provided herein can be administered alone or in combination with any other appropriate anti-cancer treatment known to one skilled in the art. For example, the selected proteases provided herein can be administered in combination with or in place of AVASTIN™ in any therapy where AVASTIN™ administration provides therapeutic benefit.

In one embodiment, the anti-cancer agent is at least one chemotherapeutic agent. In a related embodiment, the administering of the protease is in combination with at least one radiotherapy. Administration of the combination therapy will attenuate the angiogenic signal and create a pool of soluble receptor that lowers free VEGF levels. In a specific embodiment, a selected protease provided herein has an *in vitro* specificity that matches a critical region of the receptor, the Flk-1/KDR stalk, over a six amino acid region.

The selected protease polypeptides provided herein can be administered in a composition containing more than one therapeutic agent. The therapeutic agents can be the same or different, and can be, for example, therapeutic radionuclides, drugs, hormones, hormone antagonists, receptor antagonists, enzymes or proenzymes activated by another agent, autocrines, cytokines or any suitable anti-cancer agent known to those skilled in the art. In one embodiment, the anti-cancer agent co-administered with the selected protease polypeptide is AVASTIN™. Other therapeutic agents useful in the methods provided herein include toxins, anti-DNA, anti-RNA, radiolabeled oligonucleotides, such as antisense oligonucleotides, anti-protein and anti-chromatin cytotoxic or antimicrobial agents. Other therapeutic agents are known to those skilled in the art, and the use of such other therapeutic agents in accordance with the method provided herein is specifically contemplated.

The antitumor agent can be one of numerous chemotherapy agents such as an alkylating agent, an antimetabolite, a hormonal agent, an antibiotic, an antibody, an anti-cancer biological, Gleevec, colchicine, a vinca alkaloid, L-asparaginase, procarbazine, hydroxyurea, mitotane, nitrosoureas or an imidazole carboxamide. Suitable agents are those agents that promote depolarization of tubulin or prohibit tumor cell proliferation. Chemotherapeutic agents contemplated include, but are not limited to, anti-cancer agents listed in the Orange Book of Approved Drug Products With Therapeutic Equivalence Evaluations, as compiled by the Food and Drug

Administration and the U.S. Department of Health and Human Services. In addition to the above chemotherapy agents, the serine protease-like proteases provided herein also can be administered together with radiation therapy treatment. Additional treatments known in the art are contemplated.

The therapeutic agent can be a chemotherapeutic agent. Chemotherapeutic agents are known in the art and include at least the taxanes, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs, pyrimidine analogs, purine analogs, vinca alkaloids, antibiotics, enzymes, platinum coordination complexes, substituted urea, methyl hydrazine derivatives, adrenocortical suppressants, or antagonists. More specifically, the chemotherapeutic agents can be one or more agents chosen from the non-limiting group of steroids, progestins, estrogens, antiestrogens, or androgens. Even more specifically, the chemotherapy agents can be azaribine, bleomycin, bryostatin-1, busulfan, carmustine, chlorambucil, cisplatin, CPT-11, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone, diethylstilbestrol, doxorubicin, ethinyl estradiol, etoposide, fluorouracil, fluoxymesterone, gemcitabine, hydroxyprogesterone caproate, hydroxyurea, L-asparaginase, leucovorin, lomustine, mechlorethamine, medroprogesterone acetate, megestrol acetate, melphalan, mercaptopurine, methotrexate, methotrexate, mithramycin, mitomycin, mitotane, phenyl butyrate, prednisone, procarbazine, semustine streptozocin, tamoxifen, taxanes, taxol, testosterone propionate, thalidomide, thioguanine, thiotepa, uracil mustard, vinblastine, or vincristine. The use of any combinations of chemotherapy agents also is contemplated. The administration of the chemotherapeutic agent can be before, during or after the administration of the serine protease-like mutein polypeptide.

Other suitable therapeutic agents for use in combination or for co-administration with the selected protease polypeptides provided herein are selected from the group consisting of radioisotope, boron addend, immunomodulator, toxin, photoactive agent or dye, cancer chemotherapeutic drug, antiviral drug, antifungal drug, antibacterial drug, antiprotozoal drug and chemosensitizing agent (See, U.S. Pat. Nos. 4,925,648 and 4,932,412). Suitable chemotherapeutic agents are described, for example, in REMINGTON'S PHARMACEUTICAL SCIENCES, 19th Ed. (Mack Publishing Co. 1995), and in Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Goodman et al., Eds. Macmillan Publishing Co., New

York, 1980 and 2001 editions). Other suitable chemotherapeutic agents, such as experimental drugs, are known to those of skill in the art. Moreover a suitable therapeutic radioisotope is selected from the group consisting of ax-emitters, β-emitters, γ-emitters, Auger electron emitters, neutron capturing agents that emit α-particles and radioisotopes that decay by electron capture. Preferably, the radioisotope is selected from the group consisting of ^{225}Ac, ^{198}Au, ^{32}P, ^{131}I, ^{131}I, ^{90}Y, ^{186}Re, ^{188}Re, ^{67}Cu, ^{177}Lu, ^{213}Bi, ^{10}B, and ^{211}At.

Where more than one therapeutic agent is used in combination with the selected proteases provided herein, they can be of the same class or type or can be from different classes or types. For example, the therapeutic agents can comprise different radionuclides, or a drug and a radionuclide.

In another embodiment, different isotopes that are effective over different distances as a result of their individual energy emissions are used as first and second therapeutic agents in combination with the proteases provided herein. Such agents can be used to achieve more effective treatment of tumors, and are useful in patients presenting with multiple tumors of differing sizes, as in normal clinical circumstances.

Few of the available isotopes are useful for treating the very smallest tumor deposits and single cells. In these situations, a drug or toxin can be a more useful therapeutic agent for co-administration with a protease provided herein. Accordingly, in some embodiments, isotopes are used in combination with non-isotopic species such as drugs, toxins, and neutron capture agents and co-administered with a protease provided herein. Many drugs and toxins are known which have cytotoxic effects on cells, and can be used in combination with the proteases provided herein. They are to be found in compendia of drugs and toxins, such as the Merck Index, Goodman and Gilman, and the like, and in the references cited above.

Drugs that interfere with intracellular protein synthesis also can be used in combination with a protease in the therapeutic the methods herein; such drugs are known to those skilled in the art and include puromycin, cycloheximide, and ribonuclease.

The therapeutic methods provided herein can be used for cancer therapy. It is well known that radioisotopes, drugs, and toxins can be conjugated to antibodies or antibody fragments which specifically bind to markers which are produced by or

associated with cancer cells, and that such antibody conjugates can be used to target the radioisotopes, drugs or toxins to tumor sites to enhance their therapeutic efficacy and minimize side effects. Examples of these agents and methods are reviewed in Wawrzynczak and Thorpe (in Introduction to the Cellular and Molecular Biology of Cancer, L. M. Franks and N. M. Teich, eds, Chapter 18, pp. 378-410, Oxford University Press. Oxford, 1986), in Immunoconjugates: Antibody Conjugates in Radioimaging and Therapy of Cancer (C. W. Vogel, ed., 3-300, Oxford University Press, N.Y., 1987), in Dillman, R. O. (CRC Critical Reviews in Oncology/Hematology 1:357, CRC Press, Inc., 1984), in Pastan et al. (Cell 47:641, 1986) in Vitetta et al. (Science 238:1098-1104, 1987) and in Brady et al. (Int. J. Rad. Oncol. Biol. Phys. 13:1535-1544, 1987). Other examples of the use of immunoconjugates for cancer and other forms of therapy have been disclosed, inter alia, in U.S. Pat. Nos. 4,331,647, 4,348,376, 4,361,544, 4,468,457, 4,444,744, 4,460,459, 4,460,561 4,624,846, 4,818,709, 4,046,722, 4,671,958, 4,046,784, 5,332,567, 5,443,953, 5,541,297, 5,601,825, 5,635,603, 5,637,288, 5,677,427, 5,686,578, 5,698,178, 5,789,554, 5,922,302, 6,187,287, and 6,319,500.

Additionally, the treatment methods provided herein include those in which a selected protease herein is used in combination with other compounds or techniques for preventing, mitigating or reversing the side effects of certain cytotoxic agents. Examples of such combinations include, e.g., administration of IL-1 together with an antibody for rapid clearance, as described in e.g., U.S. Pat. No. 4,624,846. Such administration can be performed from 3 to 72 hours after administration of a primary therapeutic treatment with a granzyme B mutein or MT-SP1 mutein in combination with an anti-cancer agent (e.g., with a radioisotope, drug or toxin as the cytotoxic component). This can be used to enhance clearance of the conjugate, drug or toxin from the circulation and to mitigate or reverse myeloid and other hematopoietic toxicity caused by the therapeutic agent.

In another example, and as noted above, cancer therapy can involve a combination of more than one tumoricidal agent, e.g., a drug and a radioisotope, or a radioisotope and a Boron-10 agent for neutron-activated therapy, or a drug and a biological response modifier, or a fusion molecule conjugate and a biological response modifier. The cytokine can be integrated into such a therapeutic regimen to maximize the efficacy of each component thereof.

Similarly, certain antileukemic and antilymphoma antibodies conjugated with radioisotopes that are β or α-emitters can induce myeloid and other hematopoietic side effects when these agents are not solely directed to the tumor cells. This is observed particularly when the tumor cells are in the circulation and in the blood-forming organs. Concomitant and/or subsequent administration of at least one hematopoietic cytokine (e.g., growth factors, such as colony stimulating factors, such as G-CSF and GM-CSF) is preferred to reduce or ameliorate the hematopoietic side effects, while augmenting the anticancer effects.

It is well known in the art that various methods of radionuclide therapy can be used for the treatment of cancer and other pathological conditions, as described, e.g., in Harbert, "Nuclear Medicine Therapy", New York, Thieme Medical Publishers, 1087, pp. 1-340. A clinician experienced in these procedures will readily be able to adapt the cytokine adjuvant therapy described herein to such procedures to mitigate any hematopoietic side effects thereof. Similarly, therapy with cytotoxic drugs, co-administered with a protease mutein, can be used, e.g., for treatment of cancer, infectious or autoimmune diseases, and for organ rejection therapy. Such treatment is governed by analogous principles to radioisotope therapy with isotopes or radiolabeled antibodies. Thus, the ordinary skilled clinician will be able to adapt the description of cytokine use to mitigate marrow suppression and other such hematopoietic side effects by administration of the cytokine before, during and/or after the primary anti-cancer therapy.

3. Exemplary Methods of Treatment for Selected MT-SP1 Polypeptides That Cleave Complement Protein Targets

The protease polypeptides and nucleic acid molecules provided herein can be used for treatment of any condition for which activation of the complement pathway is implicated, particularly inflammatory conditions including acute inflammatory conditions, such as septic shock, and chronic inflammatory conditions, such as Rheumatoid Arthritis (RA). Acute and inflammatory conditions can be manifested as an immune-mediated disease such as for example autoimmune disease or tissue injury caused by immune-complex-mediated inflammation. A complement-mediated inflammatory condition also can be manifested as a neurodegenerative or cardiovascular disease that have inflammatory components. This section provides exemplary uses of, and administration methods for, proteases. These described

therapies are exemplary and do not limit the applications of proteases. Such methods include, but are not limited to, methods of treatment of physiological and medical conditions described and listed below. Such methods include, but are not limited to, methods of treatment of sepsis, Rheumatoid arthritis (RA), membranoproliferative glomerulonephritis (MPGN), lupus erythematosus, Multiple Sclerosis (MS), Myasthenia gravis (MG), asthma, inflammatory bowel disease, respiratory distress syndrome, immune complex (IC)-mediated acute inflammatory tissue injury, multi-organ failure, Alzheimer's Disease (AD), Ischemia-reperfusion injuries caused by events or treatments such as myocardial infarct (MI), stroke, cardiopulmonary bypass (CPB) or coronary artery bypass graft, angioplasty, or hemodialysis, or Guillan Barre syndrome.

Treatment of diseases and conditions with proteases can be effected by any suitable route of administration using suitable formulations as described herein including, but not limited to, subcutaneous injection, oral and transdermal administration. If necessary, a particular dosage and duration and treatment protocol can be empirically determined or extrapolated. For example, exemplary doses of recombinant and native protease polypeptides can be used as a starting point to determine appropriate dosages. Modified proteases that have more specificity and/or selectivity compared to a wildtype or scaffold protease can be effective at reduced dosage amounts and or frequencies. Dosage levels can be determined based on a variety of factors, such as body weight of the individual, general health, age, the activity of the specific compound employed, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, and the patient's disposition to the disease and the judgment of the treating physician. The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form with vary depending upon the host treated and the particular mode of administration.

Upon improvement of a patient's condition, a maintenance dose of a compound or compositions can be administered, if necessary; and the dosage, the dosage form, or frequency of administration, or a combination thereof can be modified. In some cases, a subject can require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

a. Immune-mediated Inflammatory Diseases

Proteases and modified proteases selected in the method described herein, including but not limited to variant MT-SP1 proteases provided herein, can be used to treat inflammatory diseases. Inflammatory diseases that can be treated with proteases include acute and chronic inflammatory diseases. Exemplary inflammatory diseases include central nervous system diseases (CNS), autoimmune diseases, airway hyper-responsiveness conditions such as in asthma, rheumatoid arthritis, inflammatory bowel disease, and immune complex (IC)-mediated acute inflammatory tissue injury.

Experimental autoimmune encephalomyelitis (EAE) can serve as a model for multiple sclerosis (MS) (Piddlesden *et al.*, (1994) *J Immunol* 152:5477). EAE can be induced in a number of genetically susceptible species by immunization with myelin and myelin components such as myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein (MOG). For example, MOG-induced EAE recapitulates essential features of human MS including the chronic, relapsing clinical disease course the pathohistological triad of inflammation, reactive gliosis, and the formation of large confluent demyelinated plaques. Proteases and modified proteases can be assessed in EAE animal models. Proteases are administered, such as by daily intraperitoneal injection, and the course and progression of symptoms is monitored compared to control animals. The levels of inflammatory complement components that can exacerbate the disease also can be measured by assaying serum complement activity in a hemolytic assay and by assaying for the deposition of complement components, such as for example C1, C3 and C9.

Complement activation modulates inflammation in diseases such as rheumatoid arthritis (RA) (Wang *et al.*, (1995) *PNAS* 92:8955). Proteases and modified proteases, including variant MT-SP1 polypeptides provided herein, can be used to treat RA. For example, proteases can be injected locally or systemically. Proteases can be dosed daily or weekly. PEGylated proteases can be used to reduce immunogenicity. In one example, type II collagen-induced arthritis (CIA) can be induced in mice as a model of autoimmune inflammatory joint disease that is histologically similar to RA characterized by inflammatory synovitis, pannus formation, and erosion of cartilage and bone. To induce CIA, bovine type II collagen (B-CII) in the presence of complete Freund's adjuvant can be injected intradermally at the base of the tail. After 21 days, mice can be reimmunized using the identical protocol. To examine the effects of a protease or modified protease, including MT-

SP1 polypeptides, 3 weeks following the initial challenge with B-CII, a protease or control can be administered intraperitoneally twice weekly for 3 weeks. Mice can be sacrificed 7 weeks following the initial immunization for histologic analysis. To assess the therapeutic affect of a protease on established disease, a protease can be administered daily for a total of 10 days following the onset of clinical arthritis in one or more limbs. The degree of swelling in the initially affected joints can be monitored by measuring paw thickness using calipers. In both models, serum can be drawn from mice for hemolytic assays and measurement of complement markers of activation such as for example C5a and C5b-9. In another example, primate models are available for RA treatments. Response of tender and swollen joints can be monitored in subjects treated with protease polypeptides and controls to assess protease treatment.

Proteases or modified proteases, including but not limited to variant MT-SP1 polypeptides provided herein, can be used to treat immune complex (IC)-mediated acute inflammatory tissue injury. IC-mediated injury is caused by a local inflammatory response against IC deposition in a tissue. The ensuing inflammatory response is characterized by edema, neutrophila, hemorrhage, and finally tissue necrosis. IC-mediated tissue injury can be studied in an *in vivo* Arthus (RPA) reaction. Briefly, in the RPA reaction, an excess of antibody (such as for example rabbit IgG anti-chicken egg albumin) is injected into the skin of animals, such as for example rats or guinea pigs, that have previously been infused intravenously with the corresponding antigen (*i.e.* chicken egg albumin) (Szalai *et al.*, (2000) *J Immunol* 164:463). Immediately before the initiation on an RPA reaction, a protease, or a bolus control, can be administered at the same time as the corresponding antigen by an intravenous injection via the right femoral vein. Alternatively, a protease can be administered during the initial hour of the RPA reaction, beginning immediately after injection of the antigen and just before dermal injection of the antibody. The effects of a protease on the generation of complement-dependent IC-mediated tissue injury can be assessed at various times after initiation of RPA by collecting blood to determine the serum hemolytic activity, and by harvesting the infected area of the skin for quantitation of lesion size.

Therapeutic proteases, such as those described herein including variant MT-SP1 polypeptides provided herein, can be used to treat sepsis and severe sepsis that

can result in lethal shock. A model of complement-mediated lethal shock can be used to test the effects of a protease as a therapeutic agent. In one such example, rats can be primed with a trace amount of lipopolysaccharide (LPS), followed by the administration of a monoclonal antibody against a membrane inhibitor of complement (anti-Crry) (Mizuno M *et al.*, (2002) *Int Arch Allergy Immunol* 127:55). A protease or control can be administered at any time during the course of initiation of lethal shock such as before LPS priming, after LPS priming, or after anti-Crry administration and the rescue of rats from lethal shock can be assessed.

b. Neurodegenerative disease

Complement activation exacerbates the progression of Alzheimer's disease (AD) and contributes to neurite loss in AD brains. Proteases and modified proteases described herein, including but not limited to variant MT-SP1 polypeptides provided herein, can be used to treat AD. Mouse models that mimic some of the neuropathological and behavioral features of AD can be used to assess the therapeutic effects of proteases. Examples of transgenic mouse models include introducing the human amyloid precursor protein (APP) or the presenilin 1 (PS1) protein with disease-producing mutations into mice under the control of an aggressive promoter. These mice develop characteristics of AD including increases in beta-amyloid plaques and dystrophic neurites. Double transgenic mice for APP and PS1 mutant proteins develop larger numbers of fibrillar beta-amyloid plaques and show activated glia and complement factors associated with the plaque. Proteases can be administered, such as by daily intraperitoneal or intravenous injections, and the course and progression of symptoms is monitored compared to control animals.

c. Cardiovascular disease

Proteases and modified proteases described herein, including but not limited to variant MT-SP1 proteases provided herein, can be used to treat cardiovascular disease. Proteases can be used in the treatment of cardiovascular diseases including ischemia reperfusion injury resulting from stroke, myocardial infarction, cardiopulmonary bypass, coronary artery bypass graft, angioplasty, or hemodialysis. Proteases also can be used in the treatment of the inflammatory response associated with cardiopulmonary bypass that can contribute to tissue injury. Generally, a protease can be administered prior to, concomitantly with, or subsequent to a treatment or event that induces a complement-mediated ischemia reperfusion injury.

In one example, a protease can be administered to a subject prior to the treatment of a subject by a complement-mediated, ischemic-injury inducing event, such as for example coronary artery bypass graft of angioplasty.

Effects of a protease on treatment of ischemia reperfusion injury can be assessed in animal models of the injury. In one such model, myocardial ischemia is induced in rabbits that have had an incision made in their anterior pericardium by placing a 3-0 silk suture around the left anterior descending (LAD) coronary artery 5-8 mm from its origin and tightening the ligature so that the vessel becomes completely occluded (Buerke *et al.*, (2001) *J Immunol* 167:5375). A protease, such as for example a variant MT-SP1 polypeptide provided herein, or a control vehicle such as saline, can be given intravenously in increasing doses as a bolus 55 minutes after the coronary occlusion (*i.e.* 5 minutes before reperfusion). Five minutes later (*i.e.* after a total of 60 minutes of ischemia) the LAD ligature can be untied and the ischemic myocardium can be reperfused for 3 hours. At the end of the reperfusion period, the ligature around the LAD is tightened. Effects of a protease on ischemia injury can be analyzed by assessing effects on myocardial necrosis, plasma creatine kinase levels, and markers of neutrophil activation such as for example myeloperoxidase activity and superoxide radical release.

In another model of complement-mediated myocardial injury sustained upon perfusion of isolated mouse hearts with Krebs-Henseleit buffer containing 6% human plasma, treatment with proteases or modified proteases can be used to limit tissue damage to the heart. In such an example, the buffer used to perfuse the hearts can be supplemented with varying doses of proteases, such as but not limited to variant proteases including MT-SP1 polypeptides polypeptides provided herein. The perfused hearts can be assayed for deposition of human C3 and C5b-9, coronary artery perfusion pressure, end-diastolic pressure, and heart rate.

Proteases and modified proteases, such as for example variant MT-SP1 polypeptides provided herein, can be used as therapeutics prior to or following Cardiopulmonary Bypass (CPB) or coronary artery bypass graft to inhibit the inflammatory immune response that often follows bypass and that can contribute to tissue injury. An *in vitro* recirculation of whole blood in an extracorporeal bypass circuit can be used to stimulate platelet and leukocyte changes and complement activation induced by CPB (Rinder *et al.* (1995) *J. Clin. Invest.* 96:1564). In such a

model, addition of a protease or modified protease or control buffer, in varying doses, can be added to a transfer pack already containing blood from a healthy donor and porcine heparin, just prior to addition of the blood to the extracorporeal circuit. Blood samples can be drawn at 5, 15, 30, 45, 60, 75, and 90 minutes after recirculation and assayed for complement studies such as for example hemolytic assays and/or complement activation assays to measure for C5a, C3a, and/or sC5b-9. A pretreatment sample of blood drawn before its addition to the extracorporeal circuit can be used as a control. Flow cytometry of blood samples can be performed to determine levels of adhesion molecules on populations of circulating leukocytes (*i.e.* neutrophils) in the blood such as for example CD11b and P-selectin levels.

K. EXAMPLES

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1

Mutant PAI-1 Inhibitors

A. Expression and purification of mutant PAI-1 inhibitors

The pPAIST7HS, recombinant plasmid carrying the cDNA of human PAI-1 (encoding mature PAI-1 containing an N-terminal Met as set forth in SEQ ID NO:396), was used as template to introduce modifications into the amino acid sequence of the PAI-1 reactive center loop. Plasmid pPAISTHS is a derivative of plasmid pPAIST7 lacking the *HindIII* site at nucleotide pair 1 and the *SalI* site at nucleotide pair 2106. Plasmid pPAIST7 was generated as described (Franke *et al.* (1990) *Biochimic et Biophysica Acta* 1037: 16-23). Briefly, the PAI-1 cDNA clone pPAI-11RB was cleaved with restriction endonucleases *ApaLI* and *PflMI*, and the 1127 bp fragment of PAI-1 containing 2 bp of the codon for residue 1 of PAI-1 and the full coding sequence for residues 2-376 of the 379-residue protein was purified by gel electrophoresis. Synthetic linkers were constructed to reconstruct both ends of the PAI-1 cDNA coding sequence and to introduce an ATG protein synthesis initiation codon immediately before the triplet encoding the first residue of mature PAI-1 generating a mature PAI-1 having a sequence of amino acids set forth in SEQ ID NO:396. In addition, to facilitate insertion of the cDNA coding region into plasmid pBR322, the linkers were designed to generate *EcoRI* and *HindIII* restriction endonuclease sites at the 5' and 3' termini, respectively, of the PAI-1 cDNA

fragment. The synthetic linkers are as follows: N-terminus, 5'AATTCTATGG-3' (SEQ ID NO:392) and 5'- TGCACCATAG-3' (SEQ ID NO:393); C-terminus, 5'-ATGGAACCCTGAA- 3' (SEQ ID NO:394) and 5'- AGCTTCAGGGTTCCATCAC-3' (SEQ ID NO:395). The linkers were treated with polynucleotide kinase before use. The synthetic linkers (10 bp at the 5' end and 13 bp at the 3' end) were then ligated with the 1127 bp *ApaLI-PflMI* DNA fragment, digested with *EcoRI* and *HindIII* and the 1146 bp *EcoRI-HindIII* fragment was isolated by gel electrophoresis and cloned into *EcoRI* and *HindIII* cleaved pBR322 (SEQ ID NO:377).

To initiate construction of the pPAIST-7 expression plasmid, the subclone in the pBR322 vector was cleaved with *EcoRI* and the linear plasmid was dephosphorylated using bacterial alkaline phosphatase. Using a 360 bp *EcoRI* DNA fragment from pC5A-48 containing the trp promoter and ribosome binding site the pPAIST-7 was generated following standard ligation.

To generate the pPAIST7HS prokaryotic expression vector (Shubeita *et al.* (1990) *J Biol. Chem.*, 265: 18379-18385), the pPAIST7 was partially digested with *HindIII* to linearize the plasmid, blunt-ended with the Klenow fragment of *E.coli* DNA polymerase I and ligated to eliminate the upstream *HindIII* site. Deletion of sequences in pPAIST7 downstream of the PAI-1 coding sequences between the *HindIII* and *SalI* sites and elimination of the *SalI* site was accomplished by sequential partial *SalI* digestion, complete *HindIII* digestion, blunt-ending with the Klenow fragment of *E.coli* DNA polymerase I, and ligation.

Mutagenesis reaction was carried out using the Multi site mutagenesis kit (Stratagene) following conditions specified by the supplier. Mutagenesis of amino acids in wild-type PAI-1 at positions P4-P1' in the reactive center loop corresponding to amino acids VSARM (SEQ ID NO:378) were made. A mutant PAI-1 was made (PAI-1/RRAR) containing replacement of the wild-type amino acid sequence VSARM with RRARM (SEQ ID NO:379) sequences in the PAI-1 reactive center loop from the P4 to P1' positions. The sequence of the RRARM mutagenic primer was: 5'-CCACAGCTGTCATAAGGAGGGCCAGAATGGCCCCCGAGGAGATC-3' (SEQ ID NO:380). A second mutant PAI-1 was made (PAI-1/69) containing replacement of the wild-type amino acid sequence VSARM with PFGRS (SEQ ID NO:389) sequences in the PAI-1 reactive center loop from the P4 to P1' positions. The sequence for the PFGRS mutagenic primer was:

5'CCACAGCTGTCATACCCTTCGGCAGAAGCGCCCCCGAGGAGATC-3' (SEQ ID NO:390). Following mutagenesis, the DNA isolated from the transformants was fully sequenced to confirm the presence of desired mutations and the absence of any additional mutations.

The mutants PAI-1/RRAR and PAI-1/69 were expressed as fusion proteins utilizing N-terminal poly histidine residues present in the pPAIST7HS vector. The expression and purification of mutant PAI-1s (*i.e.* PAI-1/RRAR and PAI-1/69) were based on methods as described in Ke *et al.* (*J Biol. Chem.*, 272: 16603-16609 (1997)). Expression of wild type and mutated variants of PAI-1 was accomplished by transforming 0.1μg DNA of pPAIST7HS vector encoding mutant PAI-1 into the *E. coli* strain BL21[DE3]pLys^S (Novagen), which synthesizes T7 RNA polymerase in the presence of isopropyl-1-thio-β-D-galactopyranoside. Bacterial cultures were grown at 37°C with vigorous shaking to an absorbance A_{595} of 1.1-1.3, and isopropyl-1-thio-β-D-galactopyranoside was added to a final concentration of 1 mM to induce the synthesis of T7 RNA polymerase and the production of PAI-1 proteins. Cultures were grown for an additional 1-2 h at 37°C and then shifted to 30°C for 2-6 h. Cells were pelleted by centrifugation at 8000 × *g* for 20 min at 4°C and resuspended in 40 ml of cold start buffer (20 mM sodium acetate, 200 mM NaCl, and 0.01% Tween 20, pH 5.6). The cell suspension was disrupted in a French pressure cell (Aminco), and cellular debris was removed by ultracentrifugation for 25 min at 32,000 × *g*.

Purification of soluble, active mutant PAI-1 was performed by injecting the lysate of *E. coli* containing soluble form of PAI-1/RRAR or PAI-1/69 onto an XK-26 column (Pharmacia Biotech Inc) packed with CM-50 Sephadex (Pharmacia, see *e.g.*, Sancho *et al.* (1994) *Eur. J. Biochem.* 224, 125-134). The column was washed with 5 column volumes of start buffer (20 mM sodium acetate, 200 mM NaCl, and 0.01% Tween 20, pH 5.6), and PAI-1 proteins were eluted using a 0.2-1.8 M linear gradient of NaCl in the same buffer. Peak fractions were collected, pooled, and concentrated using a centriplus 30 concentrator (Amicon). The concentrated fractions were used for activity measurement.

B. PAI-1 Activity Measurements

1. Active Site Titration Against Standard Trypsin

Active concentration of PAI-1/RRAR and PAI-1/69 was determined by active site titration against standard trypsin as described by Olson *et al.* (*J. Biol. Chem.*, 270:

30007 (1995)). Briefly, sequential additions of concentrated inhibitor (0.5 – 6.0 μM) were made to solutions of 1 μM β-trypsin (Sigma) and 10 μM p-aminobenzamidine probe (Sigma). Binding was monitored from the decrease in fluorescence accompanying the displacement of the bound probe from the enzyme active site as the inhibitor bound. After addition of each concentrated inhibitor a 1-2 minute equilibration time was allowed before assessment of fluorescence changes at excitation and emission wavelengths of 325 nm and 345 nm, respectively, to maximize the difference between bound and free probe fluorescence. Control titrations of just the probe with the inhibitor in the absence of the trypsin enzyme were performed to correct for background fluorescence. Inhibitor-enzyme titrations were fit by linear regression analysis.

2. Titration of standardized t-PA preparations

Mutant PAI-1s were also titrated against standardized t-PA preparations to assess activity. The inhibitory activity of wild-type PAI-1 or mutant PAI-1 was measured by a direct chromogenic assay using tPA (American Diagnostics, Inc, 100 U/μg) and the chromogenic tPA substrate H-*D*-Ile-Pro-Arg-*para*-nitroaniline substrate (S-2288, Chromogenix). Serially diluted PAI-1 (0.1 – 4.0 μg) were incubated with t-PA in a microtiter plate for a fixed time (typically, 20-60 minutes) at room temperature and the residual activity of tPA was measured by the addition of the chromogenic substrate S-2288 to a final concentration of 0.5 mM. The residual activity of t-PA following incubation with increasing concentrations of inhibitor was assessed by measuring the absorbance at 405 nm.

EXAMPLE 2

Construction of phage display libraries of u-PA variants

A. Cloning of wild-type u-PA into phagemid

To demonstrate functional display of the protease domain of u-PA on phage, high fidelity PCR was performed using primers 496 and 497, Pfu DNA polymerase and pCMV4 plasmid (SEQ ID NO:373) containing c-DNA of full length u-PA gene (SEQ ID NO:474) as a template. The primers used in the PCR amplification were as follows: 496, 5'-ACGTGGCCCAGGCGGCCTTTCAGTGTGGCCAAAAG-3' (SEQ ID NO:374); 497, 5'-TCCTGGCCGGCCTGGCCGAGCAGGCCATTCTC-3' (SEQ ID NO:375). Both the primers carry restriction sites (underlined) for *Sfi*I enzyme at the 5'terminus. After purification and *Sfi*I digestion, the PCR product was ligated to

*Sfi*I digested phagemid vector, pComb3H (SEQ ID NO:376) (Andris-Widhopf *et al.* (2000) *J Immunol Methods*, 28: 159-81). The phagemid was used for monovalent display of wild type or mutant u-PA (see below). This construct contains sequences encoding the C-terminal region of the gIIIp gene of fd phage. The presence of two *Sfi*I restriction sites in the vector with two different recognition sequences was exploited for designing the above-mentioned primers. The PCR products amplified using primers 496 and 497 enabled directional cloning of the u-PA protease domain cDNA (SEQ ID NO:475) into the phagemid (see below for ligation conditions). In the final construct, the PCR products containing sequences of the u-PA protease domain were cloned in the middle of OmpA and gIIIp sequences to display wild-type or mutant u-PA as an N-terminal gIIIp fusion.

B. Construction of mutant u-PA and phage display libraries of mutant u-PA

To construct u-PA phage display libraries, error-prone PCR amplification was carried out using the pCMV4/u-PA plasmid containing cDNA of the uPA gene as template, as set forth above, for 25 cycles in 100 µl reaction mixtures using reagents supplied with the PCR Diversify mutagenesis Kit (Clontech). Appropriate PCR conditions were followed to set up three different PCR reactions to amplify only the protease domain of the uPA gene (SEQ ID NO:475) using primers 496 and 497 from above by varying the amounts of manganese (MN2+) or dGTP as described by the manufacturer, to achieve 0.2, 0.5, or 0.9% of mutation rate incorporation into the cDNA. The amplified PCR products (805 bp, SEQ ID NO:475) were purified using a PCR purification kit (Qiagen) followed by *Sfi*I enzyme digestion. The *Sfi*I digested PCR products from each mutatgenesis reaction were used to generate three different libraries.

For library construction, the pComb3H vector (SEQ ID NO:376) was digested with *Sfi*I enzyme and the larger DNA fragment from this reaction was gel purified using a "Gel slice kit" (Qiagen). Three separate ligation reactions were carried out to construct three libraries with PCR products containing 0.2, 0.5 and 0.9% mutation rates. At least 1 µg of the gel purified vector was mixed with *Sfi*I digested PCR products (1:2 ratio) and the ligation mixtures were incubated overnight at 18°C. Next, the ligation mixtures were purified using Qiagen mini elute kit (Qiagen) and the DNA was finally eluted into 60 µl of Milli Q purified water. The purified DNA was electroporated into 400 µl of *E. coli* XL Blue1 electroporation competent cells

(Stratagene) using gene pulser (Bio Rad). The cells were then transferred to 10 ml of SOC medium (Invitrogen) and incubated at 37°C in a shaker for 1 hr followed by plating on large LB agar plates (245 mm X 245 mm) supplemented with carbenicillin (75 µg/mL). After overnight incubation of plates at 30°C the transformants were scraped using a cell scraper and the resulting cultures were grown in 2X YT medium supplemented with carbenicillin (75 µg/ml) at 37°C shaking for 2 hours. The cultures were infected with helper phage (VCS M13) at an MOI (multiplicity of infection) of 5 for amplification of the libraries. After 1 hour of growth at 37°C shaking, the cultures were supplemented with kanamycin to final concentrations of 3 µg/mL and grown overnight at 30°C with shaking. The cells were harvested and the phage particles present in the supernatant were precipitated using a PEG-NaCl solution. Simultaneously, to calculate the diversity of each library, an aliquot of the electroporated cells were plated on LB agar plates supplemented with carbenicillin (100 µg/ml) and after overnight incubation at 37°C the colonies were counted. The same methods were used to generate successive generations of u-PA phage display libraries for further improvement of identified u-PA variants against PAI-1/RRAR inhibitor. The DNA of u-PA variants identified from the previous libraries was used as template for construction of next generation libraries.

The catalytic efficiencies of wild type or u-PA phage libraries generated using random mutagenesis were analyzed using the indirect plasminogen activation assay. Briefly, 5 µl of u-PA phage (typically ~$5x10^{12}$ cfu), 0.2 µM Lys-plasminogen (American Diagnostic) and 0.62 mM Spectrozyme PL (American Diagnostica) were present in a total volume of 100 µl. Assays were performed in microtiter plates, and the optical density at 405 nm was read every 30 seconds for 1 h in a Molecular Devices Thermomax. Reactions were performed at 37°C. Inhibition of u-PA or u-PA variant phage also was assessed. Briefly, 5 µl of u-PA phages (typically ~$5x10^{12}$ cfu) were mixed with wt-PAI-1 (0.1 µM) or mutant PAI-1/RRAR inhibitor (1.0 µM) and incubated for 30 min at room temperature followed by addition of 0.62 mM Spectrozyme PL, 0.2 µM Lys-plasminogen (American Diagnostics, Inc.). The assays were read as mentioned above.

Example 3

Selection of variant u-PA from u-PA phage libraries against mutant inhibitor

A. Selection of u-PA phage/ mutant PAI-1 complexes

Mutant PAI-1/RRAR inhibitor or PAI-1/69 were used as the "bait substrate" in the panning experiment to isolate altered u-PA phage/s with improved reactivity towards the mutant substrate sequence from large, combinatorial u-PA phage display libraries described in Example 2 above. In brief, 5 µl (~ 2 X 10^{12} to ~ 1 X10^{13}) u-PA phage, containing an equal representation of u-PA phage from all three u-PA phage libraries (0.2, 0.5 and 0.9% mutagenesis frequency), was mixed with 5 µl bait substrate (from 0.1 to 1.0 µM PAI-1/RRAR or PAI-1/69) and 10 µl 10X indirect buffer pH 7.4 (0.5 M Tris, 1.0 M NaCl, 10 mM EDTA, 0.1% Tween 80) in a total volume of 100 µl (*i.e.* reaction contained 80 µl H_20). The reaction was incubated for varying times at room temperature (typically 1 hour, however, incubation time was adjusted to control the stringency of the solution).

The u-PA phage-PAI-1 inhibitor complexes were captured using $CuSO_4$ activated sepharose. Pre-activation of the chelating sepharose (200 µl; Pharmacia) was accomplished by treatment with $CuSO_4$ (100 mM). The $CuSO_4$ activated sepharose was blocked with 0.5% BSA in PBS buffer for 1 hour at room temperature. 100 µl of BSA blocked sepharose beads was added to 100 µl of the above panning mixture reaction in the presence of 800 µl of binding buffer (0.5 M NaCl, 20 mM Tris, 20 mM immidozole, pH7.4) to capture the His-tagged PAI-1 inhibitor-u-PA phage complexes. The incubation was continued for another 1 hour at room temperature. Next, the panning mixture was centrifuged for 1 min at 2000 rpm and the sepharose beads containing bound u-PA phage-PAI-1 inhibitor complexes were washed with 1 ml of binding buffer to remove unbound phages. The washing step was repeated 5-10 times and the beads containing bound complexes were transferred to new tubes after each wash to avoid any potential "carry over" of non-specific phages.

The bound u-PA phage-PAI-1/RRAR complexes were eluted in 100 µl of elution buffer (0.5M EDTA). A 95 µl aliquot of the eluted phages was used to infect 1 ml of XL-1 Blue *E. coli* cells (0.6 OD) to calculate the output of the libraries (indicating the number of phage obtained after selection). The infected bacteria were plated on large plates (245 mm X 245 mm) containing carbenicillin (75 µg/ml) to generate a library for the next round of selection.. Finally, the remaining output library (*i.e.* selected phage) was used to prepare individual phage clones for screening and/or generating a new library for the next round of selection. The concentrations of

bait substrate used in the selection and times of incubation of the library with the bait substrate were adjusted according to the desired stringency level. For example, conditions could be chosen such that <1%, 2%, 5%, 10%, or greater than 10% of the u-PA activity of the library was inhibited by the "bait PAI-1" containing the bait substrate sequence. Typically, the first round of selection was carried out using higher (*e.g.*, 0.5 μM) concentrations of bait PAI-1 and for successive rounds of selection the bait serpin concentration and incubation time with libraries were reduced. In addition, multiple stringencies can be used in parallel at each round of selection. Based on the quality of the output (e.g., signal to noise ratio of the phage output in paired +/- bait serpin selections (see description below)), and the quality of the resulting "hits" based on functional analysis, the phage output from one or more of these selections can be carried forward into the next round(s) of selection.

In parallel, control experiments were performed using the above-mentioned conditions for selection of phage from the u-PA library without bait and the phage from this control experiment was compared with the output of the library selections in the presence of bait serpin substrate. The cfu from the output of library selected in the presence of bait was normally in the range of 10^4 to 10^5 higher than the output obtained from the control selection. If higher background was observed with the control selection, the panning was repeated using more stringent conditions such as reducing incubation times, increasing concentrations of reactants (library, bait or beads) and increasing number and time of washing the selected phage bound to chelating sepharose (up to a factor of 10 or more).

B. Screening of u-PA phages with increased reactivity and catalytic efficiency towards new substrate sequences

An aliquot of eluted u-PA phages (5 μl) was mixed with XL-1Blue *E. coli* cells (100 μl) for infection and incubated at 37°C for 1 hr. The infected *E. coli* cells were then plated on LB agar plates supplemented with carbenicillin (100 μg/ml). After overnight incubation at 37°C, individual colonies were picked for phage preparations. The cells were grown in 2 ml of 2x YT supplemented with carbenicillin (100 μg/ml) and tetracycline (10 μg/ml) and phage preparation was performed as described (Sambrook, J *et al* (1989) *Molecular Cloning, A laboratory manual, Cold spring Harbor laboratory*). The identified phage were tested in the following assays to assess activity. The individual phage preparations were used in the indirect

plasminogen activation assay to identify active phages, and the active phage preparations were used for inhibition assays.

1. Indirect Plasminogen Activation Assay

The individual phage preparations were used in the indirect plasminogen activation assay to identify active u-PA phages. Briefly, 5 µl of u-PA phage (typically ~$5x10^{12}$ cfu), 0.2 µM Lys-plasminogen (American Diagnostic) and 0.62 mM Spectrozyme PL (American Diagnostica) were present in a total volume of 100 µl. Assays were performed in microtiter plates, and the optical density at 405 nm was read every 30 seconds for 1 h in a Molecular Devices Thermomax. Reactions were performed at 37°C.

2. Inhibition of u-PA phage by mutant PAI-1/RRAR

The phage that were identified as active in the indirect plasminogen activity assay were further tested for inhibition by mutant PAI-1/RRAR. Briefly, for the inhibition assays, 5 µl of active u-PA phages (typically~$5x10^{12}$ cfu) were added in duplicate wells of a microtiter plate followed by addition of a fixed concentration of mutant PAI-1 (*e.g.*, 1.0 µM) to one well and phosphate buffered saline (PBS) to the duplicate well. After mixing, the reaction was allowed to continue for a fixed time (*e.g.*, 30 min) at room temperature followed by addition of 0.62 mM Spectrozyme PL, 0.2 µM Lys-plasminogen (American Diagnostics, Inc.). For control experiments, wild-type u-PA phage was assessed under the same conditions. The plates were read at 405 nm in a spectrophotometer for 2 hrs. The selected u-PA phages that exhibited improved sensitivity for PAI-1/RRAR or PAI-1/69 as compared with wild-type u-PA phage were selected for further analysis and subjected to DNA sequencing.

3. Peptide Substrate Screening

In addition, to identify variants of u-PA phage with improved catalytic efficiency the individual phage clones were screened against an Ac-RRAR-AMC substrate. For the assay, a fixed volume of phage supernatants (*e.g.*, 35 µl) was mixed with 75 µM Ac-RRAR-AMC substrate in 1X indirect assay buffer (50 mM Tris, 100 mM NaCl, 1 mM EDTA, 0.01% Tween 80) in a total volume of 100 µl. The assay was carried out in 96-well or 384-well black assay plates (Corning) and read at 380-450 nm for 2 hrs in spectrophotometer (Molecular Devices) reader.

To confirm their improvement, the positive u-PA phages identified after inhibitor and peptide substrate screenings were re-screened using the assays set forth above.

C. Identification of Selected u-PA Mutants and Optimization of Identified Mutants

Positive phage clones were mixed with XL-1Blue *E. coli* cells for infection as mentioned above and the cultures were grown overnight with shaking at 37°C. Plasmid DNA was purified from the overnight culture using a plasmid preparation kit (Qiagen). The DNA was sent for custom sequencing using the following primers: 535- 5'-CAGCTATCGCGATTGCAG-3' (SEQ ID NO:381) ; 5542-5'GTGCGCAGCCATCCCGG-3' (SEQ ID NO:382). Amino acid residues altered in the mutant u-PA genes were identified after analyzing the sequencing data.

Table 10 below sets forth variants of u-PA identified from selection of variant u-PA from u-PA phage libraries against a PAI-1/RRAR mutant inhibitor. The mutations set forth in Table 10 below are with chymotrypsin numbering. The numbers in parentheses indicate the number of times the mutants were identified in the phage selection method. Based on results from activity assays, the best variants of u-PA phages are highlighted by underline. Amino acid sequences of a mature u-PA preproprotein (SEQ ID NO:433) containing the designated mutations are set forth in any of SEQ ID NOS: 434-445.

Table 10

u-PA Phage libraries Vs PAI-1/RRAR	Mutant name	Mutation site/s (Chymotrypsin Number)	Amino acid/s modified	SEQ ID NO:
Selection I	AR73 (2)	30	Phe – Ileu	434
	AR81	73, 89	Leu – Ala, Ileu - Val	435
Selection II & III	AR1	73	Leu-Pro	436
	AR3	217	Arg-Cys	437
	AR4 (3)	155	Leu-Pro	438
	AR7	75, 89, 138	Ser-Pro, Ileu-Val, Ileu-Thr	439
	AR32	137	Glu-Gly	440
	AR36	72, 155	Arg-Gly, Leu-Pro	441
	AR37	133	Gly-Asp	442
	AR66	160	Val-Ala	443
	AR24	38	Val-Asp	444
	AR85	132, 160	Phe-Leu, Val-Ala	445

Amino acid residues altered in the mutant u-PA gene exhibiting increased sensitivity against PAI-1/69 inhibitor following selection against the PAI-1/69 inhibitor were identified after analyzing the sequencing data as set forth above. The mutants identified from the first generation protease phage display library (I) are set forth below in Table 11. Subsequent generations of protease phage display libraries were created using the method as set forth above in Example 2B using the PCR Diversify mutagenesis kit and primers 496 and 497. For the generation II phage display library, the u-PA mutant u-PA/Ic containing a mutation corresponding to F30V based on chymotrypsin numbering was used as a template for the mutagenesis reaction. The mutants identified from the second generation protease phage display library (II) are set forth in the Table 11 below. For the generation III phage display library, the u-PA mutant u-PA-IIb or u-PA-IIb mutant containing mutations corresponding to F30V/ Y61(A)H or F30V/ K82E, respectively, based on chymotrypsin numbering were used as templates for the mutagenesis reaction. The mutants identified from the third generation protease phage display library (III) are set forth in Table 11 below. For the generation IV phage display library, the u-PA mutant u-PA/IIIa containing mutations corresponding to F30V/K82E/V159A based on chymotrypsin numbering was used as a template for the mutagenesis reaction. The mutants identified from the fourth generation protease phage display library (IV) are set forth in Table 11 below. The numbers in parentheses indicate the number of times u-PA phage were selected for that had the same mutation. The underline indicates the new mutations acquired by the mutant. Amino acid sequences of a mature u-PA preproprotein (SEQ ID NO:433) containing the designated mutations are set forth in any of SEQ ID NOS: 460-472.

Table 11

Phage libraries	Mutant name	Mutation sites	Amino acids modified	SEQ ID NO:
I	u-PA/Ia	21	Phe-Val	460
	u-PA/Ib	24	Ile-Leu	461
	u-PA/Ic (2)	30	Phe-Val	462
	u-PA/Id	30	Phe-Leu	463

II	u-PA/IIa u-PA/IIb u-PA/IIc	30, 61(A) 30, 82 30, 156	Tyr-His Lys-Glu Lys-Thr	464 465 466
III	u-PA/IIIa (8) u-PA/IIIb u-PA/IIIc u-PA/IIId (2)	30, 82, 159 30, 82, 39, 159 30, 82, 158, 159 30, 61A, 92	Val-Ala Thr-Ala, Val-Ala Thr-Ala, Val-Ala Lys-Glu	467 468 469 470
IV	u-PA/IVa u-PA/IVb	30, 82, 159, 80, 89, 187 30, 82, 159, 80, 84, 89, 187	Glu-Gly, Ile-Val, Lys-Glu Glu-Gly, Glu-Lys, Ile-Val, Lys-Glu	471 472

1. Optimization and recombination of amino acid resides 30 and 155 in Focused Phage Display Libraries against PAI-1/RRAR inhibitor

To enrich the sensitivity of u-PA variants against the PAI-1/RRAR inhibitor, amino acid 30 and amino acid 155 based on chymotrypsin numbering (identified as hot spots in the first selections as set forth in Table 10 above) were targeted for randomization and recombination using the following primers, respectively:

TC30- 5'GCCCTGGNNSGCGGCCATC- 3' (SEQ ID NO:383)

TC155- 5'GGAGCAGNNSAAAATGACTG- 3' (SEQ ID NO:384)

Mutagenesis was performed using the Quick Change multi site-directed mutagenesis kit (Stratagene) following conditions described by the manufacturer. In brief, after phosphorylation of the primers using T4 polynucelotide kinase (New England Biolabs) following conditions described by the manufacturer, three different reactions were performed for randomization of residues 30 and 155: 1) 30 individually; 2) 155 individually; and 30 plus 155 together. The DNA construct, pComb3H/u-PA variant (pARF 81), carrying mutations at residues L73A and I89V as compared to the corresponding wild type u-PA protease domain sequences, was used as a template in the mutagenesis reaction using primers TC30 (SEQ ID NO:383) and TC155 (SEQ ID NO: 384) individually for randomization of positions 30 and 155 respectively. In another reaction, these two primers were used to randomize positions 30 and 155 together in the pARF 81 variant DNA. Mutagenesis reaction was carried out using the Multi site mutagenesis kit (Stratagene) following conditions specified by the supplier. After mutagenesis, the reaction products were transformed into XL-1 Blue *E. coli* cells for library construction (See Example 2 above). The amplified u-PA

phage libraries were used for selection of improved variants of u-PA as set forth in Example 3A and 3B above.

Table 12 below sets forth variants of u-PA identified from selection against a PAI-1/RRAR mutant inhibitor of variant u-PA from focused u-PA phage libraries where all variants had background mutations at amino acid residues L73A and I89V based on chymotrypsin numbering. The mutations set forth in Table 12 below are with chymotrypsin numbering. The numbers in parentheses indicate the number of times the mutants were identified in the phage selection method. Based on results from activity assays, the best variants of u-PA phages are highlighted by underline. Amino acid sequences of a mature u-PA preproprotein (SEQ ID NO:433) containing the designated mutations are set forth in any of SEQ ID NOS: 446-459.

Table 12

Focused u-PA libraries Vs PAI-1/RRAR	Mutant Name	30(Phe)	155 (Leu)	SEQ ID NO
Selection I & II	ARF2	Thr	-	446
	ARF6	Leu	-	447
	ARF11	Val	-	448
	ARF17	Gly	-	449
	ARF16	Leu	-	450
	ARF33	-	Val	451
	ARF35	Met	-	452
	ARF36	-	Met	453
	ARF37	Met	-	454
	ARF43	Leu	-	455
	ARF47	Val	-	456
	ARF48	Leu	Met	457
	ARF103	Leu	-	458
	ARF115	Gly	Met	459

EXAMPLE 4

Expression of modified u-PA enzymes by transient transfection of COS cells.

For the expression of variant u-PA enzymes in a mammalian expression system, the positive clones identified from phage display results were used as a template (pComb3H carrying mutant u-PA protease domain sequences) for PCR

amplification of cDNA encoding the selected u-PA variant gene. Overlap extension PCR (Ho, S *et al* (1989) *Gene* 77, 51-59) was carried out using the following primers. 717- 5' -TTTCAGTGTGGCCAAAAG -3' (SEQ ID NO:385);
718, 5'-CAGAGTCTTTTGGCCACA –3' (SEQ ID NO:386);
850, 5' –GGGGTACCGCCACCATGAGAGCCCTGCTGGCGCGC-3' (SEQ ID NO:387);
851, 5' –GCTCTAGATCATCAGAGGGCCAGGCCATTCTCT-3' (SEQ ID NO:388). The primers 850 and 851 carry sequences for *Kpn*I and *Xba*I restriction enzymes (underlined) respectively.

PCR was performed in two steps to accomplish full-length amplification of mutated cDNA u-PA gene as described below. In the first step, PCR was carried out in a 100 µl reaction to amplify a 500 bp product (corresponding to the EGF and Kringle domains of u-PA) using Pfu DNA polymerase, primers 850, 718 and pCMV4 containing the full-length uPA gene (SEQ ID NO:474) as template. Similarly, another PCR was carried out to amplify the mutant u-PA protease domain (800 bp, *i.e.* corresponding to mutant sequences as compared to the wild-type sequence set forth in SEQ ID NO:475) using primers 851 and 717 with the appropriate mutant u-PA-pComb3H as template. These two PCR products were gel purified and used in the next round of PCR amplification. In the second step, the gel purified PCR products (5µl each) were used as templates in 100µl reaction mixture with primers 850 and 851. The primers 717 and 718 have overlapping complementary sequences that allowed the amplification of the full-length u-PA cDNA (1.3 kb) in the second step PCR. The PCR product was purified using a PCR purification kit (Qiagen) and then digested with *Kpn*I and *Xba*I restriction enzymes. After purification using QIAquick columns (Qiagen), the full-length u-PA gene was ligated with the pCMV4 mammalian expression vector (SEQ ID NO:373) that had been previously digested with *Kpn*I and *Xba*I. The ligation mixture was electroporated into *E. coli* XL-1Blue cells and plated on LB plates supplemented with carbenicillin (100 µg/ml). After overnight incubation of plates at 37°C, individual colonies were picked up and grown in 2 ml LB medium for plasmid purification. The plasmids were used for sequencing the entire u-PA gene using the following sequencing primers. UPAF1-5'ATGAGAGCCCTGCTGGCGCGCC-3' (SEQ ID NO:476) and
UPAF2- 5'GGAAAAGAGAATTCTACCG-3' (SEQ ID NO:477).

Mutant u-PA clones with the correct mutations, without any additional mutation(s), were prepared in large quantities using Midi Plasmid preparation kit (Qiagen) and used for electroporation into COS-1 cells using a Bio-Rad Gene Pulser. 20 μg of cDNA, 100 μg of carrier DNA, and approximately 10^7 COS-1 cells were placed into a 0.4-cm cuvette, and electroporation was performed at 320 V, 960 microfarads, and $\Omega = \infty$ (Tachias *et al.* (1995) *J Biol. Chem.*, 270: 18319-18322). Following electroporation, the transfected cells were incubated overnight at 37°C in DMEM medium (Irvine Scientific) containing 10% fetal calf serum and 5 mM sodium butyrate. Cells were then washed with serum free medium and incubated in DMEM for 48 h at 37°C. After incubation with serum-free media, conditioned media was collected and used for further characterization.

EXAMPLE 5

Characterization of Purified Mutant u-PAs

A. Measurement of enzyme concentration

The single-chain form of the mutant u-PA enzymes in conditioned media was converted into the corresponding two-chain enzyme by treatment with plasmin-sepharose (Calbiochem). The concentration of active u-PA in these media was measured by active site titration with a standard PAI-1 inhibitor preparation that had been previously titrated against a trypsin primary standard as described in Example 1 above. Total enzyme concentrations were measured by enzyme-linked immunosorbent assay following the protocols of laboratory manual, Harlow *et al* (1998) *Using Antibodies*, Cold Spring Harbor Laboratory. The ratio of these concentrations yields the fraction of u-PA variant that is active in each media.

B. Direct Chromogenic Assay of u-PA

Direct assays of u-PA activity utilized the substrate carbobenzoxy-L-γ-glutamyl (α-t-butoxy)-glycyl-arginine-p-nitroanilide monoacetate salt (Cbo-L-(γ)-Glu(α-t-βuO)-Gly-Arg-pNA AcOH; Spectrozyme® uPA, American diagnostica) (Madison *et al.* (1995) *J Biol. Chem.*, 270:7558-7562). Enzyme activity was determined by measuring the increase in absorbance of the free (pNA) generated per unit time at an absorbance of 405 nm. Kinetic assays were performed over time using enzyme concentrations between 6 and 8 nM. The concentration of Spectrazyme® uPA was varied from 25 to 150 μM in assays of two-chain u-pA, and from 25 to 200

μM in assays of the protease domain of u-PA. Reactions were performed in 96-well microtiter plates and reaction rates were assessed by measurement of absorbance at 405 nm every 30 seconds for up to 2 hours using a Spectromax M2 or M5 plate reader (Molecular Devices). The kinetic constants k_{cat}, K_m, and k_{cat}/K_m (specificity constant) were calculated by graphing the inverse of the substrate concentration versus the inverse of the velocity of absorbance at OD_{405}, and fitting to the Lineweaver-Burk equation ($1/velocity=(K_m/V_{max})(1/[S]) + 1/V_{max}$; where $V_{max}=[E]*k_{cat}$).

Table 13 below set forth the results of kinetic analysis of mutants of u-PA, identified as exhibiting increased sensitivity against PAI-1/69 inhibitor, in a direct assay of u-PA enzyme activity. The results show that each of the mutant u-PAs identified have a decreased enzyme activity as compared to wild-type u-PA as determined from the measurement of the specificity constant for cleavage (kcat/Km) of the Spectrozyme® uPA substrate. In the Table, the variants tested are those identified in Table 11 above following selection from successive generations (I to IV) of u-PA phage display libraries.

TABLE 13:

u-PA mutants	K_m (mM)	k_{cat} (s-1)	k_{cat}/K_m (M-1 s-1)	Mutant/Wt u-PA
u-PA/Ic (30)	0.745	22.3	2.9×10^5	0.30
u-PA/IIb (30, 82)	0.299	11	3.6×10^5	0.38
u-PA/IIIa (30, 82, 159)	0.239	11.6	4.8×10^5	0.50
u-PA/IIIb (30, 39, 82, 159)	0.212	9.6	4.5×10^5	0.47
u-PA/IVa (30, 80, 82, 89, 159, 187)	0.177	10	5.6×10^5	0.58
u-PA/IVb (30, 80, 82, 84, 89, 159, 187)	0.321	11	3.4×10^5	0.35
Wild type u-PA	0.174	16.6	9.5×10^5	1.0

C. Kinetic analysis of u-PA variants using flourogenic substrate

Direct assays for measuring activity of the u-PA variants against the RRAR target substrate sequence were performed utilizing an Ac-RRAR-AMC substrate. The use of 7-amino-4-methylcoumarin (AMC) fluorogenic peptide substrate is a routine method for the determination of protease specificity (Zimmerman *et al.* (1977) *Anal Biochem*, 78:47-51; Harris *et al.* (2000) *PNAS*, 97:7754-7759). Specific cleavage of the anilide bond frees the fluorogenic AMC leaving group, providing an efficient means to determine the cleavage rates for individual substrates. The substrates were

serially diluted from 0.05 to 12.0 mM and incubated in the presence of protease (9- 25 nM) in a Costar 96-well black half-area assay plate. The fluorescence from the free AMC leaving group was measured in a fluorescence spectrophotometer (Molecular Devices Gemini XPS) at an excitation wavelength (380 nm) and emission wavelength (450 nm) with reference to an AMC standard. The rate of increase in fluorescence was measured over 30 minutes with readings taken at 30 second intervals. The kinetic constants k_{cat}, K_m, and k_{cat}/K_m (specificity constant) were calculated by graphing the inverse of the substrate concentration versus the inverse of the velocity of substrate cleavage, and fitting to the Lineweaver-Burk equation ($1/velocity=(K_m/V_{max})(1/[S]) + 1/V_{max}$; where $V_{max}=[E]*k_{cat}$).

Table 14 below sets forth the results of the kinetic analysis of the u-PA variants ARF2 and ARF36 against the Ac-RRAR-AMC substrate. The results show that the specificity constant for the RRAR substrate for the selected u-PA protease variants are increased about or more than 10-fold as compared to wild-type u-PA.

TABLE 14:

Mutants	K_m (μM)	K_{cat}/K_m (M^{-1} s^{-1})	Improvement of K_{cat}/K_m mutant/Wt u-PA
u-PA/ARF2	546	434	11.7
u-PA/ARF36	614	357	9.6
Wt u-PA	381	37	1.0

D. Kinetic analysis of plasminogen activation using an indirect chromogenic assay

An indirect chromogenic assay was performed to determine the activities of the wild-type and mutant u-PA produced as purified protein preparations (Madison *et al.* (1989) *Nature*, 339: 721-724; Madison *et al.* (1990) *J Biol. Chem.*, 265: 21423-21426). In this assay, free p-nitroaniline is released from the chromogenic substrate Spectrozyme PL (H-D-norleucylhexahydrotyrosyl-lysine-p-nitroanilide diacetate salt, American Diagnostics, Inc.) by the action of plasmin generated by the action of u-PA on plasminogen. The release of free p-nitroaniline was measured spectrophotometrically at OD_{405} nm.

For the assay, 100 μl reaction mixtures containing 0.25-1 ng of the uPA enzymes to be tested, 0.62 mM Spectrozyme PL, 0.2 μM Lys-plasminogen (American

Diagnostics, Inc.), were combined in a buffer containing 50 mM Tris-HCL (pH 7.5), 0.1 M NaCl, 1.0 mM EDTA and 0.01% (v/v) Tween 80. The reaction was incubated at 37°C in 96-well, flat-bottomed microtiter plates (Costar, Inc.) and the optical density at 405 nm (OD405) was read every 30 s for 1 h in a Molecular Devices Thermomax. The kinetic constants k_{cat}, K_m, and k_{cat}/K_m (specificity constant) were calculated as described earlier (Madison, *E. L* (1989) *Nature* 339, 721-724).

Table 15 below sets forth the results of kinetic analysis of mutants of u-PA, identified as exhibiting increased sensitivity against PAI-1/69 inhibitor, in an indirect assay of u-PA enzyme activity. The results show that each of the mutant u-PAs identified have a decreased enzyme activity as compared to wild-type u-PA as determined from the indirect measurement of the specificity constant for cleavage (kcat/Km) of cleavage of the Spectrozyme® PL substrate. In the Table, the variants tested are those identified in Table 11 above following selection from successive generations (I to IV) of u-PA phage display libraries.

TABLE 15:

u-PA mutants	K_m (μM)	k_{cat} $^{(s-1)}$	k_{cat}/K_m $^{(M-1\ s-1)}$	Mutant/Wt u-PA
u-PA/Ic	9.01	24.7	2.7×10^6	0.24
u-PA/IIb	8.6	22.6	2.6×10^6	0.23
u-PA/IIIa	6.31	37.6	5.9×10^6	0.53
u-PA/IIIb	9.3	29.8	3.2×10^6	0.29
u-PA/IVa	7.03	38.7	5.5×10^6	0.50
u-PA/IVb	7.5	45.3	6.0×10^6	0.54
Wild type u-PA	6.03	70.1	1.1×10^7	1.0

E. Kinetic analysis of inhibition of mutant u-PA enzymes by wild-type PAI-1 and mutant PAI-1

The second order rate constants (k*i*) for inhibition of mutant and wild type u-PA (positive control) were determined using pseudo-first order (k*i* $<2 \times 10^6$) or second order (k*i* $>2 \times 10^6$) conditions. For each enzyme, the concentrations of enzyme and inhibitor (mutant PAI-1) were chosen to yield several data points for which the residual enzymatic activity varied between 20 and 80% of initial activity. Kinetic measurements on the rate of interaction of wild-type and mutant u-PA with wild-type and mutant PAI-1 was performed at 24°C in 0.1 M Tris-HCl buffer (pH 7.4) containing 0.1 mM EDTA and 0.1% (v/v) Tween 20. The indirect chromogenic

assay as described in Part D above was used to determine the residual enzyme activity remaining as a function of time.

The rate constants for inhibition of wild-type or mutant u-PA by PAI-1 were under pseudo-first order conditions for an excess of PAI-1 over u-PA as described previously (see *e.g.*, Holmes *et al.* (1987) *Biochemistry*, 26: 5133-5140; Beatty *et al.* (1980) *J. Biol. Chem.*, 255:3931-3934; Madison *et al.* (1990) *PNAS*, 87: 3530-3533; Madison *et al.* (1993) *Methods Enzymol.*, 223:249-271). Briefly, purified wild-type or mutant u-PA (3-50 fmol) were incubated at room temperature for 0 to 120 minutes with wild-type or mutant PAI-1 (35-1330 fmol). Following incubation, the mixtures were diluted and the residual enzymatic activity was determined in a standard chromogenic assay as set forth in D above. Data were analyzed by plotting ln (residual activity/initial activity) versus time and determining the slope of the resulting straight line. Pseudo-first order rate constants were then derived by dividing the slope by the concentration of the inhibitor in the reaction.

For second order reactions, equimolar concentrations of wild-type or mutant u-PA and wild-type or mutant PAI-1 were mixed directly in microtiter plate wells and preincubated at room temperature for periods of time varying from 0 to 30 min. Following preincubation, the mixtures were quenched with an excess of neutralizing anti-PAI antibodies and residual enzymatic activity was measured in the indirect chromogenic assay. The indirect, chromogenic assays were compared with control reactions containing no PAI-1 or to which PAI-1 was added after preincubation and addition of anti-PAI-1 antibody, plasminogen and Spectrozyme PL to the reaction mixture. Data were analyzed by plotting ln (residual activity/initial activity) versus time and determining the slope of the resulting straight line. Second order rate constants were then derived by dividing the slope by the concentration of the inhibitor in the reaction.

Table 16 below sets forth second order rate constants for inhibition of u-PA variants by PAI-1/ RRAR inhibitor. The results show that the variants ARF2 and ARF36 have about a 20-fold improvement in specificity for the PAI-1/RRAR inhibitor substrate as assessed by the increased k*i* rate constant for inhibition as compared with wild-type u-pA.

TABLE 16:		
u-PA variants	2nd order rate constant ($M^{-1}s^{-1}$)	Improvement Mutant/Wt-uPA
u-PA/ARF2	1.6×10^5	18.3
u-PA/ARF36	1.7×10^5	20.2
Wt u-PA	8.7×10^3	1.0

Tables 17 and 18 below are the results of second order rate constants of inhibition for wild-type (Table 17) or mutant PAI-1/69 inhibitor (Table 18) by wild-type u-PA or u-PA variants selected against the PAI-1/69 inhibitor. The variant u-PAs set forth in each of Tables 17 and 18 are those identified from one (I) to four (IV) successive rounds of a u-PA phage library selection as depicted in Table 11 above. The results in Table 17 show that some of the mutant u-PAs (*i.e.* u-PA/IIIa, u-PA/IIIb, and u-PA/IVa) have a slightly increased second order rate constant for inhibition as compared to wild-type u-PA and the mutants u-PA/Ic, u-PA/IIb, and u-PA/IVb have a decreased second order rate constant for inhibition as compared to wild-type u-PA. The results in Table 18 show that the second order rate constant for inhibition is dramatically increased for each of the selected u-PA variants for inhibition by the mutant PAI-1/69 inhibitor. The results show that that each of the selected variants have a greater than 13-fold improvement in specificity for the PAI-1/69 inhibitor substrate, with variants u-PA/IIIb, u-PA/IVa, and u-PA/IVb each exhibiting close to or more than a 40-fold improvement in specificity.

TABLE 17:		
u-PA mutants	2nd order rate constant ($M^{-1}s^{-1}$)	Sensitivity factor (Mutant/Wt u-PA)
u-PA/Ic	2.4×10^6	0.3
u-PA/IIb	2.9×10^6	0.3
u-PA/IIIa	9.7×10^6	1.2
u-PA/IIIb	1.3×10^7	1.6
u-PA/IVa	2.7×10^7	1.6
u-PA/IVb	6.8×10^6	0.8
Wild type u-PA	7.5×10^6	1.0

TABLE 18:

u-PA mutants	2^{nd} order rate constant ($M^{-1}s^{-1}$)	Increased sensitivity factor (Mutant/Wt u-PA)
u-PA/Ic	$1.0x10^5$	13.7
u-PA/IIb	$1.1x10^5$	15.3
u-PA/IIIa	$1.8x10^5$	24.5
u-PA/IIIb	$2.8x10^5$	37.5
u-PA/IVa	$2.7x10^5$	35.9
u-PA/IVb	$3.2x10^5$	42.6
Wild type u-PA	$7.5x10^3$	1.0

EXAMPLE 6

Selection of variant MT-SP1 from MT-SP1 phage libraries against mutant AT3 inhibitor

A mutant antithrombin III (AT3) inhibitor (SEQ ID NO:5) containing a hexa-peptide sequence in the reactive site loop (RSL) residues P4-P3-P2-P1-P1'-P2' of a wildtype AT3 corresponding to amino acid residues IAGRSL (SEQ ID NO: 478) was mutated to contain a substitution in these residues to SLGRKI (SEQ ID NO:479), corresponding to the amino acid residues of a complement C2 cleavage sequence. The mutant $AT3^{SLGR-KI}$ was used as the "bait substrate" in the protease selection experiment to isolate phage with improved reactivity towards the mutant substrate sequence from a large, combinatorial MT-SP1 phage display library. In brief, for analysis of the first generation selection, 5 µl of a 1:100 SM1 (~ 3 X 10^{13}) MT-SP1 phage library that is a low mutagenic frequency library (*i.e.*, 0.2-0.5% mutagenesis frequency) that has enzymatic activity was combined in equal representation with 5 µl of a 1:100 SM2 (~ 3 X 10^{12}) MT-SP1 phage library that contains a higher mutagenesis frequency (*i.e.* 0.9%). The phage libraries were mixed with 5 µl heparin (5 ng/µl; from stock of porcine intestinal mucosa), 5 µl bait $AT3^{SLGR-KI}$ substrate (ranging in concentrations from 0 (*i.e.* 5 µl H_20), 0.018 µM, 0.18 µM, 1.8 µM, or 18 µM) in the presence of 5 µl (18 µM) wildtype, plasma purified AT3 and 5 µl 10X MTSP activity buffer (0.5 M Tris HCl, pH 8, 0.3 M NaCl, 0.1% Tween 30) in a total volume of 50 µl (*i.e.* reaction contained 20 µl H_20). The reaction was incubated for 4.5 hours at 37°C.

The MTSP-1 phage-AT3 inhibitor complexes were captured using $CuSO_4$ activated sepharose. 200 µl of chelating sepharose (Pharmacia) was pre-activated

with $CuSO_4$ (100 mM). The $CuSO_4$ activated sepharose (100 µl) was blocked with 2 ml 0.5% BSA in PBS buffer for 1 hour at room temperature. The beads were harvested from the blocking solution by pelleting at 6500 rpm for 60 sec. followed by resuspension in 450 µl of binding buffer (0.5 M NaCl, 100 M Tris pH 8, 10 mM Imidazole, 0.1% Tween 20). 50 µl of the above panning mixture reaction was added to the $CuSO_4$ activated sepharose beads to capture the His-tagged AT3 inhibitor-MTSP-1 phage complexes. The incubation was continued for another 1 hour at room temperature. Next, the panning mixture was centrifuged for 1 min at 2000 rpm and the sepharose beads containing bound AT3 phage-MTSP-1 inhibitor complexes were washed with 500 µl of binding buffer to remove unbound phages. The washing step was repeated 5 times and the beads containing bound complexes were transferred to new tubes after each wash to avoid any potential "carry over" of non-specific phages.

The bound MT-SP1 phage- $AT3^{SLGR-KI}$ complexes were eluted in 100 µl of elution buffer (0.5 M EDTA, pH 8.0). A 50 µl aliquot of the eluted phages was used to infect 3 ml of TG1 *E. coli* actively growing cells (A600= 0.5; 0.5 OD= ~1.5 X 10^8 colonies/ml) for 20 minutes at 37°C. The infected bacteria were plated on large plates (245 mm X 245 mm) containing carbenicillin (75 µg/ml) and incubated at 30°C overnight. The next morning the plates were harvested. The colonies on each plate were counted and compared to the background plate that contained no $AT3^{SLGR-KI}$ inhibitor. The results of the colony counts are set forth in Table 19.

TABLE 19: Results of First Generation Selection

Concentration of $AT3^{SLGR-KI}$ in reaction	**Colonies from first round of selection**
18 µM $AT3^{SLGR-KI}$	Lawn
1.8 µM $AT3^{SLGR-KI}$	6088
0.18 µM $AT3^{SLGR-KI}$	1712
0.018 µM $AT3^{SLGR-KI}$	3700
0 µM $AT3^{SLGR-KI}$	840

The colonies from the $AT3^{SLGR-KI}$- containing plates were scraped into 25 ml 2YT supplemented with carbenicillin (~ 100 µg/ml) after the plates had been placed

in the cold room for 2 hours to firm up the agar. 20 ml of the 2YT bacteria containing medium was added to 500 ml 2YT containing carbenicllin and the A_{600} was determined to be 0.13. The bacteria were grown to an OD= ~0.5 and then ~ 1 $X10^{10}$ to 2.6 X 10^{13} cfu/ml of helper phage (VS M13) were added (in ~150 µl-200 µl) for amplification of the libraries. After 1 hour of growth at 37°C shaking, the cultures were supplemented with kanamycin to final concentrations of 3 µg/mL and grown overnight at 30°C with shaking. The cells were harvested and the phage particles present in the supernatant were precipitated using a PEG-NaCl solution. For analysis of the second generation of MT-SP1 phage selection, the conditions were similar to the first generation, except that reaction against the $AT3^{SLGR-KI}$ bait substrate was for only 27 minutes instead of 4.5 hours to enhance the stringency of the selection.

Following elution of the bound MT-SP1 phage- $AT3^{SLGR-KI}$ complexes as described above, 50 µl aliquot of the eluted phages were used to infect 3 ml of TG1 *E. coli* actively growing cells (A600= 0.5; 0.5 OD= ~1.5 X 10^8 colonies/ml) for 20 minutes at 37°C. The infected bacteria were plated on large plates (245 mm X 245 mm) containing carbenicillin (75 µg/ml) and incubated at 30°C overnight. The next morning the plates were harvested. The colonies on each plate were counted and compared to the background plate that contained no $AT3^{SLGR-KI}$ inhibitor. The results of the colony counts are set forth in Table 20.

TABLE 20: Results of Second Generation Selection

Concentration of $AT3^{SLGR-KI}$ in reaction	Colonies from second round of selection; (background)	Enrichment Ratio Compared to Background
18 µM $AT3^{SLGR-KI}$	2476 (165)	15:1
1.8 µM $AT3^{SLGR-KI}$	1750 (90)	19:1
0.18 µM $AT3^{SLGR-KI}$	2012 (110)	18:1
0.018 µM $AT3^{SLGR-KI}$	1824 (89)	21:1

The colonies were picked for further characterization. The cells were grown in 2 ml of 2x YT supplemented with carbenicillin (100 µg/ml) and tetracycline (10 µg/ml) and phage preparation were performed as described (Sambrook, J *et al* (1989) *Molecular Cloning, A laboratory manual, Cold spring Harbor laboratory*). The

selected phage were tested for enzymatic activity against an Ac-SLGR-ACC substrate. Further, the selected phage were selected for resistance to inactivation by wildtype AT3 or Plasma.

EXAMPLE 7

Expression and purification of Mutant AT3 Inhibitors

A. Generation of variant AT3

Mutant AT3 proteins for use as protease trap "bait substrates" were created by introducing modifications into the amino acid sequence of the AT3 reactive center loop (RCL) by using the coding region of human antithrombin III (AT3) gene (SEQ ID NO.: 612, purchased from Origene Technologies, Catalog # TC110831;) as a template. The AT3 cDNA was amplified by PCR using the forward primer having the sequence of nucleic acids set forth in SEQ ID NO.: 626: **GTCACTGACTGACGT***GGATCC*CACGGGAGCCCTGTGGACATC (which contains a stuffer sequence (shown in bold above), a BamH1 site (shown in italics), and a portion that hybridizes to the AT3 gene (shown in plain text)), and a reverse primer having the sequence of nucleic acids set forth in SEQ ID NO.: 628: GTAGCCAACCCTTGTGTTAAGGGAGGCGGAAGCCATCACCACCATCACCA CTAAGAATTC. Following amplification, the cDNA was subcloned into the pAcGP67b baculovirus transfer vector (BD Biosciences SEQ ID NO.: 494) using restriction sites Bam and EcoRI. Either a C-terminal 6xHis-tag (SEQ ID NO.: 496) or a C-terminal FLAG-tag (DYKDDDDK; SEQ ID NO.: 495) was added during this subcloning step so that AT3 mutants later could be isolated by affinity purification. The nucleotide and amino acid sequence of the cloned AT3 fusion protein, containing AT3 fused to the 6xHis tag using a four amino acid GGGS linker (SEQ ID NO.:620) are set forth in SEQ ID NOs.:613 and 614, respectively.

To make mutant AT3 bait substrates for isolating target proteases with various specificities, mutagenesis reactions were carried out using the Quikchange® site-directed mutagenesis kit (Stratagene) following the conditions specified by the supplier to introduce amino acids residues of target cleavage sequences in place of the wild-type AT3 reactive center loop (RCL) sequence, IAGRSL (SEQ ID NO.: 478) (amino acid residues 422-427 of the precursor AT3 polypeptide sequence set forth in

SEQ ID NO.: 5; and amino acid residues 390-395 of the mature AT3 polypeptide sequence set forth in SEQ ID NO.: 493).

One such mutant, AT3 (AT3/ RRVR-KE) (SEQ ID NO.: 497), was made by replacing amino acid residues of the wild-type IAGRSL amino acid sequence with amino acid residues RRVRKE (SEQ ID NO.:498) from a targeted VEGFR2 cleavage sequence. Another mutant, AT3 (AT3/ SLGR-KI) (SEQ ID NO.: 499), was made by replacing the wild-type IAGRSL amino acid sequence with amino acid residues SLGRKI (SEQ ID NO.:479) from a targeted complement C2 protein cleavage sequence.

For the Quikchange® PCR, the Wild-type AT3 RCL primer had the following sequence of nucleic acids, which is set forth in SEQ ID NO: 630: GCTGCAAGTACCGCTGTTGTGATTGCTGGCCGTTCGCTAAACCCCAACAG GGTGACTTTC. The Complement C2 target sequence primer had the following sequence of nucleic acids, which is set forth in SEQ ID NO.: 632: GCTGCAAGTACCGCTGTTGTGTCGTTAGGCCGTAAAATTAACCCCAACAGGGTGA CTTTC. The VEGFR2 Target sequence primer had the following sequence of nucleic acids, which is set forth in SEQ ID NO.: 634: GCTGCAAGTACCGCTGTTGTGCGCCGTGTGCGCAAAGAAAACCCCAACAG GGTGACTTTC.

Vectors containing the wild-type AT3 cDNA and vectors containing the mutant AT3 cDNA were each transformed and amplified in XL-1-Blue supercompetent cells (Stratagene). Plasmid DNA was purified from the cells using the Qiagen Plasmid Maxi Kit (Qiagen) following the conditions specified by the supplier.

B. Expression of AT3 mutants

Sf9 insect cells were used to express and purify both His-tagged and FLAG-tagged wild-type and mutant AT3 proteins using the AT3-containing pAcGP67b transfer vectors described above. Sf9 cells were adapted for growth in SF900 II serum-free medium (Invitrogen) and grown to 85-90% confluence in 35 mm dishes. Cells were transfected using the FlashBac® baculovirus expression system (Oxford Expression Technologies) following the conditions and protocol specified by the supplier. 500 ng of the AT3 transfer vector and 500 ng of the FlashBac® recombination vector were pre-incubated for 20 min with 5 µl of Cellfectin®

transfection reagent (Invitrogen) in 1 ml SF900 II serum-free media without antibiotics, then applied drop-wise to cells. Five (5) hours after transfection, cells were centrifuged and resuspended in 2 mL SF900 II serum-free medium with antibiotics (antibiotic/antimycotic solution; Cellgro) and were incubated at 28°C for 4 days. Virus was expanded in Sf9 cells to a maximum titer of 1 x 10^6 pfu/mL, as determined by plaque assay. Recombinant AT3 then was expressed using the High Five® (BTI-TN5B1-4) insect cell line (Invitrogen) and Excell™ 405 serum-free media (JRH Biosciences). Cells were infected at a multiplicity of infection (MOI) between 0.1 and 1 and grown in 300 mL culture volumes in 1 L Erlenmeyer flasks for 4-5 days, shaking at 125 RPM on an orbital shaking platform.

C. Affinity-based purification of wild-type and mutant AT3 proteins

For affinity-based purification of His-tagged AT3 proteins, supernatants from the cultures from Example 7B were cleared by centrifugation and filtration using a 0.45 μM filter and dialyzed into a buffer containing 50 mM Sodium Phosphate pH 7.5, 300 mM NaCl. Protein was purified by column chromatography using the BioLogic Duoflow™ chromatography apparatus (Bio-Rad) and 10 mL of TALON® cobalt metal affinity resin (Clontech). The resin-bound His-tagged protein was eluted with a linear gradient of 50 mM Sodium Phosphate pH 7.5, 300 mM NaCl and 50 mM Sodium Phosphate pH 6.5, 300 mM NaCl, 150 mM Imidazole. Fractions containing protein were combined and dialyzed into AT3 storage buffer (50 mM Sodium Phosphate pH 6.5, 300 mM NaCl, 5% glycerol). To demonstrate that the purified AT3 preparation contained active protein, an MT-SP1 inhibition (active site titration) assay, as described herein, in Example 14 below, was performed in order to measure the ability of the dialyzed AT3 to inhibit the ability of MT-SP1 to cleave a substrate. The reaction mixture from this MT-SP1 inhibition assay was assessed kinetically for cleavage of 0.4 mM Ac-RQAR-ACC (Acetyl-Arg-Gln-Ala-Arg-ACC) substrate (custom synthesis) on a SpectraMax® M5 (SpectraMax® M5 Microplate Reader, Molecular Devices) (Molecular Devices, Inc). The "ACC" in the name of this substrate refers to the 7-amino-4-carbamoylmethylcoumarin leaving group. The ACC leaving group was detected at wavelengths of Excitation (Ex) = 380, Emission (Em) = 450 and cutoff (c/o) = 435. Total yield of purified His-tagged AT3 protein was approximately 1-3 mg/L.

For affinity-based purification of FLAG-tagged AT3 proteins, supernatants from the cultures were cleared by centrifugation and filtration as described above. Cleared supernatant was dialyzed into Tris-buffered Saline (TBS) pH 7.4 and added to a fresh 1 L Erlenmeyer flask in a total volume of 300 mL. 2 mL of pre-equilibrated anti-FLAG M2 affinity gel (Sigma) was added, and the total volume was incubated on an orbital shaking platform at 125 RPM for 3 hours at 4°C. Resin-bound FLAG-tagged AT3 protein was collected by gravity using a fritted 20 mL chromatography column (Bio-Rad). The resin was washed a first time with 5 mL of TBS, once with 5 mL of TBST (TBS with 0.1% Tween-20), and a second time with 5 mL of TBS. The AT3 protein then was eluted by adding 10 mL TBS containing 0.2 mg/mL FLAG peptide (Sigma). Eluate was concentrated and dialyzed into AT3 storage buffer (50 mM Sodium Phosphate pH 6.5, 300 mM NaCl, 5% glycerol) and activity was assayed as above, using a matriptase (MT-SP1) inhibition (active site titration) assay as described above and in Example 14A below. Total yield of purified FLAG-tagged AT3 protein was approximately 0.5-1 mg/L.

These purified FLAG- and His-tagged AT3 proteins were used as protease traps for identification of proteases recognizing particular target site sequences, for example, in the methods described in the following Examples.

EXAMPLE 8

Construction of phage-display libraries of protease variants

A. Cloning of wild-type and C122S MT-SP1 protease domain (B-chain) into the pMal-C2 phagemid display vector

cDNA (SEQ ID NO.: 504) encoding a mature MT-SP1 protease domain (MT-SP1 B-chain) (SEQ ID NO.: 505), which contains amino acids 615-854 of the full-length MT-SP1 protein set forth in SEQ ID NO.: 253, was cloned, using the restrictions sites Nde1 and HindIII, into a pMal-C2 vector (SEQ ID NO.: 615) (New England Biolabs), which contains an STII leader sequence (TGAAAAAGAATATCGCATTTCTTCTTGCATCTATGTTCGTTTTTTCTATTG CTACAAACGCGTATGCA (SEQ ID NO.: 636) to facilitate secretion, and nucleic acids encoding a C-terminal domain of filamentous phage M13 GeneIII (SEQ ID NO.:616). The MT-SP1 protease domain cDNA was inserted between the leader sequence and the GeneIII domain so that the final construct contained the sequence of nucleic acids set forth in SEQ ID NO.: 510, which encodes an MT-SP1 N-terminal

GeneIII fusion protein. The encoded amino acid sequence (SEQ ID NO.: 506) of this fusion protein is set forth below, with the STII leader sequence (SEQ ID NO.: 511) in plain text, the mature MT-SP1 domain in bold and the C-terminal GeneIII (SEQ ID NO.: 512) domain in italics. The * indicates the presence of a stop codon in the nucleic acid sequence encoding the protein.

SEQ ID NO.: 506:

mkkniafllasmfvfsiatnaya**vvggtdadegewpwqvslhalgqghicgaslispnwlvsaahcyi ddrgfrysdptqwtaflglhdqsqrsapgvqerrlkriishpffndftfdydiallelekpaeyssmvr piclpdashvfpagkaiwvtgwghtqyggtgalilqkgeirvinqttcenllpqqitprmmcvgflsg gvdscqgdsggplssveadgrifqagvvswgdgcaqrnkpgvytrlplfrdwikentgv***sgsssgggs** *egggsegggsegggsgggsgsgdfdyekmanankgamtenadenalqsdakgkldsvatdygaaidgf igdvsglangngatgdfagsnsqmaqvgdgdnsplmnnfrqylpslpqsvecrpfvfsagkpyefsidcdk inlfrgvfafllyvatfmyvfstfanilrnkes*****

In addition to the wild-type MT-SP1 B-chain fusion protein, an MT-SP1 B-chain variant (CB469) - GeneIII fusion protein was generated using the method described above. The CB469 variant amino acid sequence, set forth in SEQ ID NO.: 507, was generated by substituting a serine for the cysteine at position 122 (based on chymotrypsin numbering) of the wild-type MT-SP1 protease domain sequence, which is shown in the sequence above in italics and set forth in SEQ ID NO.: 505. This CB469 sequence was cloned into the pMal-C2 vector as described above. In order to achieve improved display, the phagemid vector containing nucleic acids encoding this variant MT-SP1 fusion protein was used to generate MT-SP1 mutant phage display libraries as described in Example 8B below.

B. Mutagenesis of protease domains for the generation of mutant phage display libraries

Generation of phage display libraries containing mutated protease domains was done using standard error-prone PCR mutagenesis protocols that are known in the art (Matsumura et al., Methods Mol Biol. 2002;182:259-67; Cirino et al., Methods Mol Biol. 2003;231:3-9) as exemplified below.

1. Mutagenesis of B-chain MT-SP1 fusion proteins

For the construction of mutant MT-SP1-containing fusion proteins, the MT-SP1 CB469 cDNA was amplified from the pMal-C2 vector by error-prone PCR using the Diversify® PCR Random Mutagenesis Kit (BD Biosciences, Clonetech) and following conditions suggested by the supplier to obtain five (5) mutations per kilobase. The MT-SP1 forward primer used in this PCR, having the sequence of nucleic acids set forth in SEQIDNO.:508): GCGCAGATATCGTACCG**CATATG***AAAAAGAATATCGCATTTCTT*, was designed to hybridize within the STII leader sequence (with the residues shown in italics) and contained a Nde restriction site sequence (shown in bold). The MT-SP1 reverse Primer, having the sequence of nucleic acids set forth in SEQIDNO.:509: GTGCATGCTGACTGACT**GAGCTC***CCGCTTACCCCAGTGTTCTC*, was designed to hybridize within the 3' portion of the sequence encoding the MT-SP1 protease domain (with the residues shown in italics) and contained a Sac1 restriction site sequence (shown in bold).

2. Purification of mutagenesis products

Taq polymerase binds tightly to DNA and thus is not completely removed by the Qiagen PCR purification kit; and its presence may interfere with downstream restriction digests of PCR products (Crowe et al., Nucleic Acids Res. 1991 January 11; 19(1): 184; Wybranietz et al., Biotechniques (1998) 24, 578–580). Thus, to remove Taq polymerase from the amplified wild-type and mutant PCR products from Example 8B(1), prior to their purification, the following were added to the reaction: 5 mM EDTA, 0.5% SDS, 50 ng/µl proteinase K. To eliminate Taq polymerase, the mixture was incubated at 65°C for 15 minutes.

To ensure that there was no wild-type template remaining (which could potentially interfere with the selection methods described below), the PCR product was purified to remove template DNA. To separate the vector from the PCR product, samples were loaded onto a 1% agarose gel in the presence of 10X Orange G Gel Loading Buffer (New England Biolabs) which does not co-migrate with the PCR product or ladder. The PCR product was excised from the gel using a scalpel. The excised product was purified using either the QIAquick® Gel Extraction Kit protocols (Qiagen) or the Zymoclean™ Gel Extraction Kit (Zymoclean CA, Cat # D4001) following the conditions specified by the supplier.

For the Qiagen Gel Extraction kit, the excised gel fragment was solublized in QG Buffer and slowly passed through a Qiagen QG column, each of which has a binding capacity of about 5 – 10 μg, and does not hold more than 2 mL. A sufficient number of columns was used to accommodate the full volume of starting material. Columns were centrifuged in collector tubes at 14,000 rpm to remove any residual Buffer QG. 0.7 mL Buffer PE was added to each column and samples were incubated for 2-5 minutes. Columns then were centrifuged twice, for an additional 1 minute each, at 13,000 rpm to remove all residual PE buffer. Samples were transferred into a new 1.5mL microcentrifuge tube, followed by addition of 50μL H20 and incubation for two minutes. Bound DNA was eluted by centrifugation at 7000 rpm. Typical yield was between 30% and 60% of the starting amount of sample.

For the Zymoclean™ Gel Extraction Kit, either one or more Zymoclean™ Gel Extraction Kit columns (each of which has a 5 μg maximum binding capacity), or one or more columns from the Zymoclean™ DNA Clean & Concentrator™ Kit (each of which has a 25 μg capacity) were used, depending on the amount of starting material. Using this kit, the excised DNA fragment was transferred to a 1.5 ml microcentrifuge tube, followed by addition of three (3) volumes of ADB Buffer™ to each volume of agarose excised from the gel. Samples were incubated at 37-55°C for 5-10 minutes until the gel slice had completely dissolved. The dissolved agarose solution was transferred to a Zymo-Spin I™ Column in a Collection Tube and centrifuged at at least 10,000 rpm for 30-60 seconds. Flow through from the column was discarded. 200 μL Wash Buffer was added to the column and centrifuged at at least 10,000 rpm for 30 seconds. Flow-through was discarded and the wash step repeated. 50 μL of water was added directly to the column matrix. The minimum elution volume was 10 μL for the Zymoclean™ Gel Extraction column and 35 mL for the DNA Clean & Concentrator™ column. The column was placed into a 1.5 ml tube and centrifuged at at least 10,000 rpm for 30-60 seconds to elute DNA.

After elution using one of these two methods, samples were pooled and DNA concentration was assessed by measuring absorbance of the sample at 260 nm in a 70 μL UV cuvette, using a spectrofluorometer. DNA concentration was calculated according to the following equation: 1A260 = 50 ng/μl ds DNA.

C. Construction of protease mutant phage libraries using the pMal-C2 phagemid vector

For construction of phage display libraries expressing mutant protease domains, digested PCR products, such as those obtained from the protease PCR mutagenesis and purification described in Example 8A and B above, were ligated into the pMal-C2 phagemid vector described above. For this process, the vector was digested using Nde1 and Sac1, and the product gel purified and combined in a ligation reaction (described below) with the purified, restriction-digested PCR products. The molecular weight (MW) of the Nde1/Sac1 digested, gel purified pSTII-g3 pMal-C2 phagemid is 5835 base pairs (bp); the MW of the Nde1/Sac1 digested MT-SP1 PCR product is 806 bp. Typically, for a 2 mL ligation reaction, 7.58 μg cut vector was about 1 nM of vector and 3.14 μg cut MT-SP1 product was about 3 nM insert product.

For ligation of the MT-SP1 products, 40 μl (3 nM, 3.14 μg) of the digested, purified product was mixed with: 40 μl (1 nM, 7.58 μg) of digested, purified vector; 1510 μl H_20; 400μl 5X T4 DNA Ligase Buffer (Gibco); and 10 μl (10 units) T4 DNA Ligase (New England Biolabs). The ligation reaction was carried out overnight at 16°C or at room temperature for 4 hours in a 2 mL volume. After ligation, the DNA Ligase was heat-inactivated by incubating the ligation reaction mixture at 65°C for 15 minutes followed by addition of 4 mL ZymoResearch DNA Binding Buffer. This sample then was added, 800 μl at a time, to a 25μg ZymoResearch Column. The column was washed twice with 600 μl ZymoResearch Wash Buffer and eluted with 50 μL water, which had been pre-warmed to 42°C. Percent DNA recovery was assessed by measuring absorbance of diluted elution sample (3 μl elution in 70 μl H2O) at 260 nm using a spectrofluorometer. For example, for the 3 mL ligation above, if the A260 corresponded to 0.12 = 140 ng/μl, then the total yield was determined to be about 7 μg (which is about 70% recovery of DNA from the ligation).

The ligation product was electroporated into XL-1 blue cells, which can accommodate approximately 500 ng/μl by electroporation. 7.5 μl of a 140 ng/μl ligation was added per 200 μl XL-1 Blue Cells (Stratagene). The cells were added to a 0.2 cm gap cuvette and electroporated in a Gene Pulsar (Bio-Rad, CA) using the following conditions: Voltage (V) = 2500, Capacitance = 25 (uF), Resistance = 200 ohms. Immediately following electroporation, 1 mL SOC medium (Invitrogen) was added to the cuvette. The cells then were transferred to 25 mL SOC medium and incubated at 37°C for 20 minutes. Following this incubation five (5) small aliquots

(100 microliter) of serial 100-fold dilutions of the cells were made and plated on small 2YT Carbenicillin agar plates and incubated overnight at 37°C for counting the number of colonies (representative of the number of clones from the library generated by electroporation). In one method, the remaining culture volume was centrifuged to pellet the cells followed by resuspension in 12 mL SOC buffer and plating on large agar plates (245 mm X 245 mm) supplemented with Carbenicillin (75 ug/ml) and grown overnight at 30°C. Alternatively, to prepare phage stock from the library, the cells were added directly to 500 mL 2YT medium supplemented with Carbenicillin (75 ug/ml) with M13KO7 helper phage at 1x 10^{10} CFU/mL and grown overnight at 37°C.

EXAMPLE 9

Selection of variant protease domains from protease domain phage libraries using mutant AT3 protease traps

A. Selection of MT-SP1 phage/mutant AT3 complexes and ELISA-based readout assay

In this example, a mutant AT3 inhibitor containing the complement C2 target cleavage sequence SLGRKI, as described in Example 7 above, was used as the "bait substrate" in a panning experiment designed both to isolate and provide a readout for the presence of mutant MT-SP1-bearing phages with improved reactivity toward the target cleavage sequence. Phages were isolated from large, combinatorial MT-SP1 phage display libraries produced as described in Examples 8A, 8B and 8C above using the following procedure.

1. Interaction with and cleavage of AT3 variants by mutant MT-SP1-bearing phages

Phage-bound MT-SP1 mutants from phage libraries were first selected using mutant AT3 having the target cleavage site as follows. Each cleavage reaction was carried out in duplicate wells of a 96-well polystyrene plate (Nunc Maxysorp) for 60 minutes at 37°C, by incubating the following reaction components in a 70 µL volume: 35 µl MT-SP1 library phage at 3.14E^{12} CFU/ml; 7 µL 10X MT-SP1 Activity Buffer (0.5 M Tris-HCl, pH 7.4, 1M, NaCl, 1% Tween20); 7 µL 10 µM Low Molecular Weight Heparin (BD Biosciences); 14 µL H_2O; and 7 µL of His-tagged mutant AT3-SLGRKI. Individual cleavage reactions were carried out with the following different AT3-SLGRKI concentrations: 100 nM, 33 nM, 11 nM, 3.3 nM, 1.1 nM and 0.33 M.

Each reaction was terminated with the addition of 2 μL 100 mg/ml of the protease inhibitor 4-(2-Aminoethyl)-benzenesulfonyl fluoride (Pefabloc, Roche Diagnostics). 40 μL of a 0.55% BSA, 0.275% Tween 20 solution then was added and mixed thoroughly by pipetting up and down.

2. Capture of MT-SP1 phage-AT3 complexes using anti-His antibodies

Meanwhile, wells in another 96-well polystyrene plate (Nunc Maxysorp) were coated for 1 hour with shaking at room temperature with 100 μL of 5 ng/μl Streptavidin (Pierce) in 0.2 M Carbonate Buffer (pH 9, Pierce). The wells then were washed three times with 250 μL PBST, blocked with 200 μL of 0.2% BSA in PBS for 2 hours at room temperature, incubated for 1 hour at room temperature with 100 μl of 5ng/μl biotinylated Anti-6HIS antibody to capture His-tagged AT3 mutants, and washed thoroughly with PBST. Each mutant MT-SP1 phage sample from the AT3 cleavage reaction in Example 9A(1) then was added in duplicate to the coated 96 well plate and incubated for 1 hour at room temperature. Plates then were washed 14 times with 250 μL PBST.

3. ELISA-based readout for selection of MT-SP1 phage-AT3 complexes

After washing, the first of the two rows in the microtiter plate was used to carry out an ELISA (Enzyme-Linked Immunoassay)-based assay to obtain a readout for phage capture. To each well in this row, 100 μL of a 1:5000 dilution of an HRP conjugate anti M13 phage antibody (GE Healthcare) was added and allowed to bind for one hour. The wells in this row then were washed 8 times using a Skanwasher plate washer (Molecular Devices), followed by addition of 100 μL TMB/Peroxide substrate solution (Pierce) and incubation at room temperature for 5 minutes. This reaction was quenched with 100 μL 2M H2SO4 and assayed on a SpectraMax® plate reader (Molecular Devices) for absorbance at 450 nM. This readout was used as a surrogate for the presence of phage-AT3 complexes. In this assay, a concentration-dependent increase in absorbance was observed (based on increasing concentrations of AT3-SLGRKI bait used in the cleavage reaction in Example 9A(1)). Further, when the process was performed using successive rounds of panning as described herein, increased absorbance was observed after each round, indicating that this panning method could successively enrich the phage pool for target cleavage site affinity. These data suggest that this method can be used to select, from a phage library, mutant protease domain fusion proteins having affinity for a particular target

sequence. The ELISA assay provided a method for obtaining a readout for this selection and enrichment, using the same 96-well plate that was used for affinity-based capture and subsequent elution described in Example 9A(4) below.

4. Elution of selected MT-SP1 phage

The second of the two duplicate rows of the microtiter plate from Example 9A(2) then was used to elute specifically bound phages for use in subsequent purification and screening. To each well in this row, 100 µL 100 mM HCL was added and incubated for 5 minutes to elute the specifically bound phage. The resulting phage eluate was added to a separate well containing 33 µL of 1M Tris pH 8 for acid neutralization prior to infection. The 133 µL of neutralized phage mix then was added to 1 ml of XL-1 Blue cells growing at an OD600 of 0.5, which then were incubated for 20 minutes at 37 °C and plated out onto 2xYT agar plates (245 mm x 245 mm) supplemented with Carbenicillin. These cells were used in subsequent screening, sequencing and purification methods as described in the Examples below.

This selection and ELISA-based assay method was also used to select and assess uPA mutants from uPA libraries, such as those described in Examples 2 and 3 above.

B. Purification of selected protease domain-bearing phages

This Example describes a method for isolation of phage supernatants that had been selected using bait inhibitors. Titers (cfu/mL) of selected phages, such as those recovered in Example 9A above, were determined. Phage stocks were diluted with PBS and used to infect *E. coli* XL-1 Blue cells, growing at an OD600 of 0.5 or approximately 2.1 x 10^8 cells/mL. The desired infectivity range was 1000 – 2000 colonies per plate. Infected cells were plated onto 2YT agar supplemented with 100µg/mL Carbenicillin in square 245mm x 245mm polystyrene BioAssay (Corning) dishes and allowed to grow for 16-20 hours or until colony size were roughly 2mm in diameter. Using an automated Colony Picker, individual colonies were picked and dispersed into wells in a 96 well polypropylene plate, each well containing 150-170 uL of 2YT medium supplemented with 100µg/mL Carbenicillin and 12µg/mL Tetracycline. Control wells were inoculated with cells infected with either template phage (phage having a protease domain that had been used as the template for mutagenesis) or with phage containing fusion proteins containing inactive protease variants. The inoculated plates were sealed with an air-permeable membrane, placed

into a HiGro (GeneMachines) incubator and shaken at 400 rpm at 37°C for 14-20 hours.

After the incubation, to obtain log-phase cells, 100 µL from each well was used to inoculate a well in a deep well 96 well plate containing 1 mL 2YT medium supplemented with 100 ug/mL Carbenicillin and 12 µg/mL Tetracycline. The deep well plate then was sealed with an air-permeable membrane and placed in the HiGro® incubator with shaking at 400 rpm at 37°C with oxygen aeration until the cell density reached an OD600 of between 0.4 and 0.6. A typical incubation period was between 4 and 5 hours. After incubation, 100µL of a helper phage stock was added to each well and the plate sealed and shaken again at 400 rpm for 5-10 minutes at 37°C. After the 5-10 minutes of shaking, the plate was incubated at 37°C in a static state without shaking for 30-45 minutes. Shaking then was resumed at 400 rpm for 15-30 minutes at 37°C. Following shaking, 100 µL kanamycin solution (400µg/mL) was added to each well to yield a final concentration of 33.3 µg/mL in each well. The plate was resealed, and shaken at 400 rpm at 37°C for 12 – 16 hours. To pellet the cells, the plate then was centrifuged at 3500 – 4500 rpm for 20 minutes at 4°C. After centrifugation, supernatants, which contained isolated phage, were either used immediately for screening as described in the Examples below, or first were stored at 4°C.

C. Polyethylene Glycol (PEG) Precipitation of protease domain phage supernatants

This Example describes a method for removing potentially contaminating background protease activity (to which some characterization assays described herein below are sensitive) in purified selected phage supernatants using Polyethylene Glycol precipitation. In this method, after rescuing the MT-SP1-bearing phage supernatants (such as those selected and eluted in Example 9A) overnight (12-16 hours) with helper phage samples were centrifuged for 20 minutes at 4°C at 3500-4500 rpm and 1000 µL of supernatant was removed from each well and transferred to a well in another 96 well deep well plate.

For precipitation, 250 µL of a solution containing 20% PEG (by volume) in 2.5M NaCl was added to each well. The plate was sealed and mixed by vigorous inversion, and then placed in an ice-water bath and left static for 1-2 hours. The plate then was centrifuged for 60 minutes at 4500 rpm or for 90 minutes at 3500 rpm. The

supernatant solution from each well was decanted out and the plate was patted dry and allowed to drain for 20-30 minutes. The resultant precipitate was resuspended using PBS at a final volume equivalent to 20% of the original phage supernatant volume (200uL) to yield a 5-fold concentrate. This material either was used immediately in assays described below, or stored at 4°C until ready for testing.

EXAMPLE 10

Screening of protease domain-bearing phages having increased reactivity and catalytic efficiency towards target substrate sequences

Individual phage preparations, such as those described in Example 9B and 9C, were used in various assays to determine their specificity and/or activity.

A. Analysis of phages expressing protease domain variants by monitoring inhibition of fluorogenic peptide hydrolysis by bait proteins

As one approach for assessing mutant protease-bearing phage clones, a biochemical inhibition assay can be performed comparing the ability of an inhibitor (bait serpin) to inhibit the activity of the selected variant protease domain with its ability to inhibit the activity of the template protease domain (i.e., the "parental" protease) that was originally used in phagemid library construction. With this approach, the ability of mutant protease-bearing phages, such as those recovered in Example 9 above, to cleave a fluorogenic substrate containing a target substrate sequence is assessed in the presence and in the absence of a given concentration of inhibitor bait, and compared to the ability of the template protease domain to cleave the same sequence in the presence of the same bait. The use of fluorogenic peptide substrates is a routine method for the determination of protease specificity (Zimmerman et al. (1977) Anal Biochem, 78:47-51; Harris et al. (2000) PNAS, 97:7754-7759).

For analysis of inhibition of MT-SP1 B-chain mutants compared to inhibition of MT-SP1 B-chain template (used for mutation in Example 8B(1)), the variant AT3 (with a desired target sequence) can be used as the inhibitor and Ac-RQAR-ACC can be used as the substrate. In this substrate, specific cleavage of the anilide bond frees the fluorescent ACC leaving group, providing an efficient means to determine the cleavage rates for individual substrates.

In one example of such an assay, the ability of uPA protease-bearing phages, such as those recovered in Example 3 above, to cleave the fluorogenic substrate Ac-AGR-

AMC (SEQ ID NO.: 617) was assessed in the presence and in the absence of a given concentration of PAI bait. As described above, the use of such a 7-amino-4-methylcoumarin (AMC) fluorogenic peptide substrate is a routine method for the determination of protease specificity. In this example, 35 µL of phage supernatant (such as that obtained as described in Example 3(A)) was transferred to both a designated assay well and a designated control well in a 384-well Polypropylene plate (CoStar, #3658). 35 µL of 2x Indirect Assay Buffer containing the same PAI bait used in the selection was added to the assay wells. The concentration of bait was the same as used in the selection. 35 µL of 2x Indirect Assay Buffer (without inhibitor) was added to the corresponding control wells. The plates were incubated at 37 °C for 60 minutes. Following the mixing of the phage with inhibitor or control buffer, 10 µL of an AGR-AMC fluorogenic peptide substrate, diluted to a final assay concentration of 60 µM in Indirect Assay Buffer, was added the wells. Fluorescence was measured using a Molecular Devices SpectraMax® Plate Reader with Excitation at 380 nm, Emission set at 460 nm, using the kinetic read mode for one hour. Clones showing enhanced inhibition of the target substrate with respect to the template protease were further analyzed.

B. Analysis of variant protease activity using fluorogenic peptide substrates

To directly assess the activity and specificity of MT-SP1 mutants, an assay was performed using the fluorogenic peptide substrates Ac-RQAR-ACC (having the native autocatalytic cleavage sequence recognized by wild-type MT-SP1) and Ac-SLGR-ACC (Acetyl-Ser-Leu-Gly-Arg-ACC) having the C2 target site cleavage sequence). As noted above, the ACC in the names of these substrates represents 7-amino-4-carbamoylmethylcoumarin, which is the fluorescent leaving group. Also as noted above, the use of fluorogenic peptide substrates is a routine method for the determination of protease specificity (Zimmerman et al. (1977) Anal Biochem, 78:47-51; Harris et al. (2000) PNAS, 97:7754-7759). In this example, specific cleavage of the anilide bond frees the fluorescent ACC leaving group, providing an efficient means to determine the cleavage rates for individual substrates. In this method, 35 µL of 2x Indirect Assay Buffer was added to all test wells. 35 µL of phage supernatant (isolated as described in Example 9B) or re-suspended PEG precipitated phage (isolated as described in Example 9C) was added to each of the designated wells. After addition of the phage, the plate was centrifuged at 2000 rpm for 1 minute to remove air bubbles. 10 µL of each of the Peptide Substrates (Ac-SLGR-ACC (final

assay concentration = 125 μM)) and Ac-RQAR-ACC (final assay concentration = 60 uM)) was diluted with 1X Indirect Assay Buffer and then added individually to appropriate wells. The rate of hydrolysis (ROH), measured as Relative Fluorescence Units/second (RFU/s)); indicative of substrate cleavage, was monitored over time using a SpectraMax® M5 Microplate Reader (Molecular Devices), using the kinetic read mode.

EXAMPLE 11

Production, selection, assessment and identification of MT-SP1 mutants

A. Fluorogenic assay of B-chain MT-SP1 mutants from phagemid library

This example describes a fluorogenic assay that was carried out to analyze the activity and specificity of MT-SP1 protease domain-bearing phages produced using library produced as described in Example 8. The MT-SP1 library was prepared as described in Example 8 above, using the native B-chain of MT-SP1 that has a serine in place of the cysteine at position 122 based on chymotrypsin numbering (SEQ ID NO.: 507) as a template. The library was prepared as described above, using the pMal-C2 vector and error-prone PCR conditions recommended by the supplier to achieve an approximate mutagenesis rate of 0.5%. The yield from this mutagenesis reaction was 4 x 10^9 recombinants.

Selection of phages based on the rate of interaction with and cleavage of the variant AT3 containing the target substrate sequence (in place of the native RCL; as described in Example 7) was carried out as described in Example 9A using a polypropylene 96 well format. For this selection, 1x 10^{12} recombinant phages were mixed with 3.3 nM variant AT3 carrying an SLGRKI RCL sequence for 30 minutes. After washing, phage were eluted as described in Example 9A above, and used to infect XL-1 blue cells as described in example 9B.

Successive rounds of selection were performed to enrich for rapid interaction with and cleavage of the target substrate sequence using methods provided and described herein. For example, clones selected in the first round were subjected to a second round of selections as described herein, using 3.3, 1.1, and 0.33 nM AT3 for one hour as described in Example 9A(3).

Following the first round of selection, phage supernatant was prepared as in Example 9C using PEG precipitation from selected clones. Phage clones were screened using the method of Example 10(B) above, using, as fluorogenic substrates,

both Ac-SLGR-ACC (containing C2 target cleavage site sequence) and Ac-RQAR-ACC (containing the native cleavage sequence for the native MT-SP1). For each clone, the rate of fluorescence (ROF) determined from the Ac-SLGR-ACC assay was compared to the ROF determined from the Ac-RQAR-ACC assay as a means to compare the activity of each mutated MT-SP1 protease domain on the native substrate sequence to its activity on the target substrate sequences. The ROFs in the mutant MT-SP1 assays also were compared to the ROFs in the template (C122S) MT-SP1 assay. The results obtained with individual clones are shown in Table 21 below, which lists clone numbers, and lists the rate of fluorescence as RFU/s (relative fluorescence units per second).

Table 21: Screening of mutant MT-SP1 protease domain-bearing phage selected for cleavage rate of AT3-SLGRKI

Mutant MT-SP1 Clone Number	Ac-SLGR-ACC Rate (RFU/sec.)	Ac-RQAR-ACC Rate (RFU/sec.)
Template	1.85	15.6
CPC-0019595	7.1	33
CPC-0023085	0.8	2
CPC-0023230	1.3	4
CPC-0023401	3.9	12
CPC-0023949	0.7	2
CPC-0024129	3.8	15
CPC-0024153	2.5	6
CPC-0024527	4.3	12
CPC-0024715	3.2	12
CPC-0025366	1.3	1
CPC-0025387	6.8	14
CPC-0025533	6.9	23
CPC-0025582	1.7	3
CPC-0025720	2.5	5
CPC-0025866	1.2	4
CPC-0025876	4.0	8
CPC-0025890	10.6	33
CPC-0025941	1.0	4
CPC-0025974	9.3	41
CPC-0026100	14.8	25
CPC-0026122	6.5	31
CPC-0026125	17.4	84
CPC-0026200	7.0	21
CPC-0026219	8.0	23
CPC-0026232	7.1	15
CPC-0026597	11.0	34
CPC-0026727	0.8	2
CPC-0026761	7.8	25
CPC-0027290	3.9	12
CPC-0027306	11.0	50
CPC-0027309	8.3	50
CPC-0027326	9.1	54

Mutant MT-SP1 Clone Number	Ac-SLGR-ACC Rate (RFU/sec.)	Ac-RQAR-ACC Rate (RFU/sec.)
CPC-0027335	12.3	57
CPC-0027369	2.3	11
CPC-0027399	13.4	99
CPC-0027484	2.5	12
CPC-0027516	3.4	17
CPC-0027617	1.4	7
CPC-0027706	0.4	1
CPC-0027718	2.1	7
CPC-0027797	5.5	15
CPC-0027841	2.7	9
CPC-0028017	5.1	16
CPC-0028333	5.6	17
CPC-0028341	5.5	26

B. Identification of selected MT-SP1 mutant phages by DNA sequencing

This Example describes a method used for identification of positive phage clones that were prepared as described in the previous Examples and selected based on results from a fluorogenic assay, such as the one described in Example 10B above. For this method, individual clones were mixed with XL-1Blue *E. coli* cells for infection and the cultures grown overnight shaking at 37°C. Plasmid DNA was purified from the overnight culture using a plasmid preparation kit (Qiagen), and the DNA sent out for sequencing for identification of the mutants.

In one example of this method, the amino acid sequences of selected B-chain MT-SP1 mutants from Example 11A above were identified using the steps outlined above. The sequencing primer that was used for identification of these clones is set forth in SEQ ID NO.: 618: 5'GGTGTTTTCACGAGCACTTC3'. The results obtained by analyzing the sequencing data are set forth in Table 22 below. This table lists only mutants with residues found to be mutated in more than one isolate. Table 22 lists the amino acid mutations/positions for each clone compared with the wild-type MT-SP1 B-chain sequence (SEQ ID NO.: 505), which were determined by analysis of sequencing data. Amino acid numbering is according to chymotrypsin numbering. SEQ ID NOs. also are listed for both the sequence of amino acid residues that encodes the MT-SP1 protease domains (B-chains) containing the indicated amino acid mutations and also for the sequence of amino acid residues that encodes the full-length MT-SP1 protein having the same mutations.

Table 22: Selected MT-SP1-mutants

Mutant MT-SP1 Clone Number	Amino Acid Mutation (Chymotrypsin Numbering)	SEQ ID NO (protease domain).:	SEQ ID NO (full-length).:
CPC-0019595	C122S/I136T/N164D/T166A/F184(A)L/D217V	516	537
CPC-0023085	I41F/C122S	517	538
CPC-0024153	I41F/C122S/A126T/V244G	518	539
CPC-0025366	D23E/I41F/T98P/C122S/T144I	519	540
CPC-0025387	I41F/C122S	520	541
CPC-0025582	I41F/C122S/L171F/V244G	512	542
CPC-0025720	C122S/H143R/Q175R	522	543
CPC-0025876	I41F/C122S/L171F	523	544
CPC-0025974	C122S/R230W	524	545
CPC-0026100	I41F/C122S/I154V/V244G	525	546
CPC-0026232	I41F/L52M/C122S/V129D/Q221(A)L	526	547
CPC-0027399	F99L/C122S	527	548
CPC-0027706	F97Y/C122S/I136V/Q192H/S201I	528	549
CPC-0027797	H71R/C122S/P131S/D217V	529	550
CPC-0028017	C122S/D217V	530	551
CPC-0028333	T65K/F93L/F97Y/C122S/D217V	531	552

EXAMPLE 12

Preparation and characterization of large quantities of selected phage-bound MT-SP1 protease

A. Large-scale preparation of MT-SP1 phage

This Example describes preparation of larger quantities of selected MT-SP1 protease domain-bearing phages for analysis and subsequent use of selected protease domains in downstream methods, such as *in vitro* translation in whole MT-SP1 proteases. For this Example, single phage-bearing colonies, selected as in Example 11 above, were grown overnight in 2YT medium supplemented with Carbenicillin, at a final concentration of 50 µg/mL, and tetracycline, at a final concentration of 12µg/mL, in small sterile Corning Orange Capped Erlenmeyer Flasks overnight. To make glycerol stocks, 85 µL 60% glycerol was added to 500µl of each culture followed by storage at -80°C. The remaining volume of each culture was added to a 2L widemouth baffled flask containing 500 ml 2YT medium supplemented with Carbenicillin and Tetracycline. Alternatively, this step was performed in a 500 mL flask in a 50 mL volume. The culture was grown until an OD600 of 0.5 was reached.

M13KO7 Helper Phage was added to the culture to yield $1E^{10}$ CFU/ml and the culture incubated for 1 hour at 37° C. Kanamycin was added to a final concentration of 30µg/mL. The cultures with helper phage were rescued overnight by incubation at 37°C. Following overnight culture, samples were centrifuged at 6000 rpm for 15

minutes. One volume PEG/NaCl (20% PEG 8K/1.5 M NaCl) solution was added per 5 volumes of culture. The sample then was stirred at 4°C for 20 minutes. Samples were centrifuged at 10,000 rpm for 20 minutes and supernatants removed. After a second centrifugation step at 10,000 rpm, the pellet was resuspended in 5 mL (for the initial 500 mL volume) or 1 mL (for the initial 50 mL volume) PBS. Precipitated cells that were not resuspended were removed by brief centrifugation at 14,000 rpm for 2 minutes. Glycerol was added, at 10% by volume, to the supernatant containing the resuspended cells. The cells were frozen at -80°C.

B. Assay of prepared phage using ACC and QF substrates

This Example describes a fluorogenic assay used to assess activity and specificity of the phages prepared in Example 12A. PEG-precipitated mutant MT-SP1-bearing phage clones, prepared using the 50 mL volume culture as described in Example 12A, were normalized to $1E^{13}$ particles/ml. The phage were then assayed enzymatically using the ACC fluorogenic and QF (Quenched Fluorescence) substrates as follows. 5µL phage (at $1E^{13}$ particles/ml) was added to each well in a black Costar polypropylene half-well microtiter plate (Corning) along with 5 µL 10X MT-SP1 assay buffer, 35 µL H_2O and 5 µL substrate in a total volume of 50 µL. The substrates used in individual wells were: Ac-SLGR-ACC (120 uM final concentration), Ac-RQAR-ACC (60 uM final concentration), or the following quenched-fluorescence substrates: SLGR-KI, and RQAR-SA (both used at 0.625 uM final concentration). The Ac-SLGR-ACC substrate was used to assess cleavage, by the mutant MT-SP1 clones, of the target (complement C2) cleavage sequence, while the Ac-RQAR-ACC substrate was used to assess cleavage of the native target cleavage sequence for MT-SP1. Likewise, the SLGR-KI substrate was used to assess cleavageof the target (complement C2) cleavage sequence, while the RQAR-SA substrate was used to assess cleavage of the native target cleavage sequence for MT-SP1. The ratio of these two cleavage rates was one quantitative measure of the specificity of the selected proteases for the targeted, new cleavage sequence. Comparison of these ratios for a selected variant and the corresponding original scaffold (i.e., parental) protease indicated whether the selected protease exhibited enhanced selectivity towards the targeted, new cleavage sequence. For the ACC Readout, the SpectraMax® plate reader was set for excitation at 380 nM and to detect emission at 460 nM, with a 435 nM cutoff. For the QF readout, the SpectraMax®

plate reader was set for excitation at 490 nM, to detect emission at 520nM, with a cutoff of 515 nM. The results of this assay are set forth in Table 23 below. As above, SEQ ID NOs. are listed for both the sequence of amino acid residues that encodes the MT-SP1 protease domains (B-chains) containing the indicated amino acid mutations and also for the sequence of amino acid residues that encodes the full-length MT-SP1 protein having the same mutations, as determined by sequencing, as described in Example 11B above. RFU (relative fluorescence units) numbers correspond to the rate of hydrolysis observed in a 60 minute reaction at 37°C for each substrate.

Table 23: Kinetic assay of selected MT-SP1 protease domain-bearing phage clones

Mutant MT-SP1 Clone Number	Amino Acid Mutation (Chymotrypsin Numbering)	SEQ ID NO. (protease domain):	SEQ ID NO. (full-length):	Ac-SLGR-ACC (RFU/s)	Ac-RQAR-ACC (RFU/s)	SLGR-KI (RFU/s)	RQAR-SA (RFU/s)
Template	C122S	507	515	2.4	23.5	0.12	0.11
CPC-0028341	I41T/C122S/P173S/Q209L	531	553	10.9	56.8	0.36	0.48
CPC-0033634	F97L/C122S/F234L	533	554	6.2	37.2	0.21	0.19
CPC-0028971	C122S/Q175R	534	555	3.4	11.0	0.20	0.18
CPC-0027484	N95K/C122S	535	556	2.0	9.5	0.07	0.05
CPC-0028993	Y60(G)S/C122S	536	557	0.5	1.0	0.02	0.01

* RFU/s= Relative fluorescence units/second (Rate of hydrolysis)

EXAMPLE 13

Expression of Selected MT-SP1 Mutant proteins using in vitro translation

This example describes the expression of MT-SP1 protease domains selected and screened as in the Examples described above, that are not part of a gene III fusion protein.

A. Subcloning of MT-SP1 sequence into a modified IVEX vector

In order to express MT-SP1 protease domains selected on phage, as described in the Examples above, that are not synthesized as gene III fusion proteins, the the coding region for the MT-SP1 protease domain containing the N-terminal activation sequence and a C-terminal 6xHis tag was cloned into the pIVEX.2.3d RTS *in vitro*

translation vector (Roche; SEQ ID NO.: 559)) using the NdeI and XhoI restriction sites. The full N-terminal amino acid sequence of the pIVEX.2.3d.MT-SP1 preceding the RQAR cleavage site is set forth in SEQ ID NO.: 558: MEKTRHHHHHHSGSDCGLRSFT**RQAR**. Residues encoding MT-SP1 B-chain proteins, which had been selected using phagemid libraries as described above, assayed using fluorogenic screening methods as described in Example 10B and 11A, and sequenced as described in Example 11B, were subcloned into the pIVEX.2.3d.MT-SP1 vector using the internal SphI and BsrGI restriction sites. Phagemid selectants having mutations in the MT-SP1 sequence that were outside these internal sites were created for use in this method by PCR mutagenesis.

B. Expression of MT-SP1 by in vitro translation

Expression of MT-SP1 protease domains using an *in vitro* translation kit, the RTS 100 *E. coli* Disulfide kit (Roche Applied Science), was performed using conditions specified by the supplier with the following optimizations: The components of the 50 µl reaction solution were modified to include 12 µl of amino acid mix, 10 µl of reaction mix, 12 µl of lysate, along with the addition of 5 µl of 1 M Hepes pH 8 buffer, 2.5 µl 12 nM Tween-20, 2.5 µl of Protein Disulfide Isomerase (PDI), and 6 µl of the chaperone RTS GroE Supplement (Roche Applied Science). The 1 mL Feeding mix was also modified to include 168 µl of amino acid mix, 24 µl of methionine, 608 µl of feeding mix, 100 µl of 1 M Hepes pH 8, 50 µl of 12 nM Tween-20, and 50 µl of water. The *in vitro* translation (IVT) reaction was incubated on a plate shaker at 30°C for 18 hours.

C. Purification of His-tagged MT-SP1

Following the in vitro translation (IVT) reaction, insoluble protein was cleared by centrifugation and transferred to a fresh tube. The cleared supernatant (with a volume approximately 45 µl) was brought up to a final volume of 1 mL in 50 mM Sodium Phosphate pH 7.5, 300 mM NaCl. The solution was applied to 300 µl of pre-equilibrated TALON® resin in a 2 mL fritted chromatography column (Clontech) and allowed to flow through by gravity. The column was washed with 3 mL of a solution containing 50 mM Sodium Phosphate pH 7, 300 mM NaCl and 7.5 mM Imidazole; and eluted with 600 µl of a solution containing 50 mM Sodium Phosphate pH 6.5, 300 mM NaCl and 75 mM Imidazole. Eluate was dialyzed into phosphate-buffered saline

with 0.1% Tween-20 (PBST) and concentrated to 20 µL. Typically, the yield of purified protease was approximately 70%.

EXAMPLE 14

Characterization of mutated MT-SP1 protease domains

This Example describes the characterization of the mutated mutant MT-SP1 protease domains that were produced as in Example 13 above.

A. Active site titration of IVT reactions

To assess protease activity, active site titration of *in vitro*-translated mutant MT-SP1 protease domains was performed on cleared supernatant with the MT-SP1 inhibitor M84R Ecotin, as described (Takeuchi et al, (1999) PNAS 96,11054-11061). For this assay, IVT protein was diluted to a final concentration of 1:10,000 in 1X MT-SP1 activity buffer and incubated with 15 nM Ecotin in 1:2.5 serial dilutions for 1 hour at 30°C. The reaction was assessed kinetically for cleavage of 0.4 mM Ac-RQAR-ACC substrate on a SpectraMax® M5 Microplate Reader (Molecular Devices, Inc). The ACC leaving group was detected at wavelengths of Excitation (Ex) = 380, Emission (Em) = 450 and cutoff (c/o) = 435. The assay points showing fractional activity between 20% and 80% uninhibted activity was plotted on a graph of activity vs. Ecotin concentration, and a line plotted though the points. The x-intecept of the line was used to establish the active concentration of the IVT protease. The reaction was graphed, with the linear part of the curve representing the active concentration of the IVT protease. Thus, the active site concentration (set forth for several mutants in Table 24 below; Active Site Conc.) was determined using Active Site Titration.

B. Assay of IVT MT-SP1 protease domain mutants with ACC and QF substrates

Several IVT-produced MT-SP1 phage selectants were assessed for increased specificity for the mutant RCL cleavage site over the native RQAR MT-SP1 cleavage site by quenched fluorescence (QF) kinetic enzyme assays. IVT supernatants, cleared as described in Example 13C above, were diluted 1:10,000 in 1X MT-SP1 activity buffer and incubated with 6.25 µM of either the native RQAR-SL QF substrate or the mutant RCL C2 cleavage substrate, SLGR-KI. Cleavage was assessed using a SpectraMax® M5 Microplate Reader (Molecular Devices) with wavelengths of Ex = 490, Em = 520 and c/o = 515. The relative specificity of the IVT-produced protease for the RCL target sequence over the native sequence was calculated using the ratio of the RFU/s (Relative fluorescent units per second) for SLGR-KI and RQAR-SL. The

results are set forth in Table 24 below. In the column labeled SEQ ID NO.:, the SEQ ID NOs. setting forth the amino acid sequence of the protease domains containing the indicated amino acid mutations are listed first; and the SEQ ID NOs. setting forth the sequence of amino acid residues that encodes the full-length MT-SP1 containing the indicated amino acid mutations is shown in parentheses. RFU numbers indicate the measured relative fluorescence units (rate of hydrolysis) for each substrate.

Table 24: Kinetic assay of mutant MT-SP1 protease domains

Mutant MT-SP1 Clone Number	Amino Acid Mutation (Chymotrypsin Numbering)	SEQ ID NO.:	Active Site Conc.	Ac-SLGR-ACC RFU/s	Ac-RQAR-ACC RFU/s	Ac-SLGR-KI QF RFU/s	Ac-RQAR-SA QF RFU/s
CPC-0025720	C122S/H143R/Q175R	522 (543)	3.9	0.10	0.46	0.05	0.04
CPC-0025876	I41F/C122S/L171F	523 (544)	2.5	0.10	0.39	0.00	0.01
CPC-0027399	F99L/C122S	527 (548)	4.2	0.55	9.84	0.04	0.09
CPC-0027797	H71R/C122S/P131S/D217V	529 (550)	3.7	0.31	1.62	0.14	0.19
CPC-0028017	C122S/D217V	530 (551)	4.7	1.42	7.29	0.38	0.50
CPC-0028333	T65K/F93L/F97Y/C122S/D217V	531 (552)	3.6	1.05	5.97	0.37	0.51
Template	C122S	507 (515)	3.5	0.22	3.58	0.05	0.06

EXAMPLE 15

Expression of Selected MT-SP1 Mutant proteins as purified protein

A. Transfer of MT-SP1protease domain into pQE vector

A subset of MT-SP1 protease domain-bearing phage clones assayed in the previous Examples was selected for transfer of the MT-SP1 protease domain sequence into a pQE30expression vector that was previously modified for expression of wild-type MT-SP1 protease domain. The InFusion DryDown PCR Cloning Kit (Clonetech) was used to transfer selected clones into pQE30-MT-SP1 (SEQ ID NO.: 624) using conditions specified by the supplier and as described by Benoit et al. (2006), Protein Expression & Purification 45:66-71. For this process, a portion of the phage clone DNA encoding the MT-SP1 protease domain was amplified by polymerase chain reaction (PCR) with the pQE-Insert-F2 forward primer: **TTCACGAGACAGGCTCGT**GTTGTTGGGGGCACGGAT (SEQ ID NO.: 560) and pQE-Insert-R3 reverse primer:

CAGCTAATTAAGCTTATTATACCCCAGTGTTCTCTTT (SEQ ID NO.: 561), each carrying non-annealing 5' tails. Plasmid pQE30-MT-SP1 without the protease domain of MT-SP1 was linearized using PCR with the forward primer: pQE-Linear-F2: **ACGAGCCTGTCTCGTGAA**TGACCGCAGCCC (SEQ ID NO.: 562) and reverse primer: pQE-Linear-R1: **TAATAAGCTTAATTAGCT**GAGCTTGGACTCC (SEQ ID NO.: 563) followed by treatment of both the donor and acceptor PCR products with DpnI enzyme. For each linearizing primer sequence set forth above, the 18-nt long homology region, a non-annealing 5' primer tail, is shown in bold. Both acceptor and donor DNA were then mixed together, and the InFusion reaction was run in a 10 μL volume using conditions specified by the supplier. 2 μL of the reaction mix was transformed into 50 μL of *E. coli* TOP10F' competent cells (Invitrogen, Carlsbad, CA). Colonies were selected on LB agar plates supplemented with 100 ppm Carbenicillin. Plasmid DNA was isolated from selected clones, and sequenced using the forward primer: MT-SP1-5F: GGAGAAACCGGCAGAGTAC (SEQ ID NO.: 564) and reverse primer MT-SP1-5R: GGTTCTCGCAGGTGGTCTG (SEQ ID NO.: 565) to verify correct transfer. These primers are fully annealing.

B. Expression, refolding and purification of mutated MT-SP1 protease domains

Plasmids encoding the protease domain of MT-SP1 variants in the pQE30 vector (Qiagen) described in Example 15B above were transformed into BL21-Gold(DE3) *E. coli* cells (Stratagene). Small starter cultures containing 1 mL LB supplemented with 100 μg/mL Carbenicillin were inoculated from colonies and incubated for between 8 and 10 hours at 37°C. 100 μL of this culture was used to inoculate 50 mL of 2xYT medium supplemented with 100 μg/mL Carbenicillin and grown overnight. In 50 mL conical tubes (Corning), the cells were harvested by centrifugation then lysed. Inclusion bodies (IB) were isolated with BugBuster® Reagent (Novagen) using the conditions specified by the supplier. The IB pellets were solublized with 1 mL of a denaturing solution containing 100 mM Tris pH 8, 6 M GdmHCL and 20 mM DTT. After removal of any insoluble material by centrifugation in microcentrifuge tubes (20,000 x g for 10 min), the supernatant was diluted into 40 mL refolding solution, containing 1.5 M arginine, 100 mM Tris pH 8, 150 mM NaCl, 5 mM reduced glutathione and 50 μM oxidized glutathione, in 50 mL conical tubes (Corning). The tubes were placed horizontally on a Nutator platform (Fisher

Scientific) at 4°C for 3-4 days. The refolded, not yet activated, MT-SP1 variants then were extensively dialyzed at room temperature against 25 mM Tris pH 8, 25 mM NaCl for 3-4 days Following the removal of arginine during dialysis, MT-SP1 protease domain variants were able to activate.

Crude preparations of activated MT-SP1 protease domain variants were then chromatographed on a 5 mL HiTrap™ Q HP column (GE Healthcare) attached to an AKTA system operating in an automated mode enabling the processing of up to seven variants per round. The running buffer was 25 mM Bis-Tris pH 6.5 and purified MT-SP1 was eluted within a 50 mL gradient to 350 mM NaCl. Active fractions were pooled, then buffer exchanged into PBS + 20 mM benzamidine and concentrated to 0.5-10 mg/mL using Amicon-Ultra 15 devices (Millipore) with a MWCO of 10 kDa. Finally, aliquots were flash-frozen in liquid nitrogen and stored at -80°C.

EXAMPLE 16

Preparation of biotinylated mutant PAI inhibitor baits

This Example describes methods that were used to express and purify mutant PAI inhibitor proteins, tagged with biotin for capture on streptavidin coated surfaces, for use in selecting variant uPA proteases from uPA libraries. These mutant PAI inhibitors are also useful for selection of some variant MT-SP1 proteases from MT-SP1 libraries, depending on the MT-SP1 variant and the RCL sequence used in the PAI.

A. N-terminal Biotinylation of 6xHis-PAI-1

For biotinylation of 6xHis-PAI-1 or reactive center loop variants thereof, wild-type His-tagged PAI-1 (SEQ ID NO.: 625) and His-tagged PAI-1 variants, as described herein in Example 1, were transformed into the Rosetta-2 (DE3)pLysS host strain (Novagen). Expression was carried out essentially as described (Blouse, G. E., Perron, M. J., Thompson, J. H., Day, D. E., Link, C. A., and Shore, J. D. (2002) Biochemistry 41(40), 11997-12009), with the following modifications. Induction was carried out for three hours at 30°C in 2XYT medium supplemented with 0.2% glucose, 100 ug/mL Carbenicillin and 10 ug/mL chloramphenicol (Cm). The active fraction of 6xHis-PAI-1 then was purified from the cell lysates as described (Blouse, G. E., Perron, M. J., Kvassman, J. O., Yunus, S., Thompson, J. H., Betts, R. L.,

Lutter, L. C., and Shore, J. D. (2003) Biochemistry 42(42), 12260-12272; Kvassman, J.-O., and Shore, J. D. (1995) Fibrinolysis 9, 215-221).

6xHis-PAI-1 variants were preferentially biotinylated at the N-terminus using the disulfide cleavable reagent EZ-Link NHS-SS-PEO_4-Biotin (PIERCE, Rockford, IL #21442). Reactions were carried out at pH 6.2, for 4 hours, at 4°C on ice in a buffer containing 50 mM NaPi/300 mM NaCl/1 mM EDTA. The reaction was initiated by the addition of a 5-fold molar excess of biotinylation reagent dissolved in DMSO. The final concentration of DMSO in the reaction was maintained at below 1%. The Biotinylation reaction was quenched by the addition of 0.5 M Tris/1.0 NaCl/10 mM EDTA, pH 7.4 to a final Tris concentration of 20 mM. Excess biotinylation reagent was removed by extensive dialysis against a storage buffer containing 50 mM NaPi/300 mM NaCl/1 mM EDTA, pH 6.2. The concentration of PAI-1 in the resulting solution was confirmed using an extinction coefficient of 0.93 mL mg^{-1} cm^{-1} (see: Kvassman, J.-O., and Shore, J. D. (1995) Fibrinolysis 9, 215-221). The extent of biotinylation was determined using the EZ-Quant HABA/Avidn kit (PIERCE, Rockford, IL #28005), following the supplier-specified conditions, and was typically between 1.0 and 1.2 moles biotin per 1 mole PAI-1 variant.

B. in vivo biotinylation of PAIs: Biotinylation of BRS-TEV-OptiPAI-1^{stab} in vivo:

This Example describes a method that was used to *in vivo* biotinylate PAI. In this Example, an appropriate recognition sequence was incorporated into the gene encoding the bait molecule so that the biotin-tagging of the bait could be accomplished in growing cells, instead of being carried out with purified bait *in vitro*. A gene encoding stable PAI-1 protein (PAI-1^{stab}, having the sequence of amino acid residues set forth in SEQ ID NO.: 567), which has N150H, K154T, Q319L and M354I mutations (Berkenpas, M. B., Lawrence, D. A., and Ginsburg, D. (1995) EMBO J. 14(13), 2969-2977), was designed to contain the following regions in the following order: 1) Start codon, 2) Biotin Recognition Sequence (BRS), 3) Tobacco Etch Virus Protease Sequence (TEV) 4) PAI coding sequence 5) stop codon; with *Escherichia coli* codon optimization. This synthetic PAI-1^{stab} gene was cloned into the commercial expression vector pET21-a (Novagen, Madison, WI) (SEQ ID NO.: 566) using *Xba*I and *Hin*dIII restriction enzymes resulting in plasmid pCAT0002 (SEQ ID NO: 619), which expressed Optimized PAI-1 (OptiPAI-1; encoded by the amino acid sequence set forth in SEQ ID NO.: 621, in which amino acid residue

positions 3-17 and 20-26 correspond to the BRS and TEV sites, respectively) using the T7 expression system. Plasmid pCAT0002 was then co-transformed into *E. coli* BL21-Gold (DE3) competent cells (Stratagene, San Diego, CA) carrying the plasmid pBirA (described in Asai et al., (1999) J. Biol. Chem. 274:20079-20078), which overexpresses the *E. coli* biotin ligase, BirA. Transformants were selected on Luria-Bertani (LB) agar plates supplemented with 100 ug/mL Carbenicillin and 10 µg/mL chloramphenicol (Cm).

Expression of BRS-TEV-OptiPAI-1^{stab} (SEQ ID NO.: 621) and reactive center loop variants thereof was carried out essentially as described (Blouse, G. E., Perron, M. J., Thompson, J. H., Day, D. E., Link, C. A., and Shore, J. D. (2002) Biochemistry 41(40), 11997-12009), with the following modifications. Induction was initiated by the addition of 0.1 mM IPTG and 0.1 mM D-biotin for three hours at 30°C in 2XYT medium supplemented with 0.2% glucose, 100 µg/mL Carbenicillin and 10 µg/mL chloramphenicol (Cm). The active fraction of BRS-TEV-OptiPAI-1^{stab} was subsequently purified from the cell lysates as described (see: Blouse, G. E., Perron, M. J., Kvassman, J. O., Yunus, S., Thompson, J. H., Betts, R. L., Lutter, L. C., and Shore, J. D. (2003) Biochemistry 42(42), 12260-12272; and Kvassman, J.-O., and Shore, J. D. (1995) Fibrinolysis 9, 215-221) or by selection by chromatography on monomeric avidin (PIERCE, Rockford, IL #20227), following the conditions specified by the supplier, with the following modifications. The binding buffer contained 50 mM Tris/100 mM NaCl/1 mM EDTA/0.01% tween-80 and had a pH of 7.4; and a competitive elution buffer was used that contained this binding buffer plus 2 mM D-biotin. Biotin from the competitive elution step was removed by extensive dialysis against a storage buffer containing 50 mM NaPi/300 mM NaCl/1 mM EDTA, pH 6.2. The PAI-1 concentration was confirmed using an extinction coefficient of 0.93 mL mg^{-1} cm^{-1} as described (Kvassman, J.-O., and Shore, J. D. (1995) Fibrinolysis 9, 215-221).

C. *in vitro* Biotinylation of V1C OptiPAI-1^{stab}

This Example sets forth methods for N-terminal Biotinylation of a PAI variant. The methods described in this Example were carried out to incorporate an appropriate reactive group into the gene encoding the PAI bait molecule, such that the tagging of the bait with biotin could be accomplished after the protein had been purified, allowing position-specific labeling of the bait. In this Example, since native

PAI does not contain any cysteine residues, a cysteine codon was added to the DNA encoding the PAI gene to create a Cys-containing PAI that could then be reacted with Cys-reactive biotinylation reagents.

The N-terminal BRS-TEV sequence of OptiPAI-1, in plasmid pCAT0002 described above, was deleted with simultaneous introduction of V1C mutation using the QuikChange-XL mutagenesis Kit (Stratagene, San Diego, CA), according to supplier specifications, resulting in plasmid pCAT0051 (SEQ ID NO.: 623) expressing V1C OptiPAI-1^{stab} protein (SEQ ID NO.: 622). Plasmid pCAT0051 was transformed into *E. coli* BL21(DE3) pLysS competent cells (Stratagene, San Diego, CA). Transformants were selected on Luria-Bertani (LB) agar plates supplemented with 100 ug/mL Carbenicillin and 10 ug/mL chloramphenicol (Cm).

Expression of the V1C OptiPAI-1^{stab} protein and reactive center loop variants thereof was carried out essentially as described (Blouse, G. E., Perron, M. J., Thompson, J. H., Day, D. E., Link, C. A., and Shore, J. D. (2002) Biochemistry 41(40), 11997-12009), with the following modifications. Induction was initiated by the addition of 0.1 mM IPTG for three hours at 30°C in 2XYT medium that was supplemented with 0.2% glucose, 100 ug/mL Carbenicillin and 10 ug/mL chloramphenicol. The active fraction of the V1C OptiPAI-1^{stab} or variant thereof was purified from the cell lysates as described (Blouse, G. E., Perron, M. J., Kvassman, J. O., Yunus, S., Thompson, J. H., Betts, R. L., Lutter, L. C., and Shore, J. D. (2003) Biochemistry 42(42), 12260-12272; and Kvassman, J.-O., and Shore, J. D. (1995) Fibrinolysis 9, 215-221).

The V1C OptiPAI-1 proteins and variants were biotinylated at the engineered N-terminal cysteine residue using the thiol-reactive and reversible biotinylation reagent, EZ-Link Biotin-HPDP (*N*-(6-(Biotinamido)hexyl)-3'-(2'-pyridyldithio)-propionamide) (PIERCE, Rockford, IL #21341). Biotin conjugation was accomplished according to the supplier specifications, with some modifications, as follows. Stock solutions of biotin-HPDP were prepared at 5 mg/mL in anhydrous DMF (9.3 mM). V1C OptiPAI-1^{stab} was rapidly desalted on G-25 gel filtration column, from which it was eluted into a conjugation buffer containing 50 mM NaPi/150 mM NaCl/1 mM EDTA/0.01% Tween-80, pH 7.4. Biotinylation reactions were initiated by the addition of a 10-fold molar excess of stock Biotin-HPDP. The final concentration of dimethylformamide (DMF) was maintained below 2-3%.

Reactions were carried out for 4 hours at 25°C and the reaction progress followed using release of the pyridine-2-thione leaving group at 343 nm. Excess biotinylation reagent was removed by extensive dialysis against a storage buffer containing 50 mM NaPi/300 mM NaCl/1 mM EDTA, pH 6.2. The PAI-1 concentration was confirmed using an extinction coefficient of 0.93 mL mg^{-1} cm^{-1} as des(Kvassman, J.-O., and Shore, J. D. (1995) Fibrinolysis 9, 215-221). The extent of biotinylation was typically 1.0-1.2 moles of biotin per mole of PAI-1 variant using the EZ-Quant HABA/Avidn kit and the release of pyridin-2-thione (PIERCE, Rockford, IL #28005).

EXAMPLE 17

Screening of MT-SP1 variants from *E. coli* culture supernatants and periplasmic extracts

This Example describes two methods, each used as an alternative to screening the activity of MT-SP1 variants on phage by assaying either the protein from the *E. coli* periplasmic space or the protein from *E. coli* cell culture medium.

For both methods, 1 mL cultures were prepared as follows. 1mL of 2YT medium supplemented with 100ug/mL Carbenicillin and 12ug/mL Tetracycline were dispensed into each well of a 96 well deep well plate, and inoculated with 10μL of XL-1 Blue cells that had been infected with MT-SP1 protease domain-bearing phage overnight as described in Example 14 above, from a 96 well master plate. The deep well plate was sealed with an air-permeable membrane and placed in a HiGro shaker incubator with shaking at 400 rpm at 37°C with oxygen aeration until the cell density reached 0.4 – 0.6 OD600 (usually 4-5 hours of shaking). At that point IPTG was added to a final concentration of 0.5 mM, and growth with shaking was continued overnight. The following day, the plate was centrifuged at 3600 rpm for 20min to pellet the cells.

A. Screening of MT-SP1 variants from Preiplasmic preps

The methods in this example were used to assay the full length MT-SP1-gene III fusion proteins, and enzymatically active cleavage products of the fusion proteins, that had been transported into the *E. coli* periplasmic space. After the centrifugation at 3600 rpm, the culture supernatant was discarded and the cell pellet was used to release periplasmic proteins using either of the following conditions: Condition 1: The cell pellets were resuspended in 150 μL cold phosphate buffered saline (PBS);

the suspension was transferred a 96 well PCR plate; followed by one step freeze thawing (20 min at -80°C / 10 min in a room temperature water bath); or Condition 2: The cell pellets were resuspended in 150 uL of 3% BugBuster Protein Extraction Reagent (Novagen); the suspension was transferred to a 96 well PCR plate; and the suspension was incubated at room temperature for 30 min. Next, the cell suspensions were centrifuged for 20min at 3600 rpm at 4°C and the supernatants containing periplasmic proteins were carefully removed without disturbing the pellet. Further, the periplasmic extracts were used to determine enzyme activity of the MT-SP1 variants using appropriate substrates as described in Example 10, Section B.

B. Screening of MT-SP1 variants from supernatant preps

The methods in this example were used to assay the full length MT-SP1-gene III fusion proteins, and catalytically active fragments of the fusion protein, that had diffused from the periplasm and into the bacterial cell culture media. In this example, after centrifugation in the 1 mL culture, 10 µL of the culture supernatant were removed and assayed using the protease assay described in Example 10, Section B, except an additional 25 µL of assay buffer was added to the reaction.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

CLAIMS:

1. A method, comprising:

a) contacting a collection of proteases and/or catalytically active portions of proteases with a protease trap polypeptide to form, upon cleavage of the protease trap polypeptide by the protease or catalytically active portion thereof, stable complexes containing the protease trap polypeptide with a protease or catalytically active portion thereof in the collection; and

b) identifying or selecting a protease or catalytically active portion thereof in a complex.

2. The method of claim 1, wherein the protease trap polypeptide is modified to be cleaved by a protease having a predetermined substrate specificity and/or activity for a target substrate.

3. The method of claim 2, wherein:

the identified or selected proteases are modified compared to a template protease; and

the identified or selected proteases have an altered activity and/or specificity towards the target substrate compared to the template protease not containing the modification(s).

4. The method of any of claims 1-3, further comprising separating the complexed proteases from uncomplexed members of the collection.

5. The method of any of claims 1-3, wherein the protease trap polypeptide and a protease in the complex are covalently linked.

6. The method of any of claims 1-5, wherein:

the protease trap polypeptide is labeled for detection or separation; and

separation is effected by capture of complexes containing the detectable protease trap polypeptide with any protease or catalytically active portion thereof.

7. The method of claim 6, wherein capture is effected in suspension, solution or on a solid support.

8. The method of claim 7, wherein:

the protease trap polypeptide is attached to a solid support; and

attachment is effected before, during or subsequent to contact of the protease trap polypeptide with the collection of proteases or catalytically active portions thereof.

9. The method of claim 8, wherein the solid support is a well of an enzyme-linked immunosorbent assay (ELISA) plate.

10. The method of claim 6, wherein the protease trap polypeptide is labeled with biotin.

11. The method of claim 6, wherein:

the protease trap is labeled with a His tag; and

separation is effected by capture with a metal chelating agent.

12. The method of claim 11, wherein the metal chelating agent is selected from among nickel sulphate (NiSO4), cobalt chloride (CoCl2), copper sulphate (CuSO4) and zinc chloride (ZnCl2).

13. The method of any of claims 1-12, further comprising amplifying the protease or catalytically active portion thereof in the separated complexes.

14. The method of claim 13, wherein the protease or catalytically active portion thereof in the separated complex is displayed on a phage, and amplification is effected by infecting a host cell with the phage.

15. The method of claim 14, wherein the host cell is bacteria.

16. The method of claim 14, further comprising screening the amplified protease for specificity and/or activity towards a target substrate, wherein specificity and/or activity is assessed on bacterial cell medium, bacterial periplasm, phage supernatant or on purified protein.

17. The method of claim 16, wherein the target substrate is a polypeptide or a cleavage sequence in a polypeptide involved in the etiology of a disease or disorder.

18. The method of any of claims 1-17 that is multiplexed, wherein:

a plurality of different protease trap polypeptides are contacted with the collection; and

at least two protease trap polypeptides can be identifiably detected, whereby more than one protease is identified.

19. The method of any of claims 1-18, wherein proteases or catalytically active portions thereof in the complexes are displayed, whereby they can be amplified following identification or selection to produce a second collection of proteases and/or catalytically active portions thereof.

20. The method of claim 19, further comprising contacting the second collection with a second protease trap polypeptide to produce a second set of stable complexes.

21. The method of claim 20, wherein the second protease trap polypeptide is the same or different from the first protease trap polypeptide.

22. The method of claim 20, further comprising identifying or selecting proteases in the second set of stable complexes.

23. The method of any of claims 1-22, wherein the protease trap polypeptide is selected from among a serpin, a member of the alpha macroglobulin family, or a member of the p35 family.

24. The method of any of claims 4 and 6-23, wherein the stable complexes comprises a protease trap polypeptide covalently linked to a protease or catalytically active portion thereof.

25. A method for screening proteases to identify any proteases that have a predetermined substrate specificity, comprising:

a) contacting a collection of proteases and/or catalytically active portions of proteases with a protease trap polypeptide to form stable complexes of the protease trap polypeptide with a protease upon cleavage of the protease trap polypeptide, wherein the protease trap polypeptide is selected or modified to be cleaved by a protease having the predetermined substrate specificity; and

b) identifying a protease or caalytically active portion of a protease in a complex to thereby select a protease having predetermined substrate specificity.

26. The method of any of claims 1-25, wherein the collection contains at least 5, 10, 50, 100, 500, 10^3, 10^4, 10^5, 10^6 or more different members.

27. The method of any of claims 1-26, where the proteases or catalytically active portions thereof are serine and/or cysteine proteases.

28. The method of any of claims 1-27, wherein the proteases or catalytically active portions thereof are displayed.

29. The method of claim 28, wherein the protease or catalytically active portions thereof are displayed on a solid support, on a cell surface, or on the surface of a microorganism.

30. The method of claim 29, wherein the protease or catalytically active portion thereof are displayed on the surface of a yeast, bacterium, a virus, a phage, a nucleic acid, an mRNA molecules or on ribosomes.

31. The method of claim 29, wherein the microorganism is *E.coli*, S. cerevisiae, or a virus selected from among M13, fd, T7, or a baculovirus.

32. The method of any of claims 1-31 that is a homogeneous reaction.

33. The method of any of claims 1-28, wherein the proteases or catalytically active portions thereof are displayed in a phage display library.

34. The method of any of claims 1-33, wherein the proteases are provided as catalytically active portions of a protease.

35. The method of any of claims 1-34, wherein:

at least two different protease trap polypeptides are contacted with the collection; and

at least one of the protease trap polypeptides is detectably labeled.

36. The method of claim 35, wherein at least one protease trap polypeptide is detectable to effect capture of stable complexes containing the detectable protease trap polypeptide with a protease or catalytically active portion thereof.

37. The method of claim 35, wherein:

at least two different protease trap polypeptide are contacted with the collection;

only one protease trap polypeptide is detectably labeled; and

the other or others are each present in excesses compared to the detectably labeled protease trap polypeptide.

38. The method of claim 35, wherein the detectable label is a fluorescent label or a His tag.

39. The method of claim 38, wherein the detectable label is biotin.

40. The method of any of claims 1-38, wherein the proteases or catalytically active portions thereof are selected from among the chymotrypsin, subtilisin, caspases and the papain families of proteases.

41. The method of any of claims 1-40, wherein the protease is a serine protease, cysteine protease, or catalytically active portion thereof and is selected from among granzyme B, testisin, trypstase beta 1, kallikrein hk5, corin, kallikrein 12, DESC1 oritesase, trypstase gamma 1, kallikrein hK14, hyaluronan-binding serine

protease, tryptase, kallikrein hK15, trypsin, neutrophil elastase, mannan-binding lectin-associated serine protease-3, cathepsin G, myeloblastin, granzyme A, granzyme M, chymase, granzyme K, granzyme H, chymotrypsin B, pancreatic elastase, pancreatic endopeptidase E, pancreatic elastaste II, enteropeptidase, chymotrypsin C, prostasin, kallikrein 1, kallikrein hK2, kallikrein 3, mesotrypsin, Factor XII, plasma kallikrein KLK3, factor XI, factor IX, factor VII, factor Xa, thrombin, protein C, acrosin, hepsin, hepatocyte growth factor activator (uPA), urinary plasminogen activator (uPA), tissue plasminogen activator (tPA), plasmin, neurosin, neurotrypsin, neuropsin, kallikrein hK10, epitheliasin, prostase, chymopasin, kallikrein 11, MT-SP1, spinesin, cathepsin L, cathepsin V, cathepsin K, cathepsin S, cathepsin F, cathepsin B, papain, cruzain, subtilisin, thermitase, C5a peptidase, fervidolysin, lactocepin, furin, kexin, caspase-1, caspase-3, caspase-7, caspase-6, caspase-2, caspase-4, caspase-5, caspase-8, caspase-9, caspase-10, caspase-11, caspase-12, caspase-1, caspase-13, and caspase-14.

42. The method of any of claims 1-41, wherein the proteases or catalytically active portion thereof are selected from among urokinase plasminogen activator (u-PA), tissue plasminogen activator (t-PA) and MT-SP1.

43. The method of any of claims 1-42, wherein the protease trap polypeptides are selected from among serpins, p35 family members, alpha-macroglobulin family members or modified forms thereof.

44. The method of any of claims 1-42, wherein the protease trap polypeptide is a serpin selected from plasminogen activator inhibitor-1 (PAI-1) or antithrombin III (AT3), or modified forms thereof.

45. The method of claim 43, wherein the protease trap polypeptide is alpha2- macroglobulin, or a modified form thereof.

46. The method of any of claims 43-45, wherein the modified form contains one or more amino acid replacements, deletions, or substitutions in the reactive site of the protease trap polypeptide.

47. The method of claim 46, wherein the modification is any one or more amino acid replacements corresponding to a cleavage sequence of a target substrate.

48. The method of claim 47, wherein the target substrate is involved in the etiology of a disease or disorder.

49. The method of claim 47, wherein the target substrate is a VEGFR, a complement protein, or a substrate of tissue plasminogen activator (tPA).

50. The method of claim 49, wherein the VEGFR is VEGFR2.

51. The method of claim 49, wherein the complement protein is C2.

52. The method of claim 47, wherein the one or more amino acid modifications corresponding to a cleavage sequence has a sequence of amino acids set forth in any of SEQ ID NOS: 389, 479 and 498.

53. The method of claim 46, wherein the protease trap polypeptide is a serpin and the one or more amino acid replacements is/are in the reactive site loop of the serpin polypeptide.

54. The method of claim 53, wherein the one or more amino acid replacements are in any one or more of the P4-P2' positions.

55. The method of claim 54, wherein the serpin has a sequence of amino acids set forth in any of SEQ ID NOS: 497, 499, 610 and 611.

56. The method of claim 46, wherein the protease trap polypeptide is alpha 2 macroglobulin, and the one or more amino acid replacements are in the bait region of the polypeptide.

57. The method of claim 48, wherein the identified or selected protease or catalytically active portion thereof has altered substrate specificity for a target substrate compared with a non-target substrate.

58. The method of claim 57, wherein the non-target substrate is a substrate of the corresponding template protease.

59 The method of claim 57, wherein the substrate specificity is increased by 1.5-fold, 2-fold, 5-fold, 10-fold, 50-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold or more.

60. The method of any of claims 1-59, wherein the method of identifying proteases is performed a plurality of times, whereby the process is iterative.

61. The method of claim 60, wherein the method is performed until the protease exhibits increased substrate specificity and/or activity for a cleavage sequence in a target substrate as compared to a non-target substrate of the corresponding template protease.

62. The method of claim 60, wherein a plurality of different proteases are identified at least in the first iteration of the method.

63. The method of any of claims 60-62, further comprising comparing the amino acid sequences of the identified proteases to identify hot spots, wherein:

a hot spot is a modified locus that occurs in at least two, three, four, five or more of the identified proteases; and

a modified locus is one that is modified if the collection contains modified proteases or catalytically active portions thereof.

64. The method of any of claims 1-63, further comprising;

after identifying a first protease or proteases, preparing a second collection of proteases, wherein an identified first protease is used a template to make further mutations in the protease sequence or catalytically active portion thereof such that members of the second collection contain polypeptides having mutations of the identified first proteases and additional mutations;

then contacting the second collection with a second protease trap polypeptide that is either identical or different from the first protease trap polypeptide used to isolate the first protease or proteases, wherein the protease trap polypeptide is modified to be cleaved by a protease having the desired target substrate specificity; and

identifying a second protease(s) or catalytically active portion(s) of a protease from the collection in a complex, whereby the second identified protease(s) has greater activity or specificity towards the target substrate than the first identified protease.

65. The method of claim 63, wherein the second collection or proteases contains random or focused mutations as compared to the sequence of amino acids of the first identified template protease(s) or catalytically active portion of a protease.

66. The method of claim 65, wherein the mutations are focused mutations at hot spot positions.

67. The method of claim 66, wherein the hot spot positions are in a serine protease and are selected from among positions 30, 73, 89 and 155, based on chymotrypsin numbering.

68. The method of any of claims 1-67, wherein the formation of stable complexes is modulated by controlling one or more parameters selected from among reaction time, temperature, pH, ionic strength, library concentration and protease trap polypeptide concentration.

69. The method of any of claims 1-68, wherein the method further comprises adding a competitor to the reaction between a protease trap polypeptide and a protease or catalytically active portion thereof to thereby enhance selectivity of identified protease(s) or catalytically active portion(s).

70. The method of claim 69, wherein the competitor is human serum or plasma.

71. The method of claim 69, wherein the competitor is a cell or tissue extract or a biological fluid such as urine or blood.

72. The method of claim 69, wherein the competitor is a purified or partially purified wild type form of the protease trap.

73. The method of claim 69, wherein the competitor is a purified or partially purified wild-type form of a protease trap polypeptide or one or more specific variants of a protease trap polypeptide.

74. The method of any of claims 69-70, wherein the competitor is human plasma.

75. The method of any of claims 69-72, wherein the competitor is a purified wild-type form of the protease trap polypeptide or is a protease trap polypeptide that is a modified protease trap polypeptide.

76. An iterative method for evolving or selecting or identifying a protease or catalytically active portion thereof with specificity/selectivity and/or activity for at least two different cleavage sequences, comprising:

a) contacting a collection of proteases and/or catalytically active portions of proteases with a first protease trap polypeptide to form, upon cleavage of the protease trap polypeptide by the protease or catalytically active portion thereof, stable complexes containing the first protease trap polypeptide with a protease or catalytically active portion thereof in the collection, wherein contacting is effected in the presence of a competitor;

b) identifying or selecting proteases or catalytically active portions thereof that form complexes with the first protease trap polypeptide;

c) contacting proteases or catalytically active portion thereof that form complexes with the first protease trap polypeptide with a second protease trap polypeptide in the presence of a competitor; and

d) identifying or selecting proteases or catalytically active portions thereof that form complexes with the second protease trap polypeptide,

whereby the identified, evolved or selected protease or catalytically active portion thereof has substrate specificity and/or cleavage activity for at least two cleavage sequences.

77. The method of claim 76, wherein the at least two cleavage sequences are in one target substrate.

78. The method of claim 76, wherein the at least two cleavage sequences are in two different target substrates.

79. The method of any of claims 76-78, wherein the first and second protease trap polypeptide are different and each is modified to be cleaved by a protease having the desired substrate specificity for a different target substrate.

80. The method of any of claims 76-79, further comprising repeating steps a) and b) or a)-d) at least once more until an identified or selected protease with a desired or predetermined substrate specificity and cleavage activity to at least two cleavage sequences is isolated.

81. The method of claim 76, wherein the collection of proteases comprise amino acid mutations in positions corresponding to a template protease.

82. The method of claim 81, wherein the substrate specificity and/or cleavage activity is increased compared with the corresponding template protease.

83. The method of claim 80, wherein the substrate specificity for at least one cleavage sequence is increased compared to the corresponding template protease.

84. The method of claim 76, wherein the competitor is selected from among human serum, human plasma, a cell or tissue extract, a biological fluid such as urine or blood, a purified or partially purified wild-type form of the protease trap, and one or more specific variants of a protease trap polypeptide.

85. A method of protease selection, comprising:

a) contacting a collection of proteases or catalytically active portions thereof with a first protease trap polypeptide to form, upon cleavage of the protease trap polypeptide, covalent complexes of the protease trap polypeptide with any protease or catalytically active portion thereof in the collection;

b) separating the complexed proteases from uncomplexed protease trap polypeptide(s);

c) isolating or selecting or identifying the complexed proteases;

d) generating a second collection of proteases or catalytically active portions of proteases based on the selected proteases; and

e) repeating steps a) - c) by contacting the second collection of proteases or catalytically active portions thereof with a second protease trap polypeptide that is different from the first protease trap polypeptide to form complexes; separating the complexes; and isolating, selecting or identifying complexed proteases.

86. The method of claim 85, wherein the first and second protease trap polypeptides are modified to contain two different target substrate cleavage sequences, whereby the identified or selected protease has specificity and high cleavage activity to at least two cleavage sequences.

87. The method of claim 85 or 86 that is repeated a plurality of times.

88. The method of any of claims 85-87, wherein a collection of proteases or catalytically active portions thereof is contacted with the first and/or second protease trap polypeptide in the presence of a competitor.

89. The method of claim 88, wherein the competitor is selected from among human serum, human plasma, a cell or tissue extract, a biological fluid such as urine or blood, a purified or partially purified wild-type form of the protease trap polypeptide, and one or more specific variants of a protease trap polypeptide.

90. The method of any of claims 1-89, wherein the collections contain modified proteases.

91. The method of claim 90, wherein the modifications are random or focused or in a target region.

92. The method of any of claims 2-91, further comprising screening the complexes for substrate specificity for the cleavage sequence of the target substrate.

93. A combination, comprising;

a collection of proteases and/or catalytically active portions thereof; and

at least one protease trap polypeptide.

94. The combination of claim 93, wherein the protease trap polypeptide is selected from among serpins, p35 family members, alpha-macroglobulin family members, or modified forms thereof.

95. The combination of claim 93 or claim 94, wherein the collection of proteases and/or catalytically active portions thereof are provided in a display library.

96. The combination of claim 95, wherein the display library is a phage display library and members display at least a catalytically active portion of a protease.

97. A kit, comprising the combination of any of claims 93-96, wherein each component is separately packaged.

98. A method of modifying the substrate specificity of a serine protease, comprising modifying one or more of residues selected from among 30, 73, 89 and 155 based on chymotrypsin numbering.

99. The method of claim 98, wherein the serine protease is uPA.

100. A modified protease,

wherein the protease or catalytically active fragment thereof is of the chymotrypsin family of serine proteases; and

contains one or more mutations in any of positions corresponding to positions 30, 73, 89, and 155, based on chymotrypsin numbering, whereby substrate specificity is altered.

101. The modified protease of claim 100, wherein the protease is a modified urinary plasminogen activator (u-PA) polypeptide or catalytically active fragement therof.

102. A modified urinary plasminogen activator (u-PA) polypeptide, comprising one or more amino acid modifications corresponding to amino acid positions in a u-PA polypeptide set forth in SEQ ID NO:433, wherein:

the one or more amino acid modifications increase one or both of specificity for a target substrate or activity towards a target substrate; and

the target substrate is involved in the etiology of a disease or disorder.

103. The modified urinary plasminogen activator (u-PA) polypeptide of claim 102, wherein the target substrate is a VEGFR or a tissue plasminogen activator (t-PA) substrate.

104. The modified urinary plasminogen activator (u-PA) polypeptide of claim 103, wherein the u-PA polypeptide or catalytically active portion thereof contains one or more modifications in positions corresponding to positions selected from among positions 21, 24, 30, 39, 61(A), 80, 82, 84, 89, 92, 156, 158, 159, and 187

in a u-PA polypeptide set forth in SEQ ID NO:433, based on chymotrypsin numbering, whereby substrate specificity to a t-PA substrate, or sequence thereof, is altered.

105. The modified u-PA polypeptide of claim 103, wherein the u-PA polypeptide or catalytically active portion thereof contains one or more modifications selected from among F21V, I24L, F30V, F30L, T39A, Y61(A)H, E80G, E82E, E84K, I89V, K92E, K156T, T158A, V159A, and K187E.

106. The modified u-PA polypeptide of claim 105, wherein the u-PA polypeptide or catalytically active portion thereof contains modifications selected from among F21V; I24L; F30V; F30L; F30V/Y61(a)H; F30V/K82E; F30V/K156T; F30V/K82E/V159A; F30V/K82E/T39A/V159A; F30V/K82E/T158A/V159A; F30V/Y61(a)H/K92E; F30V/K82E/V159A/E80G/I89V/K187E; and F30V/K82E/V159A/E80G/E84K/I89V/K187E.

107. The modified urinary plasminogen activator (u-PA) polypeptide of claim 103, wherein the u-PA polypeptide or catalytically active portion thereof contains one or more modifications in positions corresponding to positions selected from among positions 38, 72, 73, 75, 132, 133, 137, 138, 155, 160, and 217 in a u-PA polypeptide set forth in SEQ ID NO:433, based on chymotrypsin numbering,whereby substrate specificity to a VEGFR-2, or sequence thereof, is altered.

108. The modified u-PA polypeptide of claim 107, wherein the u-PA polypeptide or catalytically active portion thereof contains one or more modifications selected from among V38D, R72G, L73A, L73P, S75P, F132L, G133D, E137G, I138T, L155P, L155V, L155M, V160A, and R217C.

109. The modified u-PA polypeptide of claim 107, wherein the u-PA polypeptide or catalytically active portion thereof further comprises a modification at position 30 and/or position 89, based on chymotrypsin numbering.

110. The modified u-PA polypeptide of claim 109, wherein the further modification in the u-PA polypeptide or catalytically active portion thereof is selected from among F30I, F30T, F30L, F30V, F30G, F30M, and I89V.

111. The modified u-PA polypeptide of claim 110, wherein the u-PA polypeptide or catalytically active portion thereof contains modifications selected from among L73A/I89V; L73P; R217C; L155P; S75P/I89V/I138T; E137G; R72G/L155P; G133D; V160A; V38D; F132L/V160A; L73A/I89V/F30T;

L73A/I89V/F30L; L73A/I89V/F30V; L73A/I89V/F30G; L73A/I89V/L155V; L73A/I89V/F30M; L73A/I89V/L155M; L73A/I89V/F30L/L155M; and L73A/I89V/F30G/L155M.

112. The modified u-PA polypeptide of claim 103, wherein the u-PA polypeptide or catalytically active portion thereof contains one or more modifications corresponding to mutations selected from among F30I, F30T, F30G, and F30M in a u-PA polypeptide set forth in SEQ ID NO:433, based on chymotrypsin numbering, whereby substrate specificity to a VEGFR-2, or sequence thereof, is altered.

113. The modified u-PA polypeptide of any of claims 102-112, wherein:

the u-PA polypeptide has 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity with a wild-type u-PA polypeptide set forth in SEQ ID NO:433, or an allelic or species variant thereof; and

the polypeptide includes the one or more modifications.

114. A modified MT-SP1 polypeptide or catalytically active portion thereof, comprising one or more amino acid modifications selected from among D23E, I41F, I41T, L52M, Y60(g)s, T56K, H71R, F93L, N95K, F97Y, F97L, T98P, F99L, A126T, V129D, P131S, I136T, I136V, H143R, T144I, I154V, N164D, T166A, L171F, P173S, F184(a)L, Q192H, S201I, Q209L, Q221(a)L, R230W, F234L, and V244G, based on chymotrypsin numbering, in an MT-SP1 polypeptide set forth in SEQ ID NO:253.

115. The modified MT-SP1 polypeptide of claim 114, wherein the modifications are in a cataytically active portion of an MT-SP1 having a sequence of amino acids set forth in SEQ ID NO: 505.

116. The modified MT-SP1 polypeptide of claim 114 or claim 115, wherein the modifications are in an MT-SP1 polypeptide further comprising a modification corresponding to modification of C122S in an MT-SP1 polypeptide set forth in SEQ ID NO:253, based on chymotrypsin numbering.

117. The modified MT-SP1 polypeptide of claim 116, wherein the modifications are in an MT-SP1 polypeptide having a sequence of amino acids set forth in SEQ ID NO: 507 or 517.

118. The modified MT-SP1 polypeptide of any of claims 114-117, wherein the amino acid modifications are selected from among I41F, F97Y, L171F and V244G.

119. The modified MT-SP1 polypeptide of any of claims 114-118, further comprising one or more modifications corresponding to modifications Q175R or D217V in an MT-SP1 polypeptide set forth in SEQ ID NO:253.

120. The modified MT-SP1 polypeptide of claim 119, wherein the amino acid modifications are selected from among I136T/N164D/T166A/F184(A)L/D217V; I41F; I41F/ A126T/V244G; D23E/I41F/T98P /T144I; I41F/ L171F/V244G; H143R/Q175R; I41F/ L171F; R230W; I41F /I154V/V244G; I141F/L52M/ V129D/Q221(A)L; F99L; F97Y/ I136V/Q192H/S201I; H71R/ P131S/D217V; D217V; T65K/F93L/F97Y/ D217V; I41T/ P173S/Q209L; F97L/ F234L; Q175R; N95K; and Y60(G)S.

121. The modified MT-SP1 polypeptide of any of claims 114-120, wherein the modifications increase one or both of specificity for a C2 complement protein or activity towards C2 complement protein.

122. The modified MT-SP1 polypeptide of any of claims 114-121, wherein:

the MT-SP1 polypeptide has 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity with a wild-type MT-SP1 polypeptide set forth in SEQ ID NO:253, or a catalytically active portion thereof set forth in SEQ ID NO:505, or an allelic or species variant thereof; and

the polypeptide includes the one or more modifications.

123. A pharmaceutical composition, comprising a modified u-PA polypeptide of claim 102.

124. A pharmaceutical composition, comprising a modified u-PA polypeptide of any of claims 104-106.

125. A pharmaceutical composition, comprising a modified u-PA polypeptide of any of claims 107-113.

126. A pharmaceutical composition, comprising a modified MT-SP1 polypeptide of any of claims 114-122.

127. The pharmaceutical composition of any of claim 123-126, further comprising a pharmaceutically acceptable excipient.

128. The pharmaceutical composition of claim 127, wherein the pharmaceutical composition is formulated for systemic, oral, nasal, pulmonary, local, or topical administration.

129. A kit, comprising the pharmaceutical composition of any one of claims 123-126, a device for administration of the composition and, optionally, instructions for administration.

130. A nucleic acid molecule, comprising a sequence of nucleotides that encodes any one of the modified u-PA proteases of claims 102-113.

131. A nucleic acid molecule, comprising a sequence of nucleotides that encodes any one of the modified MT-SP1 proteases of claims 114-122.

132. A vector, comprising the nucleic acid molecule of claim 130 or 131.

133. A cell, comprising the vector of claim 132.

134. A method of treatment, comprising treating a subject by administering a pharmaceutical composition of claim 124, wherein the subject has a disease or condition that is treated by administration of t-PA.

135. The method of claim 134, wherein the disease or condition is selected from among arterial thrombosis, venous thrombosis and thromboembolism, ischemic stroke, acquired coagulation disorders, disseminated intravascular coagulation, bacterial infection and periodontitis, and neurological conditions.

136. The method of claim 135, wherein the disease or conditions is thrombosis that obstructs a catheter.

137. A method of treatment, comprising treating a subject by administering a pharmaceutical composition of claim 125, wherein the subject has a disease or condition that is mediated by VEGFR-2.

138. The method of claim 137, wherein the disease or condition to be treated is an angiogenic disease.

139. The method of claim 138, wherein the angiogenic disease is selected from among cancer, macular degeneration, inflammation, and diabetes.

140. The method of claim 139, further comprising administering another anti-tumor agent.

141. A method of treatment, comprising treating a subject by administering a pharmaceutical composition of claim 126, wherein the subject has a disease or condition that is mediated by complement protein C2.

142. The method of claim 141, wherein the disease or condition selected from among autoimmune diseases, sepsis, Rheumatoid arthritis (RA), membranoproliferative glomerulonephritis (MPGN), Multiple Sclerosis (MS),

Myasthenia gravis (MG), asthma, inflammatory bowel disease, immune complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), Ischemia-reperfusion injury, macular degeneration, rejectin of a transplanted organ and Guillan-Barre syndrome.

143. The method claim 142, wherein the ischemia-reperfusion injury is caused by an event or treatment selected from among myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis.

144. The method of claims 141, wherein the disease or condition results from a treatment of a subject.

145. The method of claim 144, wherein administering a modified MT-SP1 is effected prior to treatment of a subject.

146. The method of claim 141, wherein administering a modified MT-SP1 is effected by contacting a body fluid or tissue sample *in vitro*, *ex vivo*, or *in vivo* with a modified MT-SP1.

147. The method of claim 144, wherein the treatment results in complement-mediated ischemia-reperfusion injury.

148. The method of claim 147, wherein the treatment is angioplasty or coronary artery bypass graft.

149. Use of a pharmaceutical composition of claim 124 for treatment of a disease or condition that is treated by administration of t-PA.

150. Use of a pharmaceutical composition of claim 124 in the preparation of a medicament treatment of a disease or condition that is treated by t-PA.

151. The use of claim 149 or claim 150, wherein the disease or condition is selected from among arterial thrombosis, venous thrombosis and thromboembolism, ischemic stroke, acquired coagulation disorders, disseminated intravascular coagulation, bacterial infection and periodontitis, and neurological conditions.

152. The use of claim 149 or claim 150, wherein the disease or condition is thrombosis that obstructs a catheter.

153. Use of a pharmaceutical composition of claim 125 for treatment of a disease or condition that is mediated by VEGFR-2.

154. Use of a pharmaceutical composition of claim 125 in the preparation of a medicament for treatment of a disease or condition that is mediated by VEGFR-2.

155. The use of claim 153 or claim 154, wherein the disease or condition to be treated is an angiogenic disease.

156. The use of claim 155, wherein the angiogenic disease is selected from among cancer, macular degeneration, inflammation, and diabetes.

157. The use of any of claims 153-156, further comprising administering another anti-tumor agent.

158. Use of a pharmaceutical composition of claim 126 for treatment of a disease or condition that is mediated by complement protein C2.

159. Use of a pharmaceutical composition of claim 126 for formulating a medicament for treatment of a disease of condition that is mediated by complement protein C2.

160. The use of claim 158 or 159, wherein the disease or condition selected from among autoimmune diseases, sepsis, Rheumatoid arthritis (RA), membranoproliferative glomerulonephritis (MPGN), Multiple Sclerosis (MS), Myasthenia gravis (MG), asthma, inflammatory bowel disease, immune complex (IC)-mediated acute inflammatory tissue injury, Alzheimer's Disease (AD), Ischemia-reperfusion injury, rejection of a transplanted organ, macular degeneration,and Guillan-Barre syndrome.

161. The use of claim 160, wherein the ischemia-reperfusion injury is caused by an event or treatment selected from among myocardial infarct (MI), stroke, angioplasty, coronary artery bypass graft, cardiopulmonary bypass (CPB), and hemodialysis.

162. A modified serpin polypeptide, comprising modifications in its reactive site loop corresponding to any or more of position P4-P2' with a cleavage sequence for a target substrate.

163. The modified serpin polypeptide of claim 162, wherein the target substrate is involved in the etiology of a disease or disorder.

164. The modified serpin polypeptide of claim 162 or 163, wherein the target substrate is selected from among a VEGFR, a complement protein or a t-PA substrate.

165. The modified serpin polypepide of claim 164, wherein the target substrate is a VEGFR2.

166. The modified serpin polypeptide of claim 164, wherein the complement protein is C2.

167. The modified serpin polypeptide of any of claims 162-166, wherein the serpin is plasminogen-activator inhibito-1 (PAI-1) or antithrombin-3 (AT3).

168. The modified serpin polypeptide of any of claims 162-167 having a sequence of amino acids set forth in any of SEQ ID NOS: 497, 499, 610 and 611.

169. The method of any of claims 1-40, wherein the protease is human kallikrein 8.

170. A method, comprising:

a) contacting a collection of proteases and/or catalytically active portions of proteases with a protease trap polypeptide to form, upon cleavage of the protease trap polypeptide by the protease or catalytically active portion thereof, stable complexes containing the protease trap polypeptide with a protease or catalytically active portion thereof in the collection; and

b) identifying or selecting a protease or catalytically active portion thereof in a complex, wherein the collection contains 2 different members.

SEQUENCE LISTING

<110> Catalyst Biosciences, Inc;
Torrey Pines Institute for Molecular Studies;
Madison, Edwin

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Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
        35                  40                  45
Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln
    50                  55                  60
Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
65                  70                  75                  80
Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr
                85                  90                  95
His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro
            100                 105                 110
Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn
        115                 120                 125
Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu
    130                 135                 140
Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys
145                 150                 155                 160
Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu
                165                 170                 175
Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys
            180                 185                 190
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        195                 200                 205
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    210                 215                 220
Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val
225                 230                 235                 240
Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys
                245                 250                 255
Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala
            260                 265                 270
Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu
        275                 280                 285
Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp
    290                 295                 300
Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr
305                 310                 315                 320
Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe
                325                 330                 335
Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys
            340                 345                 350
Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly
        355                 360                 365
Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met Ser Ile
    370                 375                 380
Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu
385                 390                 395                 400
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            20                  25                  30
Gln Lys Thr Asp Thr Ser His His Asp Gln Gly Asp Trp Glu Asp Leu
        35                  40                  45
Ala Cys Gln Lys Ile Ser Tyr Asn Val Thr Asp Leu Ala Phe Asp Leu
    50                  55                  60
Tyr Lys Ser Trp Leu Ile Tyr His Asn Gln His Val Leu Val Thr Pro
65                  70                  75                  80
Thr Ser Val Ala Met Ala Phe Arg Met Leu Ser Leu Gly Thr Lys Ala
                85                  90                  95
Asp Thr Arg Thr Glu Ile Leu Glu Gly Leu Asn Val Asn Leu Thr Glu
            100                 105                 110
Thr Pro Glu Ala Lys Ile His Glu Cys Phe Gln Gln Val Leu Gln Ala
        115                 120                 125
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Leu Ser Arg Pro Asp Thr Arg Leu Gln Leu Thr Thr Gly Ser Ser Leu
    130                 135                 140
Phe Val Asn Lys Ser Met Lys Leu Val Asp Thr Phe Leu Glu Asp Thr
145                 150                 155                 160
Lys Lys Leu Tyr His Ser Glu Ala Ser Ser Ile Asn Phe Arg Asp Thr
                165                 170                 175
Glu Glu Ala Lys Glu Gln Ile Asn Asn Tyr Val Glu Lys Arg Thr Gly
            180                 185                 190
Arg Lys Val Val Asp Leu Val Lys His Leu Lys Lys Asp Thr Ser Leu
        195                 200                 205
Ala Leu Val Asp Tyr Ile Ser Phe His Gly Lys Trp Lys Asp Lys Phe
    210                 215                 220
Lys Ala Glu Arg Ile Met Val Glu Gly Phe His Val Asp Asp Lys Thr
225                 230                 235                 240
Ile Ile Arg Val Pro Met Ile Asn His Leu Gly Arg Phe Asp Ile His
                245                 250                 255
Arg Asp Arg Glu Leu Ser Ser Trp Val Leu Ala Gln His Tyr Val Gly
            260                 265                 270
Asn Ala Thr Ala Phe Phe Ile Leu Pro Asp Pro Lys Lys Met Trp Gln
        275                 280                 285
Leu Glu Glu Lys Leu Thr Tyr Ser His Leu Glu Asn Ile Gln Arg Ala
    290                 295                 300
Phe Asp Ile Arg Ser Ile Asn Leu His Phe Pro Lys Leu Ser Ile Ser
305                 310                 315                 320
Gly Thr Tyr Lys Leu Lys Arg Val Pro Arg Asn Leu Gly Ile Thr Lys
                325                 330                 335
Ile Phe Ser Asn Glu Ala Asp Leu Ser Gly Val Ser Gln Glu Ala Pro
            340                 345                 350
Leu Lys Leu Ser Lys Ala Val His Val Ala Val Leu Thr Ile Asp Glu
        355                 360                 365
Lys Gly Thr Glu Ala Thr Gly Ala Pro His Leu Glu Glu Lys Ala Trp
    370                 375                 380
Ser Lys Tyr Gln Thr Val Met Phe Asn Arg Pro Phe Leu Val Ile Ile
385                 390                 395                 400
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            20                  25                  30
Arg Gln Leu Thr Ser Gly Pro Asn Gln Glu Gln Val Ser Pro Leu Thr
        35                  40                  45
Leu Leu Lys Leu Gly Asn Gln Glu Pro Gly Gly Gln Thr Ala Leu Lys
    50                  55                  60
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65                  70                  75                  80
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                85                  90                  95
Val Ala Gln Thr Ser Thr Cys Pro Asn Leu Ile Leu Ser Pro Leu Ser
            100                 105                 110
Val Ala Leu Ala Leu Ser His Leu Ala Leu Gly Ala Gln Asn His Thr
        115                 120                 125
Leu Gln Arg Leu Gln Gln Val Leu His Ala Gly Ser Gly Pro Cys Leu
    130                 135                 140
Pro His Leu Leu Ser Arg Leu Cys Gln Asp Leu Gly Pro Gly Ala Phe
145                 150                 155                 160
Arg Leu Ala Ala Arg Met Tyr Leu Gln Lys Gly Phe Pro Ile Lys Glu
                165                 170                 175
Asp Phe Leu Glu Gln Ser Glu Gln Leu Phe Gly Ala Lys Pro Val Ser
            180                 185                 190
Leu Thr Gly Lys Gln Glu Asp Asp Leu Ala Asn Ile Asn Gln Trp Val
        195                 200                 205
Lys Glu Ala Thr Glu Gly Lys Ile Gln Glu Phe Leu Ser Gly Leu Pro
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225                 230                 235                 240
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                245                 250                 255
Leu Asp Glu Gln Phe Thr Val Pro Val Glu Met Met Gln Ala Arg Thr
            260                 265                 270
Tyr Pro Leu Arg Trp Phe Leu Leu Glu Gln Pro Glu Ile Gln Val Ala
        275                 280                 285
His Phe Pro Phe Lys Asn Asn Met Ser Phe Val Val Leu Val Pro Thr
    290                 295                 300
His Phe Glu Trp Asn Val Ser Gln Val Leu Ala Asn Leu Ser Trp Asp
305                 310                 315                 320
Thr Leu His Pro Pro Leu Val Trp Glu Arg Pro Thr Lys Val Arg Leu
                325                 330                 335
Pro Lys Leu Tyr Leu Lys His Gln Met Asp Leu Val Ala Thr Leu Ser
            340                 345                 350
Gln Leu Gly Leu Gln Glu Leu Phe Gln Ala Pro Asp Leu Arg Gly Ile
        355                 360                 365
Ser Glu Gln Ser Leu Val Val Ser Gly Val Gln His Gln Ser Thr Leu
    370                 375                 380
Glu Leu Ser Glu Val Gly Val Glu Ala Ala Ala Ala Thr Ser Ile Ala
385                 390                 395                 400
Met Ser Arg Met Ser Leu Ser Ser Phe Ser Val Asn Arg Pro Phe Leu
                405                 410                 415
Phe Phe Ile Phe Glu Asp Thr Thr Gly Leu Pro Leu Phe Val Gly Ser
            420                 425                 430
Val Arg Asn Pro Asn Pro Ser Ala Pro Arg Glu Leu Lys Glu Gln Gln
        435                 440                 445
Asp Ser Pro Gly Asn Lys Asp Phe Leu Gln Ser Leu Lys Gly Phe Pro
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Asn Leu Thr Gln Glu Asn Gln Asp Arg Gly Thr His Val Asp Leu Gly
        35                  40                  45
Leu Ala Ser Ala Asn Val Asp Phe Ala Phe Ser Leu Tyr Lys Gln Leu
    50                  55                  60
Val Leu Lys Ala Pro Asp Lys Asn Val Ile Phe Ser Pro Leu Ser Ile
65                  70                  75                  80
Ser Thr Ala Leu Ala Phe Leu Ser Leu Gly Ala His Asn Thr Thr Leu
                85                  90                  95
Thr Glu Ile Leu Lys Gly Leu Lys Phe Asn Leu Thr Glu Thr Ser Glu
            100                 105                 110
Ala Glu Ile His Gln Ser Phe Gln His Leu Leu Arg Thr Leu Asn Gln
        115                 120                 125
Ser Ser Asp Glu Leu Gln Leu Ser Met Gly Asn Ala Met Phe Val Lys
    130                 135                 140
Glu Gln Leu Ser Leu Leu Asp Arg Phe Thr Glu Asp Ala Lys Arg Leu
145                 150                 155                 160
Tyr Gly Ser Glu Ala Phe Ala Thr Asp Phe Gln Asp Ser Ala Ala Ala
                165                 170                 175
Lys Lys Leu Ile Asn Asp Tyr Val Lys Asn Gly Thr Arg Gly Lys Ile
            180                 185                 190
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        195                 200                 205
Asn Tyr Ile Phe Phe Lys Ala Lys Trp Glu Met Pro Phe Asp Pro Gln
    210                 215                 220
Asp Thr His Gln Ser Arg Phe Tyr Leu Ser Lys Lys Lys Trp Val Met
225                 230                 235                 240
Val Pro Met Met Ser Leu His His Leu Thr Ile Pro Tyr Phe Arg Asp
                245                 250                 255
Glu Glu Leu Ser Cys Thr Val Val Glu Leu Lys Tyr Thr Gly Asn Ala
            260                 265                 270
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        275                 280                 285
Ala Met Leu Leu Pro Glu Thr Leu Lys Arg Trp Arg Asp Ser Leu Glu
    290                 295                 300
Phe Arg Glu Ile Gly Glu Leu Tyr Leu Pro Lys Phe Ser Ile Ser Arg
305                 310                 315                 320
Asp Tyr Asn Leu Asn Asp Ile Leu Leu Gln Leu Gly Ile Glu Glu Ala
                325                 330                 335
Phe Thr Ser Lys Ala Asp Leu Ser Gly Ile Thr Gly Ala Arg Asn Leu
            340                 345                 350
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        355                 360                 365
Gly Thr Glu Ala Ser Ala Ala Thr Ala Val Lys Ile Thr Leu Leu Ser
    370                 375                 380
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His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
        35                  40                  45
Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
    50                  55                  60
Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
65                  70                  75                  80
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
                85                  90                  95
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
            100                 105                 110
Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
        115                 120                 125
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
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Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys
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Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn
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Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp
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Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys
        195                 200                 205
Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn
    210                 215                 220
Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn
225                 230                 235                 240
Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu
                245                 250                 255
Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr
            260                 265                 270
Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
        275                 280                 285
Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
    290                 295                 300
Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
305                 310                 315                 320
```

```
Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
                325                 330                 335
Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
            340                 345                 350
Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
        355                 360                 365
Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
    370                 375                 380
Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385                 390                 395                 400
His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
                405                 410                 415
Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val
            420                 425                 430
Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
        435                 440                 445
Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
    450                 455                 460


<210> 6
<211> 499
<212> PRT
<213> Homo sapiens

<220>
<223> Heparin cofactor 2 precursor   SERPIND1

<400> 6
Met Lys His Ser Leu Asn Ala Leu Leu Ile Phe Leu Ile Ile Thr Ser
 1               5                  10                  15
Ala Trp Gly Gly Ser Lys Gly Pro Leu Asp Gln Leu Glu Lys Gly Gly
            20                  25                  30
Glu Thr Ala Gln Ser Ala Asp Pro Gln Trp Glu Gln Leu Asn Asn Lys
        35                  40                  45
Asn Leu Ser Met Pro Leu Leu Pro Ala Asp Phe His Lys Glu Asn Thr
    50                  55                  60
Val Thr Asn Asp Trp Ile Pro Glu Gly Glu Glu Asp Asp Asp Tyr Leu
65                  70                  75                  80
Asp Leu Glu Lys Ile Phe Ser Glu Asp Asp Asp Tyr Ile Asp Ile Val
                85                  90                  95
Asp Ser Leu Ser Val Ser Pro Thr Asp Ser Asp Val Ser Ala Gly Asn
            100                 105                 110
Ile Leu Gln Leu Phe His Gly Lys Ser Arg Ile Gln Arg Leu Asn Ile
        115                 120                 125
Leu Asn Ala Lys Phe Ala Phe Asn Leu Tyr Arg Val Leu Lys Asp Gln
    130                 135                 140
Val Asn Thr Phe Asp Asn Ile Phe Ile Ala Pro Val Gly Ile Ser Thr
145                 150                 155                 160
Ala Met Gly Met Ile Ser Leu Gly Leu Lys Gly Glu Thr His Glu Gln
                165                 170                 175
Val His Ser Ile Leu His Phe Lys Asp Phe Val Asn Ala Ser Ser Lys
            180                 185                 190
Tyr Glu Ile Thr Thr Ile His Asn Leu Phe Arg Lys Leu Thr His Arg
        195                 200                 205
Leu Phe Arg Arg Asn Phe Gly Tyr Thr Leu Arg Ser Val Asn Asp Leu
    210                 215                 220
```

```
Tyr Ile Gln Lys Gln Phe Pro Ile Leu Leu Asp Phe Lys Thr Lys Val
225                 230                 235                 240
Arg Glu Tyr Tyr Phe Ala Glu Ala Gln Ile Ala Asp Phe Ser Asp Pro
                245                 250                 255
Ala Phe Ile Ser Lys Thr Asn Asn His Ile Met Lys Leu Thr Lys Gly
            260                 265                 270
Leu Ile Lys Asp Ala Leu Glu Asn Ile Asp Pro Ala Thr Gln Met Met
        275                 280                 285
Ile Leu Asn Cys Ile Tyr Phe Lys Gly Ser Trp Val Asn Lys Phe Pro
    290                 295                 300
Val Glu Met Thr His Asn His Asn Phe Arg Leu Asn Glu Arg Glu Val
305                 310                 315                 320
Val Lys Val Ser Met Met Gln Thr Lys Gly Asn Phe Leu Ala Ala Asn
                325                 330                 335
Asp Gln Glu Leu Asp Cys Asp Ile Leu Gln Leu Glu Tyr Val Gly Gly
            340                 345                 350
Ile Ser Met Leu Ile Val Val Pro His Lys Met Ser Gly Met Lys Thr
        355                 360                 365
Leu Glu Ala Gln Leu Thr Pro Arg Val Val Glu Arg Trp Gln Lys Ser
    370                 375                 380
Met Thr Asn Arg Thr Arg Glu Val Leu Leu Pro Lys Phe Lys Leu Glu
385                 390                 395                 400
Lys Asn Tyr Asn Leu Val Glu Ser Leu Lys Leu Met Gly Ile Arg Met
                405                 410                 415
Leu Phe Asp Lys Asn Gly Asn Met Ala Gly Ile Ser Asp Gln Arg Ile
            420                 425                 430
Ala Ile Asp Leu Phe Lys His Gln Gly Thr Ile Thr Val Asn Glu Glu
        435                 440                 445
Gly Thr Gln Ala Thr Thr Val Thr Thr Val Gly Phe Met Pro Leu Ser
    450                 455                 460
Thr Gln Val Arg Phe Thr Val Asp Arg Pro Phe Leu Phe Leu Ile Tyr
465                 470                 475                 480
Glu His Arg Thr Ser Cys Leu Leu Phe Met Gly Arg Val Ala Asn Pro
                485                 490                 495
Ser Arg Ser
```

<210> 7
<211> 500
<212> PRT
<213> Homo sapiens

<220>
<223> Plasma protease C1 inhibitor precursor SERPING1

```
<400> 7
Met Ala Ser Arg Leu Thr Leu Leu Thr Leu Leu Leu Leu Leu Leu Ala
 1               5                  10                  15
Gly Asp Arg Ala Ser Ser Asn Pro Asn Ala Thr Ser Ser Ser Ser Gln
            20                  25                  30
Asp Pro Glu Ser Leu Gln Asp Arg Gly Glu Gly Lys Val Ala Thr Thr
        35                  40                  45
Val Ile Ser Lys Met Leu Phe Val Glu Pro Ile Leu Glu Val Ser Ser
    50                  55                  60
Leu Pro Thr Thr Asn Ser Thr Thr Asn Ser Ala Thr Lys Ile Thr Ala
65                  70                  75                  80
```

```
Asn Thr Thr Asp Glu Pro Thr Thr Gln Pro Thr Thr Glu Pro Thr Thr
                85                  90                  95
Gln Pro Thr Ile Gln Pro Thr Gln Pro Thr Thr Gln Leu Pro Thr Asp
            100                 105                 110
Ser Pro Thr Gln Pro Thr Thr Gly Ser Phe Cys Pro Gly Pro Val Thr
        115                 120                 125
Leu Cys Ser Asp Leu Glu Ser His Ser Thr Glu Ala Val Leu Gly Asp
    130                 135                 140
Ala Leu Val Asp Phe Ser Leu Lys Leu Tyr His Ala Phe Ser Ala Met
145                 150                 155                 160
Lys Lys Val Glu Thr Asn Met Ala Phe Ser Pro Phe Ser Ile Ala Ser
                165                 170                 175
Leu Leu Thr Gln Val Leu Leu Gly Ala Gly Glu Asn Thr Lys Thr Asn
            180                 185                 190
Leu Glu Ser Ile Leu Ser Tyr Pro Lys Asp Phe Thr Cys Val His Gln
        195                 200                 205
Ala Leu Lys Gly Phe Thr Thr Lys Gly Val Thr Ser Val Ser Gln Ile
    210                 215                 220
Phe His Ser Pro Asp Leu Ala Ile Arg Asp Thr Phe Val Asn Ala Ser
225                 230                 235                 240
Arg Thr Leu Tyr Ser Ser Ser Pro Arg Val Leu Ser Asn Asn Ser Asp
                245                 250                 255
Ala Asn Leu Glu Leu Ile Asn Thr Trp Val Ala Lys Asn Thr Asn Asn
            260                 265                 270
Lys Ile Ser Arg Leu Leu Asp Ser Leu Pro Ser Asp Thr Arg Leu Val
        275                 280                 285
Leu Leu Asn Ala Ile Tyr Leu Ser Ala Lys Trp Lys Thr Thr Phe Asp
    290                 295                 300
Pro Lys Lys Thr Arg Met Glu Pro Phe His Phe Lys Asn Ser Val Ile
305                 310                 315                 320
Lys Val Pro Met Met Asn Ser Lys Lys Tyr Pro Val Ala His Phe Ile
                325                 330                 335
Asp Gln Thr Leu Lys Ala Lys Val Gly Gln Leu Gln Leu Ser His Asn
            340                 345                 350
Leu Ser Leu Val Ile Leu Val Pro Gln Asn Leu Lys His Arg Leu Glu
        355                 360                 365
Asp Met Glu Gln Ala Leu Ser Pro Ser Val Phe Lys Ala Ile Met Glu
    370                 375                 380
Lys Leu Glu Met Ser Lys Phe Gln Pro Thr Leu Leu Thr Leu Pro Arg
385                 390                 395                 400
Ile Lys Val Thr Thr Ser Gln Asp Met Leu Ser Ile Met Glu Lys Leu
                405                 410                 415
Glu Phe Phe Asp Phe Ser Tyr Asp Leu Asn Leu Cys Gly Leu Thr Glu
            420                 425                 430
Asp Pro Asp Leu Gln Val Ser Ala Met Gln His Gln Thr Val Leu Glu
        435                 440                 445
Leu Thr Glu Thr Gly Val Glu Ala Ala Ala Ala Ser Ala Ile Ser Val
    450                 455                 460
Ala Arg Thr Leu Leu Val Phe Glu Val Gln Gln Pro Phe Leu Phe Val
465                 470                 475                 480
Leu Trp Asp Gln Gln His Lys Phe Pro Val Phe Met Gly Arg Val Tyr
                485                 490                 495
Asp Pro Arg Ala
            500
```

<210> 8

<211> 406
<212> PRT
<213> Homo sapiens

<220>
<223> Plasma serine protease inhibitor precursor
SERPINA5

<400> 8

```
Met Gln Leu Phe Leu Leu Leu Cys Leu Val Leu Leu Ser Pro Gln Gly
 1               5                  10                  15

Ala Ser Leu His Arg His His Pro Arg Glu Met Lys Lys Arg Val Glu
            20                  25                  30
Asp Leu His Val Gly Ala Thr Val Ala Pro Ser Ser Arg Arg Asp Phe
        35                  40                  45
Thr Phe Asp Leu Tyr Arg Ala Leu Ala Ser Ala Ala Pro Ser Gln Asn
    50                  55                  60
Ile Phe Phe Ser Pro Val Ser Ile Ser Met Ser Leu Ala Met Leu Ser
65                  70                  75                  80
Leu Gly Ala Gly Ser Ser Thr Lys Met Gln Ile Leu Glu Gly Leu Gly
                85                  90                  95
Leu Asn Leu Gln Lys Ser Ser Glu Lys Glu Leu His Arg Gly Phe Gln
            100                 105                 110
Gln Leu Leu Gln Glu Leu Asn Gln Pro Arg Asp Gly Phe Gln Leu Ser
        115                 120                 125
Leu Gly Asn Ala Leu Phe Thr Asp Leu Val Val Asp Leu Gln Asp Thr
    130                 135                 140
Phe Val Ser Ala Met Lys Thr Leu Tyr Leu Ala Asp Thr Phe Pro Thr
145                 150                 155                 160
Asn Phe Arg Asp Ser Ala Gly Ala Met Lys Gln Ile Asn Asp Tyr Val
                165                 170                 175
Ala Lys Gln Thr Lys Gly Lys Ile Val Asp Leu Leu Lys Asn Leu Asp
            180                 185                 190
Ser Asn Ala Val Val Ile Met Val Asn Tyr Ile Phe Phe Lys Ala Lys
        195                 200                 205
Trp Glu Thr Ser Phe Asn His Lys Gly Thr Gln Glu Gln Asp Phe Tyr
    210                 215                 220
Val Thr Ser Glu Thr Val Val Arg Val Pro Met Met Ser Arg Glu Asp
225                 230                 235                 240
Gln Tyr His Tyr Leu Leu Asp Arg Asn Leu Ser Cys Arg Val Val Gly
                245                 250                 255
Val Pro Tyr Gln Gly Asn Ala Thr Ala Leu Phe Ile Leu Pro Ser Glu
            260                 265                 270
Gly Lys Met Gln Gln Val Glu Asn Gly Leu Ser Glu Lys Thr Leu Arg
        275                 280                 285
Lys Trp Leu Lys Met Phe Lys Lys Arg Gln Leu Glu Leu Tyr Leu Pro
    290                 295                 300
Lys Phe Ser Ile Glu Gly Ser Tyr Gln Leu Glu Lys Val Leu Pro Ser
305                 310                 315                 320
Leu Gly Ile Ser Asn Val Phe Thr Ser His Ala Asp Leu Ser Gly Ile
                325                 330                 335
Ser Asn His Ser Asn Ile Gln Val Ser Glu Met Val His Lys Ala Val
            340                 345                 350
Val Glu Val Asp Glu Ser Gly Thr Arg Ala Ala Ala Ala Thr Gly Thr

        355                 360                 365
```

```
Ile Phe Thr Phe Arg Ser Ala Arg Leu Asn Ser Gln Arg Leu Val Phe
    370                 375                 380
Asn Arg Pro Phe Leu Met Phe Ile Val Asp Asn Asn Ile Leu Phe Leu
385                 390                 395                 400
Gly Lys Val Asn Arg Pro
                405
```

<210> 9
<211> 427
<212> PRT
<213> Homo sapiens

<220>
<223> Kallistatin precursor SERPINA4

<400> 9

```
Met His Leu Ile Asp Tyr Leu Leu Leu Leu Leu Val Gly Leu Leu Ala
 1               5                  10                  15
Leu Ser His Gly Gln Leu His Val Glu His Asp Gly Glu Ser Cys Ser
            20                  25                  30
Asn Ser Ser His Gln Gln Ile Leu Glu Thr Gly Glu Gly Ser Pro Ser
        35                  40                  45
Leu Lys Ile Ala Pro Ala Asn Ala Asp Phe Ala Phe Arg Phe Tyr Tyr
    50                  55                  60
Leu Ile Ala Ser Glu Thr Pro Gly Lys Asn Ile Phe Phe Ser Pro Leu
65                  70                  75                  80
Ser Ile Ser Ala Ala Tyr Ala Met Leu Ser Leu Gly Ala Cys Ser His
                85                  90                  95
Ser Arg Ser Gln Ile Leu Glu Gly Leu Gly Phe Asn Leu Thr Glu Leu
            100                 105                 110
Ser Glu Ser Asp Val His Arg Gly Phe Gln His Leu Leu His Thr Leu
        115                 120                 125
Asn Leu Pro Gly His Gly Leu Glu Thr Arg Val Gly Ser Ala Leu Phe
    130                 135                 140
Leu Ser His Asn Leu Lys Phe Leu Ala Lys Phe Leu Asn Asp Thr Met
145                 150                 155                 160
Ala Val Tyr Glu Ala Lys Leu Phe His Thr Asn Phe Tyr Asp Thr Val
                165                 170                 175
Gly Thr Ile Gln Leu Ile Asn Asp His Val Lys Lys Glu Thr Arg Gly
            180                 185                 190
Lys Ile Val Asp Leu Val Ser Glu Leu Lys Lys Asp Val Leu Met Val
        195                 200                 205
Leu Val Asn Tyr Ile Tyr Phe Lys Ala Leu Trp Glu Lys Pro Phe Ile
    210                 215                 220
Ser Ser Arg Thr Thr Pro Lys Asp Phe Tyr Val Asp Glu Asn Thr Thr
225                 230                 235                 240
Val Arg Val Pro Met Met Leu Gln Asp Gln Glu His His Trp Tyr Leu
                245                 250                 255
His Asp Arg Tyr Leu Pro Cys Ser Val Leu Arg Met Asp Tyr Lys Gly
            260                 265                 270
Asp Ala Thr Val Phe Phe Ile Leu Pro Asn Gln Gly Lys Met Arg Glu
        275                 280                 285
Ile Glu Glu Val Leu Thr Pro Glu Met Leu Met Arg Trp Asn Asn Leu
    290                 295                 300
Leu Arg Lys Arg Asn Phe Tyr Lys Lys Leu Glu Leu His Leu Pro Lys
305                 310                 315                 320
```

```
Phe Ser Ile Ser Gly Ser Tyr Val Leu Asp Gln Ile Leu Pro Arg Leu
                  325                 330                 335
Gly Phe Thr Asp Leu Phe Ser Lys Trp Ala Asp Leu Ser Gly Ile Thr
             340                 345                 350
Lys Gln Gln Lys Leu Glu Ala Ser Lys Ser Phe His Lys Ala Thr Leu
         355                 360                 365
Asp Val Asp Glu Ala Gly Thr Glu Ala Ala Ala Ala Thr Ser Phe Ala
     370                 375                 380
Ile Lys Phe Phe Ser Ala Gln Thr Asn Arg His Ile Leu Arg Phe Asn
385                 390                 395                 400
Arg Pro Phe Leu Val Val Ile Phe Ser Thr Ser Thr Gln Ser Val Leu
                  405                 410                 415
Phe Leu Gly Lys Val Val Asp Pro Thr Lys Pro
             420                 425


<210> 10
<211> 410
<212> PRT
<213> Homo sapiens

<220>
<223> Neuroserpin precursor   SERPINII

<400> 10
Met Ala Phe Leu Gly Leu Phe Ser Leu Leu Val Leu Gln Ser Met Ala
 1               5                  10                  15
Thr Gly Ala Thr Phe Pro Glu Glu Ala Ile Ala Asp Leu Ser Val Asn
            20                  25                  30
Met Tyr Asn Arg Leu Arg Ala Thr Gly Glu Asp Glu Asn Ile Leu Phe
        35                  40                  45
Ser Pro Leu Ser Ile Ala Leu Ala Met Gly Met Met Glu Leu Gly Ala
    50                  55                  60
Gln Gly Ser Thr Gln Lys Glu Ile Arg His Ser Met Gly Tyr Asp Ser
65                  70                  75                  80
Leu Lys Asn Gly Glu Glu Phe Ser Phe Leu Lys Glu Phe Ser Asn Met
                85                  90                  95
Val Thr Ala Lys Glu Ser Gln Tyr Val Met Lys Ile Ala Asn Ser Leu
            100                 105                 110
Phe Val Gln Asn Gly Phe His Val Asn Glu Glu Phe Leu Gln Met Met
        115                 120                 125
Lys Lys Tyr Phe Asn Ala Ala Val Asn His Val Asp Phe Ser Gln Asn
    130                 135                 140
Val Ala Val Ala Asn Tyr Ile Asn Lys Trp Val Glu Asn Asn Thr Asn
145                 150                 155                 160
Asn Leu Val Lys Asp Leu Val Ser Pro Arg Asp Phe Asp Ala Ala Thr
                165                 170                 175
Tyr Leu Ala Leu Ile Asn Ala Val Tyr Phe Lys Gly Asn Trp Lys Ser
            180                 185                 190
Gln Phe Arg Pro Glu Asn Thr Arg Thr Phe Ser Phe Thr Lys Asp Asp
        195                 200                 205
Glu Ser Glu Val Gln Ile Pro Met Met Tyr Gln Gln Gly Glu Phe Tyr
    210                 215                 220
Tyr Gly Glu Phe Ser Asp Gly Ser Asn Glu Ala Gly Gly Ile Tyr Gln
225                 230                 235                 240
Val Leu Glu Ile Pro Tyr Glu Gly Asp Glu Ile Ser Met Met Leu Val
                245                 250                 255
```

```
Leu Ser Arg Gln Glu Val Pro Leu Ala Thr Leu Glu Pro Leu Val Lys
            260                 265                 270
Ala Gln Leu Val Glu Glu Trp Ala Asn Ser Val Lys Lys Gln Lys Val
        275                 280                 285
Glu Val Tyr Leu Pro Arg Phe Thr Val Glu Gln Glu Ile Asp Leu Lys
    290                 295                 300
Asp Val Leu Lys Ala Leu Gly Ile Thr Glu Ile Phe Ile Lys Asp Ala
305                 310                 315                 320
Asn Leu Thr Gly Leu Ser Asp Asn Lys Glu Ile Phe Leu Ser Lys Ala
                325                 330                 335
Ile His Lys Ser Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala
            340                 345                 350
Ala Val Ser Gly Met Ile Ala Ile Ser Arg Met Ala Val Leu Tyr Pro
        355                 360                 365
Gln Val Ile Val Asp His Pro Phe Phe Phe Leu Ile Arg Asn Arg Arg
    370                 375                 380
Thr Gly Thr Ile Leu Phe Met Gly Arg Val Met His Pro Glu Thr Met
385                 390                 395                 400
Asn Thr Ser Gly His Asp Phe Glu Glu Leu
                405                 410
```

<210> 11
<211> 402
<212> PRT
<213> Homo sapiens

<220>
<223> Plasminogen activator inhibitor 1 precursor
SERPINE1

<400> 11

```
Met Gln Met Ser Pro Ala Leu Thr Cys Leu Val Leu Gly Leu Ala Leu
 1               5                  10                  15
Val Phe Gly Glu Gly Ser Ala Val His His Pro Pro Ser Tyr Val Ala
            20                  25                  30
His Leu Ala Ser Asp Phe Gly Val Arg Val Phe Gln Gln Val Ala Gln
        35                  40                  45
Ala Ser Lys Asp Arg Asn Val Val Phe Ser Pro Tyr Gly Val Ala Ser
    50                  55                  60
Val Leu Ala Met Leu Gln Leu Thr Thr Gly Gly Glu Thr Gln Gln Gln
65                  70                  75                  80
Ile Gln Ala Ala Met Gly Phe Lys Ile Asp Asp Lys Gly Met Ala Pro
                85                  90                  95
Ala Leu Arg His Leu Tyr Lys Glu Leu Met Gly Pro Trp Asn Lys Asp
            100                 105                 110
Glu Ile Ser Thr Thr Asp Ala Ile Phe Val Gln Arg Asp Leu Lys Leu
        115                 120                 125
Val Gln Gly Phe Met Pro His Phe Phe Arg Leu Phe Arg Ser Thr Val
    130                 135                 140
Lys Gln Val Asp Phe Ser Glu Val Glu Arg Ala Arg Phe Ile Ile Asn
145                 150                 155                 160
Asp Trp Val Lys Thr His Thr Lys Gly Met Ile Ser Asn Leu Leu Gly
                165                 170                 175
Lys Gly Ala Val Asp Gln Leu Thr Arg Leu Val Leu Val Asn Ala Leu
            180                 185                 190
Tyr Phe Asn Gly Gln Trp Lys Thr Pro Phe Pro Asp Ser Ser Thr His
```

```
        195                 200                 205
Arg Arg Leu Phe His Lys Ser Asp Gly Ser Thr Val Ser Val Pro Met
    210                 215                 220
Met Ala Gln Thr Asn Lys Phe Asn Tyr Thr Glu Phe Thr Thr Pro Asp
225                 230                 235                 240
Gly His Tyr Tyr Asp Ile Leu Glu Leu Pro Tyr His Gly Asp Thr Leu
                245                 250                 255
Ser Met Phe Ile Ala Ala Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala
            260                 265                 270
Leu Thr Asn Ile Leu Ser Ala Gln Leu Ile Ser His Trp Lys Gly Asn
        275                 280                 285
Met Thr Arg Leu Pro Arg Leu Leu Val Leu Pro Lys Phe Ser Leu Glu
    290                 295                 300
Thr Glu Val Asp Leu Arg Lys Pro Leu Glu Asn Leu Gly Met Thr Asp
305                 310                 315                 320
Met Phe Arg Gln Phe Gln Ala Asp Phe Thr Ser Leu Ser Asp Gln Glu
                325                 330                 335
Pro Leu His Val Ala Gln Ala Leu Gln Lys Val Lys Ile Glu Val Asn
            340                 345                 350
Glu Ser Gly Thr Val Ala Ser Ser Ser Thr Ala Val Ile Val Ser Ala
        355                 360                 365
Arg Met Ala Pro Glu Glu Ile Ile Met Asp Arg Pro Phe Leu Phe Val
    370                 375                 380
Val Arg His Asn Pro Thr Gly Thr Val Leu Phe Met Gly Gln Val Met
385                 390                 395                 400
Glu Pro
```

<210> 12
<211> 405
<212> PRT
<213> Homo sapiens

<220>
<223> Myoepithelium-derived serine protease inhibitor
SERPIN12

<400> 12

```
Met Asp Thr Ile Phe Leu Trp Ser Leu Leu Leu Leu Phe Phe Gly Ser
 1               5                  10                  15
Gln Ala Ser Arg Cys Ser Ala Gln Lys Asn Thr Glu Phe Ala Val Asp
            20                  25                  30
Leu Tyr Gln Glu Val Ser Leu Ser His Lys Asp Asn Ile Ile Phe Ser
        35                  40                  45
Pro Leu Gly Ile Thr Leu Val Leu Glu Met Val Gln Leu Gly Ala Lys
    50                  55                  60
Gly Lys Ala Gln Gln Gln Ile Arg Gln Thr Leu Lys Gln Gln Glu Thr
65                  70                  75                  80
Ser Ala Gly Glu Glu Phe Phe Val Leu Lys Ser Phe Phe Ser Ala Ile
                85                  90                  95
Ser Glu Lys Lys Gln Glu Phe Thr Phe Asn Leu Ala Asn Ala Leu Tyr
            100                 105                 110
Leu Gln Glu Gly Phe Thr Val Lys Glu Gln Tyr Leu His Gly Asn Lys
        115                 120                 125
Glu Phe Phe Gln Ser Ala Ile Lys Leu Val Asp Phe Gln Asp Ala Lys
```

```
    130                 135                 140
Ala Cys Ala Glu Met Ile Ser Thr Trp Val Glu Arg Lys Thr Asp Gly
145                 150                 155                 160
Lys Ile Lys Asp Met Phe Ser Gly Glu Glu Phe Gly Pro Leu Thr Arg
                165                 170                 175
Leu Val Leu Val Asn Ala Ile Tyr Phe Lys Gly Asp Trp Lys Gln Lys
            180                 185                 190
Phe Arg Lys Glu Asp Thr Gln Leu Ile Asn Phe Thr Lys Lys Asn Gly
        195                 200                 205
Ser Thr Val Lys Ile Pro Met Met Lys Ala Leu Leu Arg Thr Lys Tyr
    210                 215                 220
Gly Tyr Phe Ser Glu Ser Ser Leu Asn Tyr Gln Val Leu Glu Leu Ser
225                 230                 235                 240
Tyr Lys Gly Asp Glu Phe Ser Leu Ile Ile Ile Leu Pro Ala Glu Gly
                245                 250                 255
Met Asp Ile Glu Glu Val Glu Lys Leu Ile Thr Ala Gln Gln Ile Leu
            260                 265                 270
Lys Trp Leu Ser Glu Met Gln Glu Glu Glu Val Glu Ile Ser Leu Pro
        275                 280                 285
Arg Phe Lys Val Glu Gln Lys Val Asp Phe Lys Asp Val Leu Tyr Ser
    290                 295                 300
Leu Asn Ile Thr Glu Ile Phe Ser Gly Gly Cys Asp Leu Ser Gly Ile
305                 310                 315                 320
Thr Asp Ser Ser Glu Val Tyr Val Ser Gln Val Thr Gln Lys Val Phe
                325                 330                 335
Phe Glu Ile Asn Glu Asp Gly Ser Glu Ala Ala Thr Ser Thr Gly Ile
            340                 345                 350
His Ile Pro Val Ile Met Ser Leu Ala Gln Ser Gln Phe Ile Ala Asn
        355                 360                 365
His Pro Phe Leu Phe Ile Met Lys His Asn Pro Thr Glu Ser Ile Leu
    370                 375                 380
Phe Met Gly Arg Val Thr Asn Pro Asp Thr Gln Glu Ile Lys Gly Arg
385                 390                 395                 400

Asp Leu Asp Ser Leu
                405


<210> 13
<211> 444
<212> PRT
<213> Homo sapiens

<220>
<223> Protein Z-dependent protease inhibitor precursor
      SERPINA10

<400> 13
Met Lys Val Val Pro Ser Leu Leu Leu Ser Val Leu Leu Ala Gln Val
 1               5                  10                  15
Trp Leu Val Pro Gly Leu Ala Pro Ser Pro Gln Ser Pro Glu Thr Pro
            20                  25                  30
Ala Pro Gln Asn Gln Thr Ser Arg Val Val Gln Ala Pro Lys Glu Glu
        35                  40                  45
Glu Glu Asp Glu Gln Glu Ala Ser Glu Glu Lys Ala Ser Glu Glu Glu
    50                  55                  60
Lys Ala Trp Leu Met Ala Ser Arg Gln Gln Leu Ala Lys Glu Thr Ser
```

```
65                  70                  75                  80
Asn Phe Gly Phe Ser Leu Leu Arg Lys Ile Ser Met Arg His Asp Gly
                85                  90                  95
Asn Met Val Phe Ser Pro Phe Gly Met Ser Leu Ala Met Thr Gly Leu
            100                 105                 110
Met Leu Gly Ala Thr Gly Pro Thr Glu Thr Gln Ile Lys Arg Gly Leu
        115                 120                 125
His Leu Gln Ala Leu Lys Pro Thr Lys Pro Gly Leu Leu Pro Ser Leu
    130                 135                 140
Phe Lys Gly Leu Arg Glu Thr Leu Ser Arg Asn Leu Glu Leu Gly Leu
145                 150                 155                 160
Thr Gln Gly Ser Phe Ala Phe Ile His Lys Asp Phe Asp Val Lys Glu
                165                 170                 175
Thr Phe Phe Asn Leu Ser Lys Arg Tyr Phe Asp Thr Glu Cys Val Pro
            180                 185                 190
Met Asn Phe Arg Asn Ala Ser Gln Ala Lys Arg Leu Met Asn His Tyr
        195                 200                 205
Ile Asn Lys Glu Thr Arg Gly Lys Ile Pro Lys Leu Phe Asp Glu Ile
    210                 215                 220
Asn Pro Glu Thr Lys Leu Ile Leu Val Asp Tyr Ile Leu Phe Lys Gly
225                 230                 235                 240
Lys Trp Leu Thr Pro Phe Asp Pro Val Phe Thr Glu Val Asp Thr Phe
                245                 250                 255
His Leu Asp Lys Tyr Lys Thr Ile Lys Val Pro Met Met Tyr Gly Ala
            260                 265                 270
Gly Lys Phe Ala Ser Thr Phe Asp Lys Asn Phe Arg Cys His Val Leu
        275                 280                 285
Lys Leu Pro Tyr Gln Gly Asn Ala Thr Met Leu Val Val Leu Met Glu
    290                 295                 300
Lys Met Gly Asp His Leu Ala Leu Glu Asp Tyr Leu Thr Thr Asp Leu
305                 310                 315                 320
Val Glu Thr Trp Leu Arg Asn Met Lys Thr Arg Asn Met Glu Val Phe
                325                 330                 335
Phe Pro Lys Phe Lys Leu Asp Gln Lys Tyr Glu Met His Glu Leu Leu
            340                 345                 350
Arg Gln Met Gly Ile Arg Arg Ile Phe Ser Pro Phe Ala Asp Leu Ser
        355                 360                 365
Glu Leu Ser Ala Thr Gly Arg Asn Leu Gln Val Ser Arg Val Leu Gln
    370                 375                 380
Arg Thr Val Ile Glu Val Asp Glu Arg Gly Thr Glu Ala Val Ala Gly
385                 390                 395                 400
Ile Leu Ser Glu Ile Thr Ala Tyr Ser Met Pro Pro Val Ile Lys Val
                405                 410                 415
Asp Arg Pro Phe His Phe Met Ile Tyr Glu Glu Thr Ser Gly Met Leu
            420                 425                 430
Leu Phe Leu Gly Arg Val Val Asn Pro Thr Leu Leu
        435                 440
```

<210> 14
<211> 398
<212> PRT
<213> Homo sapiens

<220>
<223> Glia-derived nexin precursor SERPINE2

<400> 14
Met Asn Trp His Leu Pro Leu Phe Leu Leu Ala Ser Val Thr Leu Pro
1 5 10 15
Ser Ile Cys Ser His Phe Asn Pro Leu Ser Leu Glu Glu Leu Gly Ser
20 25 30
Asn Thr Gly Ile Gln Val Phe Asn Gln Ile Val Lys Ser Arg Pro His
35 40 45
Asp Asn Ile Val Ile Ser Pro His Gly Ile Ala Ser Val Leu Gly Met
50 55 60
Leu Gln Leu Gly Ala Asp Gly Arg Thr Lys Lys Gln Leu Ala Met Val
65 70 75 80

Met Arg Tyr Gly Val Asn Gly Val Gly Lys Ile Leu Lys Lys Ile Asn
85 90 95
Lys Ala Ile Val Ser Lys Lys Asn Lys Asp Ile Val Thr Val Ala Asn
100 105 110
Ala Val Phe Val Lys Asn Ala Ser Glu Ile Glu Val Pro Phe Val Thr
115 120 125
Arg Asn Lys Asp Val Phe Gln Cys Glu Val Arg Asn Val Asn Phe Glu
130 135 140
Asp Pro Ala Ser Ala Cys Asp Ser Ile Asn Ala Trp Val Lys Asn Glu
145 150 155 160
Thr Arg Asp Met Ile Asp Asn Leu Leu Ser Pro Asp Leu Ile Asp Gly
165 170 175
Val Leu Thr Arg Leu Val Leu Val Asn Ala Val Tyr Phe Lys Gly Leu
180 185 190
Trp Lys Ser Arg Phe Gln Pro Glu Asn Thr Lys Lys Arg Thr Phe Val
195 200 205
Ala Ala Asp Gly Lys Ser Tyr Gln Val Pro Met Leu Ala Gln Leu Ser
210 215 220
Val Phe Arg Cys Gly Ser Thr Ser Ala Pro Asn Asp Leu Trp Tyr Asn
225 230 235 240
Phe Ile Glu Leu Pro Tyr His Gly Glu Ser Ile Ser Met Leu Ile Ala
245 250 255
Leu Pro Thr Glu Ser Ser Thr Pro Leu Ser Ala Ile Ile Pro His Ile
260 265 270
Ser Thr Lys Thr Ile Asp Ser Trp Met Ser Ile Met Val Pro Lys Arg
275 280 285
Val Gln Val Ile Leu Pro Lys Phe Thr Ala Val Ala Gln Thr Asp Leu
290 295 300
Lys Glu Pro Leu Lys Val Leu Gly Ile Thr Asp Met Phe Asp Ser Ser
305 310 315 320
Lys Ala Asn Phe Ala Lys Ile Thr Thr Gly Ser Glu Asn Leu His Val
325 330 335
Ser His Ile Leu Gln Lys Ala Lys Ile Glu Val Ser Glu Asp Gly Thr
340 345 350
Lys Ala Ser Ala Ala Thr Thr Ala Ile Leu Ile Ala Arg Ser Ser Pro
355 360 365
Pro Trp Phe Ile Val Asp Arg Pro Phe Leu Phe Phe Ile Arg His Asn
370 375 380
Pro Thr Gly Ala Val Leu Phe Met Gly Gln Ile Asn Lys Pro
385 390 395

<210> 15
<211> 379
<212> PRT

<213> Homo sapiens

<220>
<223> Leukocyte elastase inhibitor SERPINB1

<400> 15
Met Glu Gln Leu Ser Ser Ala Asn Thr Arg Phe Ala Leu Asp Leu Phe
1 5 10 15
Leu Ala Leu Ser Glu Asn Asn Pro Ala Gly Asn Ile Phe Ile Ser Pro
20 25 30
Phe Ser Ile Ser Ser Ala Met Ala Met Val Phe Leu Gly Thr Arg Gly
35 40 45
Asn Thr Ala Ala Gln Leu Ser Lys Thr Phe His Phe Asn Thr Val Glu
50 55 60
Glu Val His Ser Arg Phe Gln Ser Leu Asn Ala Asp Ile Asn Lys Arg
65 70 75 80
Gly Ala Ser Tyr Ile Leu Lys Leu Ala Asn Arg Leu Tyr Gly Glu Lys
85 90 95
Thr Tyr Asn Phe Leu Pro Glu Phe Leu Val Ser Thr Gln Lys Thr Tyr
100 105 110
Gly Ala Asp Leu Ala Ser Val Asp Phe Gln His Ala Ser Glu Asp Ala
115 120 125
Arg Lys Thr Ile Asn Gln Trp Val Lys Gly Gln Thr Glu Gly Lys Ile
130 135 140
Pro Glu Leu Leu Ala Ser Gly Met Val Asp Asn Met Thr Lys Leu Val
145 150 155 160
Leu Val Asn Ala Ile Tyr Phe Lys Gly Asn Trp Lys Asp Lys Phe Met
165 170 175
Lys Glu Ala Thr Thr Asn Ala Pro Phe Arg Leu Asn Lys Lys Asp Arg
180 185 190
Lys Thr Val Lys Met Met Tyr Gln Lys Lys Lys Phe Ala Tyr Gly Tyr
195 200 205
Ile Glu Asp Leu Lys Cys Arg Val Leu Glu Leu Pro Tyr Gln Gly Glu
210 215 220
Glu Leu Ser Met Val Ile Leu Leu Pro Asp Asp Ile Glu Asp Glu Ser
225 230 235 240
Thr Gly Leu Lys Lys Ile Glu Glu Gln Leu Thr Leu Glu Lys Leu His
245 250 255
Glu Trp Thr Lys Pro Glu Asn Leu Asp Phe Ile Glu Val Asn Val Ser
260 265 270
Leu Pro Arg Phe Lys Leu Glu Glu Ser Tyr Thr Leu Asn Ser Asp Leu
275 280 285
Ala Arg Leu Gly Val Gln Asp Leu Phe Asn Ser Ser Lys Ala Asp Leu
290 295 300
Ser Gly Met Ser Gly Ala Arg Asp Ile Phe Ile Ser Lys Ile Val His
305 310 315 320
Lys Ser Phe Val Glu Val Asn Glu Glu Gly Thr Glu Ala Ala Ala Ala
325 330 335
Thr Ala Gly Ile Ala Thr Phe Cys Met Leu Met Pro Glu Glu Asn Phe
340 345 350
Thr Ala Asp His Pro Phe Leu Phe Phe Ile Arg His Asn Ser Ser Gly
355 360 365
Ser Ile Leu Phe Leu Gly Arg Phe Ser Ser Pro
370 375

<210> 16

<211> 415
<212> PRT
<213> Homo sapiens

<220>
<223> Plasminogen activator inhibitor 2 precursor
SERPINB2

<400> 16
Met Glu Asp Leu Cys Val Ala Asn Thr Leu Phe Ala Leu Asn Leu Phe
1 5 10 15
Lys His Leu Ala Lys Ala Ser Pro Thr Gln Asn Leu Phe Leu Ser Pro
20 25 30
Trp Ser Ile Ser Ser Thr Met Ala Met Val Tyr Met Gly Ser Arg Gly
35 40 45
Ser Thr Glu Asp Gln Met Ala Lys Val Leu Gln Phe Asn Glu Val Gly
50 55 60
Ala Asn Ala Val Thr Pro Met Thr Pro Glu Asn Phe Thr Ser Cys Gly
65 70 75 80
Phe Met Gln Gln Ile Gln Lys Gly Ser Tyr Pro Asp Ala Ile Leu Gln
85 90 95
Ala Gln Ala Ala Asp Lys Ile His Ser Ser Phe Arg Ser Leu Ser Ser
100 105 110
Ala Ile Asn Ala Ser Thr Gly Asn Tyr Leu Leu Glu Ser Val Asn Lys
115 120 125
Leu Phe Gly Glu Lys Ser Ala Ser Phe Arg Glu Glu Tyr Ile Arg Leu
130 135 140
Cys Gln Lys Tyr Tyr Ser Ser Glu Pro Gln Ala Val Asp Phe Leu Glu
145 150 155 160
Cys Ala Glu Glu Ala Arg Lys Lys Ile Asn Ser Trp Val Lys Thr Gln
165 170 175
Thr Lys Gly Lys Ile Pro Asn Leu Leu Pro Glu Gly Ser Val Asp Gly
180 185 190
Asp Thr Arg Met Val Leu Val Asn Ala Val Tyr Phe Lys Gly Lys Trp
195 200 205

Lys Thr Pro Phe Glu Lys Lys Leu Asn Gly Leu Tyr Pro Phe Arg Val
210 215 220
Asn Ser Ala Gln Arg Thr Pro Val Gln Met Met Tyr Leu Arg Glu Lys
225 230 235 240
Leu Asn Ile Gly Tyr Ile Glu Asp Leu Lys Ala Gln Ile Leu Glu Leu
245 250 255
Pro Tyr Ala Gly Asp Val Ser Met Phe Leu Leu Leu Pro Asp Glu Ile
260 265 270
Ala Asp Val Ser Thr Gly Leu Glu Leu Leu Glu Ser Glu Ile Thr Tyr
275 280 285
Asp Lys Leu Asn Lys Trp Thr Ser Lys Asp Lys Met Ala Glu Asp Glu
290 295 300
Val Glu Val Tyr Ile Pro Gln Phe Lys Leu Glu Glu His Tyr Glu Leu
305 310 315 320
Arg Ser Ile Leu Arg Ser Met Gly Met Glu Asp Ala Phe Asn Lys Gly
325 330 335
Arg Ala Asn Phe Ser Gly Met Ser Glu Arg Asn Asp Leu Phe Leu Ser
340 345 350
Glu Val Phe His Gln Ala Met Val Asp Val Asn Glu Glu Gly Thr Glu
355 360 365
Ala Ala Ala Gly Thr Gly Gly Val Met Thr Gly Arg Thr Gly His Gly

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    370                 375                 380
Gly Pro Gln Phe Val Ala Asp His Pro Phe Leu Phe Leu Ile Met His
385                 390                 395                 400
Lys Ile Thr Asn Cys Ile Leu Phe Phe Gly Arg Phe Ser Ser Pro
                405                 410                 415


<210> 17
<211> 376
<212> PRT
<213> Homo sapiens

<220>
<223> Placental thrombin inhibitor   SERPINB6


<400> 17
Met Asp Val Leu Ala Glu Ala Asn Gly Thr Phe Ala Leu Asn Leu Leu
 1               5                  10                  15
Lys Thr Leu Gly Lys Asp Asn Ser Lys Asn Val Phe Phe Ser Pro Met
            20                  25                  30
Ser Met Ser Cys Ala Leu Ala Met Val Tyr Met Gly Ala Lys Gly Asn
        35                  40                  45
Thr Ala Ala Gln Met Ala Gln Ile Leu Ser Phe Asn Lys Ser Gly Gly
    50                  55                  60
Gly Gly Asp Ile His Gln Gly Phe Gln Ser Leu Leu Thr Glu Val Asn
65                  70                  75                  80
Lys Thr Gly Thr Gln Tyr Leu Leu Arg Val Ala Asn Arg Leu Phe Gly
                85                  90                  95
Glu Lys Ser Cys Asp Phe Leu Ser Ser Phe Arg Asp Ser Cys Gln Lys
            100                 105                 110
Phe Tyr Gln Ala Glu Met Glu Glu Leu Asp Phe Ile Ser Ala Val Glu
        115                 120                 125
Lys Ser Arg Lys His Ile Asn Thr Trp Val Ala Glu Lys Thr Glu Gly
    130                 135                 140
Lys Ile Ala Glu Leu Leu Ser Pro Gly Ser Val Asp Pro Leu Thr Arg
145                 150                 155                 160
Leu Val Leu Val Asn Ala Val Tyr Phe Arg Gly Asn Trp Asp Glu Gln
                165                 170                 175
Phe Asp Lys Glu Asn Thr Glu Glu Arg Leu Phe Lys Val Ser Lys Asn
            180                 185                 190
Glu Glu Lys Pro Val Gln Met Met Phe Lys Gln Ser Thr Phe Lys Lys
        195                 200                 205
Thr Tyr Ile Gly Glu Ile Phe Thr Gln Ile Leu Val Leu Pro Tyr Val
    210                 215                 220
Gly Lys Glu Leu Asn Met Ile Ile Met Leu Pro Asp Glu Thr Thr Asp
225                 230                 235                 240
Leu Arg Thr Val Glu Lys Glu Leu Thr Tyr Glu Lys Phe Val Glu Trp
                245                 250                 255
Thr Arg Leu Asp Met Met Asp Glu Glu Glu Val Glu Val Ser Leu Pro
            260                 265                 270
Arg Phe Lys Leu Glu Glu Ser Tyr Asp Met Glu Ser Val Leu Arg Asn
        275                 280                 285
Leu Gly Met Thr Asp Ala Phe Glu Leu Gly Lys Ala Asp Phe Ser Gly
    290                 295                 300
Met Ser Gln Thr Asp Leu Ser Leu Ser Lys Val Val His Lys Ser Phe
305                 310                 315                 320
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Val Glu Val Asn Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Ala Ala
                325                 330                 335
Ile Met Met Met Arg Cys Ala Arg Phe Val Pro Arg Phe Cys Ala Asp
            340                 345                 350
His Pro Phe Leu Phe Phe Ile Gln His Ser Lys Thr Asn Gly Ile Leu
        355                 360                 365
Phe Cys Gly Arg Phe Ser Ser Pro
    370                 375


<210> 18
<211> 397
<212> PRT
<213> Homo sapiens

<220>
<223> Bomapin   SERPINB10

<400> 18
Met Asp Ser Leu Ala Thr Ser Ile Asn Gln Phe Ala Leu Glu Leu Ser
 1               5                  10                  15
Lys Lys Leu Ala Glu Ser Ala Gln Gly Lys Asn Ile Phe Phe Ser Ser
            20                  25                  30
Trp Ser Ile Ser Thr Ser Leu Thr Ile Val Tyr Leu Gly Ala Lys Gly
        35                  40                  45
Thr Thr Ala Ala Gln Met Ala Gln Val Leu Gln Phe Asn Arg Asp Gln
    50                  55                  60
Gly Val Lys Cys Asp Pro Glu Ser Glu Lys Lys Arg Lys Met Glu Phe
65                  70                  75                  80
Asn Leu Ser Asn Ser Glu Glu Ile His Ser Asp Phe Gln Thr Leu Ile
                85                  90                  95
Ser Glu Ile Leu Lys Pro Asn Asp Asp Tyr Leu Leu Lys Thr Ala Asn
            100                 105                 110
Ala Ile Tyr Gly Glu Lys Thr Tyr Ala Phe His Asn Lys Tyr Leu Glu
        115                 120                 125
Asp Met Lys Thr Tyr Phe Gly Ala Glu Pro Gln Pro Val Asn Phe Val
    130                 135                 140
Glu Ala Ser Asp Gln Ile Arg Lys Asp Ile Asn Ser Trp Val Glu Arg
145                 150                 155                 160
Gln Thr Glu Gly Lys Ile Gln Asn Leu Leu Pro Asp Asp Ser Val Asp
                165                 170                 175
Ser Thr Thr Arg Met Ile Leu Val Asn Ala Leu Tyr Phe Lys Gly Ile
            180                 185                 190
Trp Glu His Gln Phe Leu Val Gln Asn Thr Thr Glu Lys Pro Phe Arg
        195                 200                 205
Ile Asn Glu Thr Thr Ser Lys Pro Val Gln Met Met Phe Met Lys Lys
    210                 215                 220
Lys Leu His Ile Phe His Ile Glu Lys Pro Lys Ala Val Gly Leu Gln
225                 230                 235                 240
Leu Tyr Tyr Lys Ser Arg Asp Leu Ser Leu Leu Ile Leu Leu Pro Glu
                245                 250                 255
Asp Ile Asn Gly Leu Glu Gln Leu Glu Lys Ala Ile Thr Tyr Glu Lys
            260                 265                 270
Leu Asn Glu Trp Thr Ser Ala Asp Met Met Glu Leu Tyr Glu Val Gln
        275                 280                 285
Leu His Leu Pro Lys Phe Lys Leu Glu Asp Ser Tyr Asp Leu Lys Ser
    290                 295                 300
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Thr Leu Ser Ser Met Gly Met Ser Asp Ala Phe Ser Gln Ser Lys Ala
305                 310                 315                 320
Asp Phe Ser Gly Met Ser Ser Ala Arg Asn Leu Phe Leu Ser Asn Val
                325                 330                 335
Phe His Lys Ala Phe Val Glu Ile Asn Glu Gln Gly Thr Glu Ala Ala
            340                 345                 350
Ala Gly Ser Gly Ser Glu Ile Asp Ile Arg Ile Arg Val Pro Ser Ile
        355                 360                 365
Glu Phe Asn Ala Asn His Pro Phe Leu Phe Phe Ile Arg His Asn Lys
    370                 375                 380
Thr Asn Thr Ile Leu Phe Tyr Gly Arg Leu Cys Ser Pro
385                 390                 395


<210> 19
<211> 392
<212> PRT
<213> Homo sapiens

<220>
<223> Epipen   SERPINB11

<400> 19
Met Gly Ser Leu Ser Thr Ala Asn Val Glu Phe Cys Leu Asp Val Phe
 1               5                  10                  15
Lys Glu Leu Asn Ser Asn Asn Ile Gly Asp Asn Ile Phe Phe Ser Ser
            20                  25                  30
Leu Ser Leu Leu Tyr Ala Leu Ser Met Val Leu Leu Gly Ala Arg Gly
        35                  40                  45
Glu Thr Ala Glu Gln Leu Glu Lys Val Leu His Phe Ser His Thr Val
    50                  55                  60
Asp Ser Leu Lys Pro Gly Phe Lys Asp Ser Pro Lys Cys Ser Gln Ala
65                  70                  75                  80
Gly Arg Ile His Ser Glu Phe Gly Val Glu Phe Ser Gln Ile Asn Gln
                85                  90                  95
Pro Asp Ser Asn Cys Thr Leu Ser Ile Ala Asn Arg Leu Tyr Gly Thr

            100                 105                 110
Lys Thr Met Ala Phe His Gln Gln Tyr Leu Ser Cys Ser Glu Lys Trp
        115                 120                 125
Tyr Gln Ala Arg Leu Gln Thr Val Asp Phe Glu Gln Ser Thr Glu Glu
    130                 135                 140
Thr Arg Lys Met Ile Asn Ala Trp Val Glu Asn Lys Thr Asn Gly Lys
145                 150                 155                 160
Val Ala Asn Leu Phe Gly Lys Ser Thr Ile Asp Pro Ser Ser Val Met
                165                 170                 175
Val Leu Val Asn Ile Ile Tyr Phe Lys Gly Gln Arg Gln Asn Lys Phe
            180                 185                 190
Gln Val Arg Glu Thr Val Lys Ser Pro Phe Gln Leu Ser Glu Gly Lys
        195                 200                 205
Asn Val Thr Val Glu Met Met Tyr Gln Ile Gly Thr Phe Lys Leu Ala
    210                 215                 220
Phe Val Lys Glu Pro Gln Met Gln Val Leu Glu Leu Pro Tyr Val Asn
225                 230                 235                 240
Asn Lys Leu Ser Met Ile Ile Leu Leu Pro Val Gly Ile Ala Asn Leu
                245                 250                 255
Lys Gln Ile Glu Lys Gln Leu Asn Ser Gly Thr Phe His Glu Trp Thr
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            260                 265                 270
Ser Ser Ser Asn Met Met Glu Arg Glu Val Glu Val His Leu Pro Arg
        275                 280                 285
Phe Lys Leu Glu Ile Lys Tyr Glu Leu Asn Ser Leu Leu Lys Pro Leu
    290                 295                 300
Gly Val Thr Asp Leu Phe Asn Gln Val Lys Ala Asp Leu Ser Gly Met
305                 310                 315                 320
Ser Pro Thr Lys Gly Leu Tyr Leu Ser Lys Ala Ile His Lys Ser Tyr
                325                 330                 335
Leu Asp Val Ser Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Gly Asp
            340                 345                 350
Ser Ile Ala Val Lys Ser Leu Pro Met Arg Ala Gln Phe Lys Ala Asn
        355                 360                 365
His Pro Phe Leu Phe Phe Ile Arg His Thr His Thr Asn Thr Ile Leu
    370                 375                 380
Phe Cys Gly Lys Leu Ala Ser Pro
385                 390


<210> 20
<211> 405
<212> PRT
<213> Homo sapiens

<220>
<223> Yukopin   SERPINB12

<400> 20
Met Asp Ser Leu Val Thr Ala Asn Thr Lys Phe Cys Phe Asp Leu Phe
 1               5                  10                  15
Gln Glu Ile Gly Lys Asp Asp Arg His Lys Asn Ile Phe Phe Ser Pro
            20                  25                  30
Leu Ser Leu Ser Ala Ala Leu Gly Met Val Arg Leu Gly Ala Arg Ser
        35                  40                  45
Asp Ser Ala His Gln Ile Asp Glu Val Leu His Phe Asn Glu Phe Ser
    50                  55                  60
Gln Asn Glu Ser Lys Glu Pro Asp Pro Cys Leu Lys Ser Asn Lys Gln
65                  70                  75                  80
Lys Ala Gly Ser Leu Asn Asn Glu Ser Gly Leu Val Ser Cys Tyr Phe
                85                  90                  95
Gly Gln Leu Leu Ser Lys Leu Asp Arg Ile Lys Thr Asp Tyr Thr Leu
            100                 105                 110
Ser Ile Ala Asn Arg Leu Tyr Gly Glu Gln Glu Phe Pro Ile Cys Gln
        115                 120                 125
Glu Tyr Leu Asp Gly Val Ile Gln Phe Tyr His Thr Thr Ile Glu Ser
    130                 135                 140
Val Asp Phe Gln Lys Asn Pro Glu Lys Ser Arg Gln Glu Ile Asn Phe
145                 150                 155                 160
Trp Val Glu Cys Gln Ser Gln Gly Lys Ile Lys Glu Leu Phe Ser Lys
                165                 170                 175
Asp Ala Ile Asn Ala Glu Thr Val Leu Val Leu Val Asn Ala Val Tyr
            180                 185                 190
Phe Lys Ala Lys Trp Glu Thr Tyr Phe Asp His Glu Asn Thr Val Asp
        195                 200                 205
Ala Pro Phe Cys Leu Asn Ala Asn Glu Asn Lys Ser Val Lys Met Met
    210                 215                 220
Thr Gln Lys Gly Leu Tyr Arg Ile Gly Phe Ile Glu Glu Val Lys Ala
```

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225                 230                 235                 240
Gln Ile Leu Glu Met Arg Tyr Thr Lys Gly Lys Leu Ser Met Phe Val
                245                 250                 255
Leu Leu Pro Ser His Ser Lys Asp Asn Leu Lys Gly Leu Glu Glu Leu
            260                 265                 270
Glu Arg Lys Ile Thr Tyr Glu Lys Met Val Ala Trp Ser Ser Ser Glu
        275                 280                 285
Asn Met Ser Glu Glu Ser Val Val Leu Ser Phe Pro Arg Phe Thr Leu
    290                 295                 300
Glu Asp Ser Tyr Asp Leu Asn Ser Ile Leu Gln Asp Met Gly Ile Thr
305                 310                 315                 320
Asp Ile Phe Asp Glu Thr Arg Ala Asp Leu Thr Gly Ile Ser Pro Ser
                325                 330                 335
Pro Asn Leu Tyr Leu Ser Lys Ile Ile His Lys Thr Phe Val Glu Val
            340                 345                 350
Asp Glu Asn Gly Thr Gln Ala Ala Ala Ala Thr Gly Ala Val Val Ser
        355                 360                 365
Glu Arg Ser Leu Arg Ser Trp Val Glu Phe Asn Ala Asn His Pro Phe
    370                 375                 380
Leu Phe Phe Ile Arg His Asn Lys Thr Gln Thr Ile Leu Phe Tyr Gly
385                 390                 395                 400
Arg Val Cys Ser Pro
                405
```

<210> 21
<211> 391
<212> PRT
<213> Homo sapiens

<220>
<223> Headpin SERPINB13

<400> 21

```
Met Asp Ser Leu Gly Ala Val Ser Thr Arg Leu Gly Phe Asp Leu Phe
 1               5                  10                  15
Lys Glu Leu Lys Lys Thr Asn Asp Gly Asn Ile Phe Phe Ser Pro Val
            20                  25                  30
Gly Ile Leu Thr Ala Ile Gly Met Val Leu Leu Gly Thr Arg Gly Ala
        35                  40                  45
Thr Ala Ser Gln Leu Glu Glu Val Phe His Ser Glu Lys Glu Thr Lys
    50                  55                  60
Ser Ser Arg Ile Lys Ala Glu Glu Lys Glu Val Ile Glu Asn Thr Glu
65                  70                  75                  80
Ala Val His Gln Gln Phe Gln Lys Phe Leu Thr Glu Ile Ser Lys Leu
                85                  90                  95
Thr Asn Asp Tyr Glu Leu Asn Ile Thr Asn Arg Leu Phe Gly Glu Lys
            100                 105                 110
Thr Tyr Leu Phe Leu Gln Lys Tyr Leu Asp Tyr Val Glu Lys Tyr Tyr
        115                 120                 125
His Ala Ser Leu Glu Pro Val Asp Phe Val Asn Ala Ala Asp Glu Ser
    130                 135                 140
Arg Lys Lys Ile Asn Ser Trp Val Glu Ser Lys Thr Asn Glu Lys Ile
145                 150                 155                 160
Lys Asp Leu Phe Pro Asp Gly Ser Ile Ser Ser Ser Thr Lys Leu Val
                165                 170                 175
Leu Val Asn Met Val Tyr Phe Lys Gly Gln Trp Asp Arg Glu Phe Lys
```

```
            180                 185                 190
Lys Glu Asn Thr Lys Glu Glu Lys Phe Trp Met Asn Lys Ser Thr Ser
        195                 200                 205
Lys Ser Val Gln Met Met Thr Gln Ser His Ser Phe Ser Phe Thr Phe
    210                 215                 220
Leu Glu Asp Leu Gln Ala Lys Ile Leu Gly Ile Pro Tyr Lys Asn Asn
225                 230                 235                 240
Asp Leu Ser Met Phe Val Leu Leu Pro Asn Asp Ile Asp Gly Leu Glu
                245                 250                 255
Lys Ile Ile Asp Lys Ile Ser Pro Glu Lys Leu Val Glu Trp Thr Ser
            260                 265                 270
Pro Gly His Met Glu Glu Arg Lys Val Asn Leu His Leu Pro Arg Phe
        275                 280                 285
Glu Val Glu Asp Gly Tyr Asp Leu Glu Ala Val Leu Ala Ala Met Gly
    290                 295                 300
Met Gly Asp Ala Phe Ser Glu His Lys Ala Asp Tyr Ser Gly Met Ser
305                 310                 315                 320
Ser Gly Ser Gly Leu Tyr Ala Gln Lys Phe Leu His Ser Ser Phe Val
                325                 330                 335
Ala Val Thr Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Gly Ile Gly
            340                 345                 350
Phe Thr Val Thr Ser Ala Pro Gly His Glu Asn Val His Cys Asn His
        355                 360                 365
Pro Phe Leu Phe Phe Ile Arg His Asn Glu Ser Asn Ser Ile Leu Phe
    370                 375                 380
Phe Gly Arg Phe Ser Ser Pro
385                 390


<210> 22
<211> 390
<212> PRT
<213> Homo sapiens

<220>
<223> Squamous cell carcinoma antigen 1   SERPINB3

<400> 22
Met Asn Ser Leu Ser Glu Ala Asn Thr Lys Phe Met Phe Asp Leu Phe
 1               5                  10                  15
Gln Gln Phe Arg Lys Ser Lys Glu Asn Asn Ile Phe Tyr Ser Pro Ile
            20                  25                  30
Ser Ile Thr Ser Ala Leu Gly Met Val Leu Leu Gly Ala Lys Asp Asn
        35                  40                  45
Thr Ala Gln Gln Ile Lys Lys Val Leu His Phe Asp Gln Val Thr Glu
    50                  55                  60
Asn Thr Thr Gly Lys Ala Ala Thr Tyr His Val Asp Arg Ser Gly Asn
65                  70                  75                  80
Val His His Gln Phe Gln Lys Leu Leu Thr Glu Phe Asn Lys Ser Thr
                85                  90                  95
Asp Ala Tyr Glu Leu Lys Ile Ala Asn Lys Leu Phe Gly Glu Lys Thr
            100                 105                 110
Tyr Leu Phe Leu Gln Glu Tyr Leu Asp Ala Ile Lys Lys Phe Tyr Gln
        115                 120                 125
Thr Ser Val Glu Ser Val Asp Phe Ala Asn Ala Pro Glu Glu Ser Arg
    130                 135                 140
Lys Lys Ile Asn Ser Trp Val Glu Ser Gln Thr Asn Glu Lys Ile Lys
```

```
145                 150                 155                 160
Asn Leu Ile Pro Glu Gly Asn Ile Gly Ser Asn Thr Thr Leu Val Leu
                165                 170                 175
Val Asn Ala Ile Tyr Phe Lys Gly Gln Trp Glu Lys Lys Phe Asn Lys
            180                 185                 190
Glu Asp Thr Lys Glu Glu Lys Phe Trp Pro Asn Lys Asn Thr Tyr Lys
        195                 200                 205
Ser Ile Gln Met Met Arg Gln Tyr Thr Ser Phe His Phe Ala Ser Leu
    210                 215                 220
Glu Asp Val Gln Ala Lys Val Leu Glu Ile Pro Tyr Lys Gly Lys Asp
225                 230                 235                 240
Leu Ser Met Ile Val Leu Leu Pro Asn Glu Ile Asp Gly Leu Gln Lys
                245                 250                 255
Leu Glu Glu Lys Leu Thr Ala Glu Lys Leu Met Glu Trp Thr Ser Leu
            260                 265                 270
Gln Asn Met Arg Glu Thr Arg Val Asp Leu His Leu Pro Arg Phe Lys
        275                 280                 285
Val Glu Glu Ser Tyr Asp Leu Lys Asp Thr Leu Arg Thr Met Gly Met
    290                 295                 300
Val Asp Ile Phe Asn Gly Asp Ala Asp Leu Ser Gly Met Thr Gly Ser
305                 310                 315                 320
Arg Gly Leu Val Leu Ser Gly Val Leu His Lys Ala Phe Val Glu Val
                325                 330                 335
Thr Glu Glu Gly Ala Glu Ala Ala Ala Ala Thr Ala Val Val Gly Phe
            340                 345                 350
Gly Ser Ser Pro Thr Ser Thr Asn Glu Glu Phe His Cys Asn His Pro
        355                 360                 365
Phe Leu Phe Phe Ile Arg Gln Asn Lys Thr Asn Ser Ile Leu Phe Tyr
    370                 375                 380
Gly Arg Phe Ser Ser Pro
385                 390
```

<210> 23
<211> 390
<212> PRT
<213> Homo sapiens

<220>
<223> Squamous cell carcinoma antigen 2 SERPINB4

<400> 23

```
Met Asn Ser Leu Ser Glu Ala Asn Thr Lys Phe Met Phe Asp Leu Phe
 1               5                  10                  15
Gln Gln Phe Arg Lys Ser Lys Glu Asn Asn Ile Phe Tyr Ser Pro Ile
            20                  25                  30
Ser Ile Thr Ser Ala Leu Gly Met Val Leu Leu Gly Ala Lys Asp Asn
        35                  40                  45
Thr Ala Gln Gln Ile Ser Lys Val Leu His Phe Asp Gln Val Thr Glu
    50                  55                  60
Asn Thr Thr Glu Lys Ala Ala Thr Tyr His Val Asp Arg Ser Gly Asn
65                  70                  75                  80
Val His His Gln Phe Gln Lys Leu Leu Thr Glu Phe Asn Lys Ser Thr
                85                  90                  95
Asp Ala Tyr Glu Leu Lys Ile Ala Asn Lys Leu Phe Gly Glu Lys Thr
            100                 105                 110
Tyr Gln Phe Leu Gln Glu Tyr Leu Asp Ala Ile Lys Lys Phe Tyr Gln
```

```
        115                 120                 125
Thr Ser Val Glu Ser Thr Asp Phe Ala Asn Ala Pro Glu Glu Ser Arg
    130                 135                 140
Lys Lys Ile Asn Ser Trp Val Glu Ser Gln Thr Asn Glu Lys Ile Lys
145                 150                 155                 160
Asn Leu Phe Pro Asp Gly Thr Ile Gly Asn Asp Thr Thr Leu Val Leu
                165                 170                 175
Val Asn Ala Ile Tyr Phe Lys Gly Gln Trp Glu Asn Lys Phe Lys Lys
            180                 185                 190
Glu Asn Thr Lys Glu Glu Lys Phe Trp Pro Asn Lys Asn Thr Tyr Lys
        195                 200                 205
Ser Val Gln Met Met Arg Gln Tyr Asn Ser Phe Asn Phe Ala Leu Leu
    210                 215                 220
Glu Asp Val Gln Ala Lys Val Leu Glu Ile Pro Tyr Lys Gly Lys Asp
225                 230                 235                 240
Leu Ser Met Ile Val Leu Leu Pro Asn Glu Ile Asp Gly Leu Gln Lys
                245                 250                 255
Leu Glu Glu Lys Leu Thr Ala Glu Lys Leu Met Glu Trp Thr Ser Leu
            260                 265                 270
Gln Asn Met Arg Glu Thr Cys Val Asp Leu His Leu Pro Arg Phe Lys
        275                 280                 285
Met Glu Glu Ser Tyr Asp Leu Lys Asp Thr Leu Arg Thr Met Gly Met
    290                 295                 300
Val Asn Ile Phe Asn Gly Asp Ala Asp Leu Ser Gly Met Thr Trp Ser
305                 310                 315                 320
His Gly Leu Ser Val Ser Lys Val Leu His Lys Ala Phe Val Glu Val
                325                 330                 335
Thr Glu Glu Gly Val Glu Ala Ala Ala Ala Thr Ala Val Val Val Val
            340                 345                 350
Glu Leu Ser Ser Pro Ser Thr Asn Glu Glu Phe Cys Cys Asn His Pro
        355                 360                 365
Phe Leu Phe Phe Ile Arg Gln Asn Lys Thr Asn Ser Ile Leu Phe Tyr
    370                 375                 380
Gly Arg Phe Ser Ser Pro
385                 390
```

<210> 24
<211> 380
<212> PRT
<213> Homo sapiens

<220>
<223> Megsin SERPINB7

<400> 24

```
Met Ala Ser Leu Ala Ala Ala Asn Ala Glu Phe Cys Phe Asn Leu Phe
 1               5                  10                  15
Arg Glu Met Asp Asp Asn Gln Gly Asn Gly Asn Val Phe Phe Ser Ser
            20                  25                  30
Leu Ser Leu Phe Ala Ala Leu Ala Leu Val Arg Leu Gly Ala Gln Asp
        35                  40                  45
Asp Ser Leu Ser Gln Ile Asp Lys Leu Leu His Val Asn Thr Ala Ser
    50                  55                  60
Gly Tyr Gly Asn Ser Ser Asn Ser Gln Ser Gly Leu Gln Ser Gln Leu
65                  70                  75                  80
Lys Arg Val Phe Ser Asp Ile Asn Ala Ser His Lys Asp Tyr Asp Leu
```

```
                85                  90                  95
Ser Ile Val Asn Gly Leu Phe Ala Glu Lys Val Tyr Gly Phe His Lys
            100                 105                 110
Asp Tyr Ile Glu Cys Ala Glu Lys Leu Tyr Asp Ala Lys Val Glu Arg
        115                 120                 125
Val Asp Phe Thr Asn His Leu Glu Asp Thr Arg Arg Asn Ile Asn Lys
    130                 135                 140
Trp Val Glu Asn Glu Thr His Gly Lys Ile Lys Asn Val Ile Gly Glu
145                 150                 155                 160
Gly Gly Ile Ser Ser Ser Ala Val Met Val Leu Val Asn Ala Val Tyr
                165                 170                 175
Phe Lys Gly Lys Trp Gln Ser Ala Phe Thr Lys Ser Glu Thr Ile Asn
            180                 185                 190
Cys His Phe Lys Ser Pro Lys Cys Ser Gly Lys Ala Val Ala Met Met
        195                 200                 205
His Gln Glu Arg Lys Phe Asn Leu Ser Val Ile Glu Asp Pro Ser Met
    210                 215                 220
Lys Ile Leu Glu Leu Arg Tyr Asn Gly Gly Ile Asn Met Tyr Val Leu
225                 230                 235                 240
Leu Pro Glu Asn Asp Leu Ser Glu Ile Glu Asn Lys Leu Thr Phe Gln
                245                 250                 255
Asn Leu Met Glu Trp Thr Asn Pro Arg Arg Met Thr Ser Lys Tyr Val
            260                 265                 270
Glu Val Phe Phe Pro Gln Phe Lys Ile Glu Lys Asn Tyr Glu Met Lys
        275                 280                 285
Gln Tyr Leu Arg Ala Leu Gly Leu Lys Asp Ile Phe Asp Glu Ser Lys
    290                 295                 300
Ala Asp Leu Ser Gly Ile Ala Ser Gly Gly Arg Leu Tyr Ile Ser Arg
305                 310                 315                 320
Met Met His Lys Ser Tyr Ile Glu Val Thr Glu Glu Gly Thr Glu Ala
                325                 330                 335
Thr Ala Ala Thr Gly Ser Asn Ile Val Glu Lys Gln Leu Pro Gln Ser
            340                 345                 350
Thr Leu Phe Arg Ala Asp His Pro Phe Leu Phe Val Ile Arg Lys Asp
        355                 360                 365
Asp Ile Ile Leu Phe Ser Gly Lys Val Ser Cys Pro
    370                 375                 380


<210> 25
<211> 374
<212> PRT
<213> Homo sapiens

<220>
<223> Cytoplasmic antiproteinase 2   SERPINB8


<400> 25
Met Asp Asp Leu Cys Glu Ala Asn Gly Thr Phe Ala Ile Ser Leu Phe
 1               5                  10                  15
Lys Ile Leu Gly Glu Glu Asp Asn Ser Arg Asn Val Phe Phe Ser Pro
            20                  25                  30
Met Ser Ile Ser Ser Ala Leu Ala Met Val Phe Met Gly Ala Lys Gly
        35                  40                  45
Ser Thr Ala Ala Gln Met Ser Gln Ala Leu Cys Leu Tyr Lys Asp Gly
    50                  55                  60
```

```
Asp Ile His Arg Gly Phe Gln Ser Leu Leu Ser Glu Val Asn Arg Thr
65                  70                  75                  80
Gly Thr Gln Tyr Leu Leu Arg Thr Ala Asn Arg Leu Phe Gly Glu Lys
                85                  90                  95
Thr Cys Asp Phe Leu Pro Asp Phe Lys Glu Tyr Cys Gln Lys Phe Tyr
            100                 105                 110
Gln Ala Glu Leu Glu Glu Leu Ser Phe Ala Glu Asp Thr Glu Glu Cys
        115                 120                 125
Arg Lys His Ile Asn Asp Trp Val Ala Glu Lys Thr Glu Gly Lys Ile
    130                 135                 140
Ser Glu Val Leu Asp Ala Gly Thr Val Asp Pro Leu Thr Lys Leu Val
145                 150                 155                 160
Leu Val Asn Ala Ile Tyr Phe Lys Gly Lys Trp Asn Glu Gln Phe Asp
                165                 170                 175
Arg Lys Tyr Thr Arg Gly Met Leu Phe Lys Thr Asn Glu Glu Lys Lys
            180                 185                 190
Thr Val Gln Met Met Phe Lys Glu Ala Lys Phe Lys Met Gly Tyr Ala
        195                 200                 205
Asp Glu Val His Thr Gln Val Leu Glu Leu Pro Tyr Val Glu Glu Glu
    210                 215                 220
Leu Ser Met Val Ile Leu Leu Pro Asp Asp Asn Thr Asp Leu Ala Val
225                 230                 235                 240
Val Glu Lys Ala Leu Thr Tyr Glu Lys Phe Lys Ala Trp Thr Asn Ser
                245                 250                 255
Glu Lys Leu Thr Lys Ser Lys Val Gln Val Phe Leu Pro Arg Leu Lys
            260                 265                 270
Leu Glu Glu Ser Tyr Asp Leu Glu Pro Phe Leu Arg Arg Leu Gly Met
        275                 280                 285
Ile Asp Ala Phe Asp Glu Ala Lys Ala Asp Phe Ser Gly Met Ser Thr

    290                 295                 300
Glu Lys Asn Val Pro Leu Ser Lys Val Ala His Lys Cys Phe Val Glu
305                 310                 315                 320
Val Asn Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Ala Val Val Arg
                325                 330                 335
Asn Ser Arg Cys Ser Arg Met Glu Pro Arg Phe Cys Ala Asp His Pro
            340                 345                 350
Phe Leu Phe Phe Ile Arg Arg His Lys Thr Asn Cys Ile Leu Phe Cys
        355                 360                 365
Gly Arg Phe Ser Ser Pro
    370


<210> 26
<211> 376
<212> PRT
<213> Homo sapiens

<220>
<223> Cytoplasmic antiproteinase 3   SERPINB9

<400> 26
Met Glu Thr Leu Ser Asn Ala Ser Gly Thr Phe Ala Ile Arg Leu Leu
 1               5                  10                  15
Lys Ile Leu Cys Gln Asp Asn Pro Ser His Asn Val Phe Cys Ser Pro
            20                  25                  30
Val Ser Ile Ser Ser Ala Leu Ala Met Val Leu Leu Gly Ala Lys Gly
```

```
        35                  40                  45
Asn Thr Ala Thr Gln Met Ala Gln Ala Leu Ser Leu Asn Thr Glu Glu
    50                  55                  60
Asp Ile His Arg Ala Phe Gln Ser Leu Leu Thr Glu Val Asn Lys Ala
65                  70                  75                  80
Gly Thr Gln Tyr Leu Leu Arg Thr Ala Asn Arg Leu Phe Gly Glu Lys
                85                  90                  95
Thr Cys Gln Phe Leu Ser Thr Phe Lys Glu Ser Cys Leu Gln Phe Tyr
            100                 105                 110
His Ala Glu Leu Lys Glu Leu Ser Phe Ile Arg Ala Ala Glu Glu Ser
        115                 120                 125
Arg Lys His Ile Asn Thr Trp Val Ser Lys Lys Thr Glu Gly Lys Ile
    130                 135                 140
Glu Glu Leu Leu Pro Gly Ser Ser Ile Asp Ala Glu Thr Arg Leu Val
145                 150                 155                 160
Leu Val Asn Ala Ile Tyr Phe Lys Gly Lys Trp Asn Glu Pro Phe Asp
                165                 170                 175
Glu Thr Tyr Thr Arg Glu Met Pro Phe Lys Ile Asn Gln Glu Glu Gln
            180                 185                 190
Arg Pro Val Gln Met Met Tyr Gln Glu Ala Thr Phe Lys Leu Ala His
        195                 200                 205
Val Gly Glu Val Arg Ala Gln Leu Leu Glu Leu Pro Tyr Ala Arg Lys
    210                 215                 220
Glu Leu Ser Leu Leu Val Leu Leu Pro Asp Asp Gly Val Glu Leu Ser
225                 230                 235                 240
Thr Val Glu Lys Ser Leu Thr Phe Glu Lys Leu Thr Ala Trp Thr Lys
                245                 250                 255
Pro Asp Cys Met Lys Ser Thr Glu Val Glu Val Leu Leu Pro Lys Phe
            260                 265                 270
Lys Leu Gln Glu Asp Tyr Asp Met Glu Ser Val Leu Arg His Leu Gly
        275                 280                 285
Ile Val Asp Ala Phe Gln Gln Gly Lys Ala Asp Leu Ser Ala Met Ser
    290                 295                 300
Ala Glu Arg Asp Leu Cys Leu Ser Lys Phe Val His Lys Ser Phe Val
305                 310                 315                 320
Glu Val Asn Glu Glu Gly Thr Glu Ala Ala Ala Ala Ser Ser Cys Phe
                325                 330                 335
Val Val Ala Glu Cys Cys Met Glu Ser Gly Pro Arg Phe Cys Ala Asp
            340                 345                 350
His Pro Phe Leu Phe Phe Ile Arg His Asn Arg Ala Asn Ser Ile Leu
        355                 360                 365
Phe Cys Gly Arg Phe Ser Ser Pro
    370                 375
```

<210> 27
<211> 376
<212> PRT
<213> Homo sapiens

<220>
<223> Placental thrombin inhibitor SERPINB6

<400> 27

```
Met Asp Val Leu Ala Glu Ala Asn Gly Thr Phe Ala Leu Asn Leu Leu
 1               5                  10                  15
Lys Thr Leu Gly Lys Asp Asn Ser Lys Asn Val Phe Phe Ser Pro Met
```

```
            20                  25                  30
Ser Met Ser Cys Ala Leu Ala Met Val Tyr Met Gly Ala Lys Gly Asn
        35                  40                  45
Thr Ala Ala Gln Met Ala Gln Ile Leu Ser Phe Asn Lys Ser Gly Gly
    50                  55                  60
Gly Gly Asp Ile His Gln Gly Phe Gln Ser Leu Leu Thr Glu Val Asn
65                  70                  75                  80
Lys Thr Gly Thr Gln Tyr Leu Leu Arg Val Ala Asn Arg Leu Phe Gly
                85                  90                  95
Glu Lys Ser Cys Asp Phe Leu Ser Ser Phe Arg Asp Ser Cys Gln Lys
            100                 105                 110
Phe Tyr Gln Ala Glu Met Glu Glu Leu Asp Phe Ile Ser Ala Val Glu
        115                 120                 125
Lys Ser Arg Lys His Ile Asn Thr Trp Val Ala Glu Lys Thr Glu Gly
    130                 135                 140
Lys Ile Ala Glu Leu Leu Ser Pro Gly Ser Val Asp Pro Leu Thr Arg
145                 150                 155                 160
Leu Val Leu Val Asn Ala Val Tyr Phe Arg Gly Asn Trp Asp Glu Gln
                165                 170                 175
Phe Asp Lys Glu Asn Thr Glu Glu Arg Leu Phe Lys Val Ser Lys Asn
            180                 185                 190
Glu Glu Lys Pro Val Gln Met Met Phe Lys Gln Ser Thr Phe Lys Lys
        195                 200                 205
Thr Tyr Ile Gly Glu Ile Phe Thr Gln Ile Leu Val Leu Pro Tyr Val
    210                 215                 220
Gly Lys Glu Leu Asn Met Ile Ile Met Leu Pro Asp Glu Thr Thr Asp
225                 230                 235                 240
Leu Arg Thr Val Glu Lys Glu Leu Thr Tyr Glu Lys Phe Val Glu Trp
                245                 250                 255
Thr Arg Leu Asp Met Met Asp Glu Glu Glu Val Glu Val Ser Leu Pro
            260                 265                 270
Arg Phe Lys Leu Glu Glu Ser Tyr Asp Met Glu Ser Val Leu Arg Asn
        275                 280                 285
Leu Gly Met Thr Asp Ala Phe Glu Leu Gly Lys Ala Asp Phe Ser Gly
    290                 295                 300
Met Ser Gln Thr Asp Leu Ser Leu Ser Lys Val Val His Lys Ser Phe
305                 310                 315                 320
Val Glu Val Asn Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Ala Ala
                325                 330                 335
Ile Met Met Met Arg Cys Ala Arg Phe Val Pro Arg Phe Cys Ala Asp
            340                 345                 350
His Pro Phe Leu Phe Phe Ile Gln His Ser Lys Thr Asn Gly Ile Leu
        355                 360                 365
Phe Cys Gly Arg Phe Ser Ser Pro
    370                 375
```

<210> 28
<211> 485
<212> PRT
<213> Homo sapiens

<220>
<223> Angiotensinogen precursor SERPINA8

<400> 28
Met Arg Lys Arg Ala Pro Gln Ser Glu Met Ala Pro Ala Gly Val Ser

```
 1               5                  10                  15
Leu Arg Ala Thr Ile Leu Cys Leu Leu Ala Trp Ala Gly Leu Ala Ala
            20                  25                  30
Gly Asp Arg Val Tyr Ile His Pro Phe His Leu Val Ile His Asn Glu
        35                  40                  45
Ser Thr Cys Glu Gln Leu Ala Lys Ala Asn Ala Gly Lys Pro Lys Asp
    50                  55                  60
Pro Thr Phe Ile Pro Ala Pro Ile Gln Ala Lys Thr Ser Pro Val Asp
65                  70                  75                  80
Glu Lys Ala Leu Gln Asp Gln Leu Val Leu Val Ala Ala Lys Leu Asp
                85                  90                  95
Thr Glu Asp Lys Leu Arg Ala Ala Met Val Gly Met Leu Ala Asn Phe
            100                 105                 110
Leu Gly Phe Arg Ile Tyr Gly Met His Ser Glu Leu Trp Gly Val Val
        115                 120                 125
His Gly Ala Thr Val Leu Ser Pro Thr Ala Val Phe Gly Thr Leu Ala
    130                 135                 140
Ser Leu Tyr Leu Gly Ala Leu Asp His Thr Ala Asp Arg Leu Gln Ala
145                 150                 155                 160
Ile Leu Gly Val Pro Trp Lys Asp Lys Asn Cys Thr Ser Arg Leu Asp
                165                 170                 175
Ala His Lys Val Leu Ser Ala Leu Gln Ala Val Gln Gly Leu Leu Val
            180                 185                 190
Ala Gln Gly Arg Ala Asp Ser Gln Ala Gln Leu Leu Leu Ser Thr Val
        195                 200                 205
Val Gly Val Phe Thr Ala Pro Gly Leu His Leu Lys Gln Pro Phe Val
    210                 215                 220
Gln Gly Leu Ala Leu Tyr Thr Pro Val Val Leu Pro Arg Ser Leu Asp
225                 230                 235                 240
Phe Thr Glu Leu Asp Val Ala Ala Glu Lys Ile Asp Arg Phe Met Gln
                245                 250                 255
Ala Val Thr Gly Trp Lys Thr Gly Cys Ser Leu Met Gly Ala Ser Val
            260                 265                 270
Asp Ser Thr Leu Ala Phe Asn Thr Tyr Val His Phe Gln Gly Lys Met
        275                 280                 285
Lys Gly Phe Ser Leu Leu Ala Glu Pro Gln Glu Phe Trp Val Asp Asn
    290                 295                 300
Ser Thr Ser Val Ser Val Pro Met Leu Ser Gly Met Gly Thr Phe Gln
305                 310                 315                 320
His Trp Ser Asp Ile Gln Asp Asn Phe Ser Val Thr Gln Val Pro Phe
                325                 330                 335
Thr Glu Ser Ala Cys Leu Leu Leu Ile Gln Pro His Tyr Ala Ser Asp
            340                 345                 350
Leu Asp Lys Val Glu Gly Leu Thr Phe Gln Gln Asn Ser Leu Asn Trp
        355                 360                 365
Met Lys Lys Leu Ser Pro Arg Thr Ile His Leu Thr Met Pro Gln Leu
    370                 375                 380
Val Leu Gln Gly Ser Tyr Asp Leu Gln Asp Leu Leu Ala Gln Ala Glu
385                 390                 395                 400
Leu Pro Ala Ile Leu His Thr Glu Leu Asn Leu Gln Lys Leu Ser Asn
                405                 410                 415
Asp Arg Ile Arg Val Gly Glu Val Leu Asn Ser Ile Phe Phe Glu Leu
            420                 425                 430
Glu Ala Asp Glu Arg Glu Pro Thr Glu Ser Thr Gln Gln Leu Asn Lys
        435                 440                 445
Pro Glu Val Leu Glu Val Thr Leu Asn Arg Pro Phe Leu Phe Ala Val
    450                 455                 460
```

```
Tyr Asp Gln Ser Ala Thr Ala Leu His Phe Leu Gly Arg Val Ala Asn
465                 470                 475                 480
Pro Leu Ser Thr Ala
                485
```

<210> 29
<211> 405
<212> PRT
<213> Homo sapiens

<220>
<223> Corticosteroid-binding globulin precursor SERPINA6

<400> 29

```
Met Pro Leu Leu Leu Tyr Thr Cys Leu Leu Trp Leu Pro Thr Ser Gly
 1               5                  10                  15
Leu Trp Thr Val Gln Ala Met Asp Pro Asn Ala Ala Tyr Val Asn Met
            20                  25                  30
Ser Asn His His Arg Gly Leu Ala Ser Ala Asn Val Asp Phe Ala Phe
        35                  40                  45
Ser Leu Tyr Lys His Leu Val Ala Leu Ser Pro Lys Lys Asn Ile Phe
    50                  55                  60
Ile Ser Pro Val Ser Ile Ser Met Ala Leu Ala Met Leu Ser Leu Gly
65                  70                  75                  80
Thr Cys Gly His Thr Arg Ala Gln Leu Leu Gln Gly Leu Gly Phe Asn
                85                  90                  95
Leu Thr Glu Arg Ser Glu Thr Glu Ile His Gln Gly Phe Gln His Leu
            100                 105                 110
His Gln Leu Phe Ala Lys Ser Asp Thr Ser Leu Glu Met Thr Met Gly
        115                 120                 125
Asn Ala Leu Phe Leu Asp Gly Ser Leu Glu Leu Leu Glu Ser Phe Ser
    130                 135                 140
Ala Asp Ile Lys His Tyr Tyr Glu Ser Glu Val Leu Ala Met Asn Phe
145                 150                 155                 160
Gln Asp Trp Ala Thr Ala Ser Arg Gln Ile Asn Ser Tyr Val Lys Asn
                165                 170                 175
Lys Thr Gln Gly Lys Ile Val Asp Leu Phe Ser Gly Leu Asp Ser Pro
            180                 185                 190
Ala Ile Leu Val Leu Val Asn Tyr Ile Phe Phe Lys Gly Thr Trp Thr
        195                 200                 205
Gln Pro Phe Asp Leu Ala Ser Thr Arg Glu Glu Asn Phe Tyr Val Asp
    210                 215                 220
Glu Thr Thr Val Val Lys Val Pro Met Met Leu Gln Ser Ser Thr Ile
225                 230                 235                 240
Ser Tyr Leu His Asp Ser Glu Leu Pro Cys Gln Leu Val Gln Met Asn
                245                 250                 255
Tyr Val Gly Asn Gly Thr Val Phe Phe Ile Leu Pro Asp Lys Gly Lys
            260                 265                 270
Met Asn Thr Val Ile Ala Ala Leu Ser Arg Asp Thr Ile Asn Arg Trp
        275                 280                 285
Ser Ala Gly Leu Thr Ser Ser Gln Val Asp Leu Tyr Ile Pro Lys Val
    290                 295                 300
Thr Ile Ser Gly Val Tyr Asp Leu Gly Asp Val Leu Glu Glu Met Gly
305                 310                 315                 320
Ile Ala Asp Leu Phe Thr Asn Gln Ala Asn Phe Ser Arg Ile Thr Gln
                325                 330                 335
```

```
Asp Ala Gln Leu Lys Ser Ser Lys Val Val His Lys Ala Val Leu Gln
            340                 345                 350
Leu Asn Glu Glu Gly Val Asp Thr Ala Gly Ser Thr Gly Val Thr Leu
        355                 360                 365
Asn Leu Thr Ser Lys Pro Ile Ile Leu Arg Phe Asn Gln Pro Phe Ile
    370                 375                 380
Ile Met Ile Phe Asp His Phe Thr Trp Ser Ser Leu Phe Leu Ala Arg
385                 390                 395                 400
Val Met Asn Pro Val
                405
```

<210> 30
<211> 417
<212> PRT
<213> Homo sapiens

<220>
<223> 47 kDa heat shock protein precursor SERPINH1

<400> 30

```
Met Arg Ser Leu Leu Leu Gly Thr Leu Cys Leu Leu Ala Val Ala Leu
 1               5                  10                  15
Ala Ala Glu Val Lys Lys Pro Val Glu Ala Ala Ala Pro Gly Thr Ala
            20                  25                  30
Glu Lys Leu Ser Ser Lys Ala Thr Thr Leu Ala Glu Pro Ser Thr Gly
        35                  40                  45
Leu Ala Phe Ser Leu Tyr Gln Ala Met Ala Lys Asp Gln Ala Val Glu
    50                  55                  60
Asn Ile Leu Val Ser Pro Val Val Val Ala Ser Ser Leu Gly Leu Val
65                  70                  75                  80
Ser Leu Gly Gly Lys Ala Thr Thr Ala Ser Gln Ala Lys Ala Val Leu
                85                  90                  95
Ser Ala Glu Gln Leu Arg Asp Glu Glu Val His Ala Gly Leu Gly Glu
            100                 105                 110
Leu Leu Arg Ser Leu Ser Asn Ser Thr Ala Arg Asn Val Thr Trp Lys
        115                 120                 125
Leu Gly Ser Arg Leu Tyr Gly Pro Ser Ser Val Ser Phe Ala Asp Asp
    130                 135                 140
Phe Val Arg Ser Ser Lys Gln His Tyr Asn Cys Glu His Ser Lys Ile
145                 150                 155                 160
Asn Phe Pro Asp Lys Arg Ser Ala Leu Gln Ser Ile Asn Glu Trp Ala
                165                 170                 175
Ala Gln Thr Thr Asp Gly Lys Leu Pro Glu Val Thr Lys Asp Val Glu
            180                 185                 190
Arg Thr Asp Gly Ala Leu Leu Val Asn Ala Met Phe Phe Lys Pro His
        195                 200                 205
Trp Asp Glu Lys Phe His His Lys Met Val Asp Asn Arg Gly Phe Met
    210                 215                 220
Val Thr Arg Ser Tyr Thr Val Gly Val Thr Met Met His Arg Thr Gly
225                 230                 235                 240
Leu Tyr Asn Tyr Tyr Asp Asp Glu Lys Glu Lys Leu Gln Leu Val Glu
                245                 250                 255
Met Pro Leu Ala His Lys Leu Ser Ser Leu Ile Ile Leu Met Pro His
            260                 265                 270
His Val Glu Pro Leu Glu Arg Leu Glu Lys Leu Leu Thr Lys Glu Gln
        275                 280                 285
```

```
Leu Lys Ile Trp Met Gly Lys Met Gln Lys Lys Ala Val Ala Ile Ser
    290                 295                 300
Leu Pro Lys Gly Val Val Glu Val Thr His Asp Leu Gln Lys His Leu
305                 310                 315                 320
Ala Gly Leu Gly Leu Thr Glu Ala Ile Asp Lys Asn Lys Ala Asp Leu
                325                 330                 335
Ser Arg Met Ser Gly Lys Lys Asp Leu Tyr Leu Ala Ser Val Phe His
            340                 345                 350
Ala Thr Ala Phe Glu Leu Asp Thr Asp Gly Asn Pro Phe Asp Gln Asp
        355                 360                 365
Ile Tyr Gly Arg Glu Glu Leu Arg Ser Pro Lys Leu Phe Tyr Ala Asp
    370                 375                 380
His Pro Phe Ile Phe Leu Val Arg Asp Thr Gln Ser Gly Ser Leu Leu
385                 390                 395                 400
Phe Ile Gly Arg Leu Val Arg Leu Lys Gly Asp Lys Met Arg Asp Glu
                405                 410                 415
Leu
```

<210> 31
<211> 418
<212> PRT
<213> Homo sapiens

<220>
<223> Pigment epithelium-derived factor precursor
SERPINF1

<400> 31

```
Met Gln Ala Leu Val Leu Leu Leu Cys Ile Gly Ala Leu Leu Gly His
 1               5                  10                  15
Ser Ser Cys Gln Asn Pro Ala Ser Pro Pro Glu Glu Gly Ser Pro Asp
            20                  25                  30
Pro Asp Ser Thr Gly Ala Leu Val Glu Glu Glu Asp Pro Phe Phe Lys
        35                  40                  45
Val Pro Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp
    50                  55                  60
Leu Tyr Arg Val Arg Ser Ser Met Ser Pro Thr Thr Asn Val Leu Leu
65                  70                  75                  80
Ser Pro Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala
                85                  90                  95
Glu Gln Arg Thr Glu Ser Ile Ile His Arg Ala Leu Tyr Tyr Asp Leu
            100                 105                 110
Ile Ser Ser Pro Asp Ile His Gly Thr Tyr Lys Glu Leu Leu Asp Thr
        115                 120                 125
Val Thr Ala Pro Gln Lys Asn Leu Lys Ser Ala Ser Arg Ile Val Phe
    130                 135                 140
Glu Lys Lys Leu Arg Ile Lys Ser Ser Phe Val Ala Pro Leu Glu Lys
145                 150                 155                 160
Ser Tyr Gly Thr Arg Pro Arg Val Leu Thr Gly Asn Pro Arg Leu Asp
                165                 170                 175
Leu Gln Glu Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Leu
            180                 185                 190
Ala Arg Ser Thr Lys Glu Ile Pro Asp Glu Ile Ser Ile Leu Leu Leu
        195                 200                 205
Gly Val Ala His Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg
```

```
    210                 215                 220
Lys Thr Ser Leu Glu Asp Phe Tyr Leu Asp Glu Glu Arg Thr Val Arg
225                 230                 235                 240
Val Pro Met Met Ser Asp Pro Lys Ala Val Leu Arg Tyr Gly Leu Asp
                245                 250                 255
Ser Asp Leu Ser Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met
            260                 265                 270
Ser Ile Ile Phe Phe Leu Pro Leu Lys Val Thr Gln Asn Leu Thr Leu
        275                 280                 285
Ile Glu Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu
    290                 295                 300
Leu Lys Thr Val Gln Ala Val Leu Thr Val Pro Lys Leu Lys Leu Ser
305                 310                 315                 320
Tyr Glu Gly Glu Val Thr Lys Ser Leu Gln Glu Met Lys Leu Gln Ser
                325                 330                 335
Leu Phe Asp Ser Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys
            340                 345                 350
Leu Thr Gln Val Glu His Arg Ala Gly Phe Glu Trp Asn Glu Asp Gly
        355                 360                 365
Ala Gly Thr Thr Pro Ser Pro Gly Leu Gln Pro Ala His Leu Thr Phe
    370                 375                 380
Pro Leu Asp Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp
385                 390                 395                 400
Thr Asp Thr Gly Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg
                405                 410                 415
Gly Pro
```

<210> 32
<211> 375
<212> PRT
<213> Homo sapiens

<220>
<223> Maspin SERPINB5

```
<400> 32
Met Asp Ala Leu Gln Leu Ala Asn Ser Ala Phe Ala Val Asp Leu Phe
 1               5                  10                  15
Lys Gln Leu Cys Glu Lys Glu Pro Leu Gly Asn Val Leu Phe Ser Pro
            20                  25                  30
Ile Cys Leu Ser Thr Ser Leu Ser Leu Ala Gln Val Gly Ala Lys Gly
        35                  40                  45
Asp Thr Ala Asn Glu Ile Gly Gln Val Leu His Phe Glu Asn Val Lys

    50                  55                  60
Asp Ile Pro Phe Gly Phe Gln Thr Val Thr Ser Asp Val Asn Lys Leu
65                  70                  75                  80
Ser Ser Phe Tyr Ser Leu Lys Leu Ile Lys Arg Leu Tyr Val Asp Lys
                85                  90                  95
Ser Leu Asn Leu Ser Thr Glu Phe Ile Ser Ser Thr Lys Arg Pro Tyr
            100                 105                 110
Ala Lys Glu Leu Glu Thr Val Asp Phe Lys Asp Lys Leu Glu Glu Thr
        115                 120                 125
Lys Gly Gln Ile Asn Asn Ser Ile Lys Asp Leu Thr Asp Gly His Phe
    130                 135                 140
```

```
Glu Asn Ile Leu Ala Asp Asn Ser Val Asn Asp Gln Thr Lys Ile Leu
145                 150                 155                 160
Val Val Asn Ala Ala Tyr Phe Val Gly Lys Trp Met Lys Lys Phe Pro
                165                 170                 175
Glu Ser Glu Thr Lys Glu Cys Pro Phe Arg Leu Asn Lys Thr Asp Thr
            180                 185                 190
Lys Pro Val Gln Met Met Asn Met Glu Ala Thr Phe Cys Met Gly Asn
        195                 200                 205
Ile Asp Ser Ile Asn Cys Lys Ile Ile Glu Leu Pro Phe Gln Asn Lys
    210                 215                 220
His Leu Ser Met Phe Ile Leu Leu Pro Lys Asp Val Glu Asp Glu Ser
225                 230                 235                 240
Thr Gly Leu Glu Lys Ile Glu Lys Gln Leu Asn Ser Glu Ser Leu Ser
                245                 250                 255
Gln Trp Thr Asn Pro Ser Thr Met Ala Asn Ala Lys Val Lys Leu Ser
            260                 265                 270
Ile Pro Lys Phe Lys Val Glu Lys Met Ile Asp Pro Lys Ala Cys Leu
        275                 280                 285
Glu Asn Leu Gly Leu Lys His Ile Phe Ser Glu Asp Thr Ser Asp Phe
    290                 295                 300
Ser Gly Met Ser Glu Thr Lys Gly Val Ala Leu Ser Asn Val Ile His
305                 310                 315                 320
Lys Val Cys Leu Glu Ile Thr Glu Asp Gly Gly Asp Ser Ile Glu Val
                325                 330                 335
Pro Gly Ala Arg Ile Leu Gln His Lys Asp Glu Leu Asn Ala Asp His
            340                 345                 350
Pro Phe Ile Tyr Ile Ile Arg His Asn Lys Thr Arg Asn Ile Ile Phe
        355                 360                 365
Phe Gly Lys Phe Cys Ser Pro
    370                 375
```

<210> 33
<211> 418
<212> PRT
<213> Homo sapiens

<220>
<223> Collagen-binding protein 2 precursor SERPINH2

<400> 33

```
Met Arg Ser Leu Leu Leu Leu Ser Ala Phe Cys Leu Leu Glu Ala Ala
 1               5                  10                  15
Leu Ala Ala Glu Val Lys Lys Pro Ala Ala Ala Ala Ala Pro Gly Thr
            20                  25                  30
Ala Glu Lys Leu Ser Pro Lys Ala Ala Thr Leu Ala Glu Arg Ser Ala
        35                  40                  45
Gly Leu Ala Phe Ser Leu Tyr Gln Ala Met Ala Lys Asp Gln Ala Val
    50                  55                  60
Glu Asn Ile Leu Val Ser Pro Val Val Val Ala Ser Ser Leu Gly Leu
65                  70                  75                  80
Val Ser Leu Gly Gly Lys Ala Thr Thr Ala Ser Gln Ala Lys Ala Val
                85                  90                  95
Leu Ser Ala Glu Gln Leu Arg Asp Glu Glu Val His Ala Gly Leu Gly
            100                 105                 110
Glu Leu Leu Arg Ser Leu Ser Asn Ser Thr Ala Arg Asn Val Thr Trp
        115                 120                 125
```

```
Lys Leu Gly Ser Arg Leu Tyr Gly Pro Ser Ser Val Ser Phe Ala Asp
    130                 135                 140
Asp Phe Val Arg Ser Ser Lys Gln His Tyr Asn Cys Glu His Ser Lys
145                 150                 155                 160
Ile Asn Phe Arg Asp Lys Arg Ser Ala Leu Gln Ser Ile Asn Glu Trp
                165                 170                 175
Ala Ala Gln Thr Thr Asp Gly Lys Leu Pro Glu Val Thr Lys Asp Val
            180                 185                 190
Glu Arg Thr Asp Gly Ala Leu Leu Val Asn Ala Met Phe Phe Lys Pro
        195                 200                 205
His Trp Asp Glu Lys Phe His His Lys Met Val Asp Asn Arg Gly Phe
    210                 215                 220
Met Val Thr Arg Ser Tyr Thr Val Gly Val Met Met Met His Arg Thr
225                 230                 235                 240
Gly Leu Tyr Asn Tyr Tyr Asp Asp Glu Lys Glu Lys Leu Gln Ile Val
                245                 250                 255
Glu Met Pro Leu Ala His Lys Leu Ser Ser Leu Ile Ile Leu Met Pro
            260                 265                 270
His His Val Glu Pro Leu Glu Arg Leu Glu Lys Leu Leu Thr Lys Glu
        275                 280                 285
Gln Leu Lys Ile Trp Met Gly Lys Met Gln Lys Lys Ala Val Ala Ile
    290                 295                 300
Ser Leu Pro Lys Gly Val Val Glu Val Thr His Asp Leu Gln Lys His
305                 310                 315                 320
Leu Ala Gly Leu Gly Leu Thr Glu Ala Ile Asp Lys Asn Lys Ala Asp
                325                 330                 335
Leu Ser Arg Met Ser Gly Lys Lys Asp Leu Tyr Leu Ala Ser Val Phe
            340                 345                 350
His Ala Thr Ala Phe Glu Leu Asp Thr Asp Gly Asn Pro Phe Asp Gln
        355                 360                 365
Asp Ile Tyr Gly Arg Glu Glu Leu Arg Ser Pro Lys Leu Phe Tyr Ala
    370                 375                 380
Asp His Pro Phe Ile Phe Leu Val Arg Asp Thr Gln Ser Gly Ser Leu
385                 390                 395                 400
Leu Phe Ile Gly Arg Leu Val Arg Pro Lys Gly Asp Lys Met Arg Asp
                405                 410                 415
Glu Leu
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<210> 34
<211> 415
<212> PRT
<213> Homo sapiens

<220>
<223> Thyroxine-binding globulin precursor SERPINA7

<400> 34

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Met Ser Pro Phe Leu Tyr Leu Val Leu Leu Val Leu Gly Leu His Ala
 1               5                  10                  15
Thr Ile His Cys Ala Ser Pro Glu Gly Lys Val Thr Ala Cys His Ser
            20                  25                  30
Ser Gln Pro Asn Ala Thr Leu Tyr Lys Met Ser Ser Ile Asn Ala Asp
        35                  40                  45
Phe Ala Phe Asn Leu Tyr Arg Arg Phe Thr Val Glu Thr Pro Asp Lys
    50                  55                  60
```

```
Asn Ile Phe Phe Ser Pro Val Ser Ile Ser Ala Ala Leu Val Met Leu
65                  70                  75                  80
Ser Phe Gly Ala Cys Cys Ser Thr Gln Thr Glu Ile Val Glu Thr Leu
                85                  90                  95
Gly Phe Asn Leu Thr Asp Thr Pro Met Val Glu Ile Gln His Gly Phe
            100                 105                 110
Gln His Leu Ile Cys Ser Leu Asn Phe Pro Lys Lys Glu Leu Glu Leu
        115                 120                 125
Gln Ile Gly Asn Ala Leu Phe Ile Gly Lys His Leu Lys Pro Leu Ala
    130                 135                 140
Lys Phe Leu Asn Asp Val Lys Thr Leu Tyr Glu Thr Glu Val Phe Ser
145                 150                 155                 160
Thr Asp Phe Ser Asn Ile Ser Ala Ala Lys Gln Glu Ile Asn Ser His
                165                 170                 175
Val Glu Met Gln Thr Lys Gly Lys Val Val Gly Leu Ile Gln Asp Leu
            180                 185                 190
Lys Pro Asn Thr Ile Met Val Leu Val Asn Tyr Ile His Phe Lys Ala
        195                 200                 205
Gln Trp Ala Asn Pro Phe Asp Pro Ser Lys Thr Glu Asp Ser Ser Ser
    210                 215                 220
Phe Leu Ile Asp Lys Thr Thr Thr Val Gln Val Pro Met Met His Gln
225                 230                 235                 240
Met Glu Gln Tyr Tyr His Leu Val Asp Met Glu Leu Asn Cys Thr Val
                245                 250                 255
Leu Gln Met Asp Tyr Ser Lys Asn Ala Leu Ala Leu Phe Val Leu Pro
            260                 265                 270
Lys Glu Gly Gln Met Glu Ser Val Glu Ala Ala Met Ser Ser Lys Thr
        275                 280                 285
Leu Lys Lys Trp Asn Arg Leu Leu Gln Lys Gly Trp Val Asp Leu Phe
    290                 295                 300
Val Pro Lys Phe Ser Ile Ser Ala Thr Tyr Asp Leu Gly Ala Thr Leu
305                 310                 315                 320
Leu Lys Met Gly Ile Gln His Ala Tyr Ser Glu Asn Ala Asp Phe Ser
                325                 330                 335
Gly Leu Thr Glu Asp Asn Gly Leu Lys Leu Ser Asn Ala Ala His Lys
            340                 345                 350
Ala Val Leu His Ile Gly Glu Lys Gly Thr Glu Ala Ala Ala Val Pro
        355                 360                 365
Glu Val Glu Leu Ser Asp Gln Pro Glu Asn Thr Phe Leu His Pro Ile
    370                 375                 380
Ile Gln Ile Asp Arg Ser Phe Met Leu Leu Ile Leu Glu Arg Ser Thr
385                 390                 395                 400
Arg Ser Ile Leu Phe Leu Gly Lys Val Val Asn Pro Thr Glu Ala
                405                 410                 415
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<210> 35
<211> 417
<212> PRT
<213> Homo sapiens

<220>
<223> Germinal center B-cell expressed transcript 1
protein
SERPINA9

<400> 35

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Met Ala Ser Tyr Leu Tyr Gly Val Leu Phe Ala Val Gly Leu Cys Ala
 1               5                  10                  15
Pro Ile Tyr Cys Val Ser Pro Ala Asn Ala Pro Ser Ala Tyr Pro Arg
            20                  25                  30
Pro Ser Ser Thr Lys Ser Thr Pro Ala Ser Gln Val Tyr Ser Leu Asn
        35                  40                  45
Thr Asp Phe Ala Phe Arg Leu Tyr Arg Arg Leu Val Leu Glu Thr Pro
    50                  55                  60
Ser Gln Asn Ile Phe Phe Ser Pro Val Ser Val Ser Thr Ser Leu Ala
65                  70                  75                  80
Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr Gln Ile Leu Gln
                85                  90                  95
Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser Ala Ile His Gln
            100                 105                 110
Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro Ser Lys Asp Leu
        115                 120                 125
Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys Glu Leu Gln Leu
    130                 135                 140
Gln Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr Glu Ala Glu Val
145                 150                 155                 160
Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln Ala Arg Ile Asn
                165                 170                 175
Ser His Val Lys Lys Lys Thr Gln Gly Lys Val Val Asp Ile Ile Gln
            180                 185                 190
Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn His Ile Phe Phe
        195                 200                 205
Lys Ala Lys Trp Glu Lys Pro Phe His Pro Glu Tyr Thr Arg Lys Asn
    210                 215                 220
Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val His Val Pro Met Met
225                 230                 235                 240
His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr Glu Leu Asn Cys
                245                 250                 255
Phe Val Leu Gln Met Asp Tyr Lys Gly Asp Ala Val Ala Phe Phe Val
            260                 265                 270
Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln Ala Leu Ser Ala
        275                 280                 285
Arg Thr Leu Arg Lys Trp Ser His Ser Leu Gln Lys Arg Trp Ile Glu
    290                 295                 300
Val Phe Ile Pro Arg Phe Ser Ile Ser Ala Ser Tyr Asn Leu Glu Thr
305                 310                 315                 320
Ile Leu Pro Lys Met Gly Ile Gln Asn Ala Phe Asp Lys Asn Ala Asp
                325                 330                 335
Phe Ser Gly Ile Ala Lys Arg Asp Ser Leu Gln Val Ser Lys Ala Thr
            340                 345                 350
His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr Glu Ala Thr Ala
        355                 360                 365
Ala Thr Thr Thr Lys Phe Ile Val Arg Ser Lys Asp Gly Pro Ser Tyr
    370                 375                 380
Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met Ile Thr Asn Lys
385                 390                 395                 400
Ala Thr Asp Gly Ile Leu Phe Leu Gly Lys Val Glu Asn Pro Thr Lys
                405                 410                 415
Ser
```

<210> 36

<211> 414
<212> PRT
<213> Homo sapiens

<220>
<223> Vaspin SERPINA12

<400> 36
Met Asn Pro Thr Leu Gly Leu Ala Ile Phe Leu Ala Val Leu Leu Thr
1 5 10 15
Val Lys Gly Leu Leu Lys Pro Ser Phe Ser Pro Arg Asn Tyr Lys Ala
20 25 30
Leu Ser Glu Val Gln Gly Trp Lys Gln Arg Met Ala Ala Lys Glu Leu
35 40 45
Ala Arg Gln Asn Met Asp Leu Gly Phe Lys Leu Leu Lys Lys Leu Ala
50 55 60
Phe Tyr Asn Pro Gly Arg Asn Ile Phe Leu Ser Pro Leu Ser Ile Ser
65 70 75 80
Thr Ala Phe Ser Met Leu Cys Leu Gly Ala Gln Asp Ser Thr Leu Asp
85 90 95
Glu Ile Lys Gln Gly Phe Asn Phe Arg Lys Met Pro Glu Lys Asp Leu
100 105 110
His Glu Gly Phe His Tyr Ile Ile His Glu Leu Thr Gln Lys Thr Gln
115 120 125
Asp Leu Lys Leu Ser Ile Gly Asn Thr Leu Phe Ile Asp Gln Arg Leu
130 135 140
Gln Pro Gln Arg Lys Phe Leu Glu Asp Ala Lys Asn Phe Tyr Ser Ala
145 150 155 160
Glu Thr Ile Leu Thr Asn Phe Gln Asn Leu Glu Met Ala Gln Lys Gln
165 170 175
Ile Asn Asp Phe Ile Ser Gln Lys Thr His Gly Lys Ile Asn Asn Leu
180 185 190
Ile Glu Asn Ile Asp Pro Gly Thr Val Met Leu Leu Ala Asn Tyr Ile
195 200 205
Phe Phe Arg Ala Arg Trp Lys His Glu Phe Asp Pro Asn Val Thr Lys
210 215 220
Glu Glu Asp Phe Phe Leu Glu Lys Asn Ser Ser Val Lys Val Pro Met
225 230 235 240
Met Phe Arg Ser Gly Ile Tyr Gln Val Gly Tyr Asp Asp Lys Leu Ser
245 250 255
Cys Thr Ile Leu Glu Ile Pro Tyr Gln Lys Asn Ile Thr Ala Ile Phe
260 265 270
Ile Leu Pro Asp Glu Gly Lys Leu Lys His Leu Glu Lys Gly Leu Gln
275 280 285
Val Asp Thr Phe Ser Arg Trp Lys Thr Leu Leu Ser Arg Arg Val Val
290 295 300
Asp Val Ser Val Pro Arg Leu His Met Thr Gly Thr Phe Asp Leu Lys
305 310 315 320
Lys Thr Leu Ser Tyr Ile Gly Val Ser Lys Ile Phe Glu Glu His Gly
325 330 335
Asp Leu Thr Lys Ile Ala Pro His Arg Ser Leu Lys Val Gly Glu Ala
340 345 350
Val His Lys Ala Glu Leu Lys Met Asp Glu Arg Gly Thr Glu Gly Ala
355 360 365
Ala Gly Thr Gly Ala Gln Thr Leu Pro Met Glu Thr Pro Leu Val Val
370 375 380
Lys Ile Asp Lys Pro Tyr Leu Leu Leu Ile Tyr Ser Glu Lys Ile Pro

385 390 395 400
Ser Val Leu Phe Leu Gly Lys Ile Val Asn Pro Ile Gly Lys
405 410

<210> 37
<211> 422
<212> PRT
<213> Homo sapiens

<220>
<223> Serpin A11 precursor SERPINA11

<400> 37
Met Gly Pro Ala Trp Leu Trp Leu Leu Gly Thr Gly Ile Leu Ala Ser
1 5 10 15
Val His Cys Gln Pro Leu Leu Ala His Gly Asp Lys Ser Leu Gln Gly
20 25 30
Pro Gln Pro Pro Arg His Gln Leu Ser Glu Pro Ala Pro Ala Tyr His
35 40 45
Arg Ile Thr Pro Thr Ile Thr Asn Phe Ala Leu Arg Leu Tyr Lys Glu
50 55 60
Leu Ala Ala Asp Ala Pro Gly Asn Ile Phe Phe Ser Pro Val Ser Ile
65 70 75 80
Ser Thr Thr Leu Ala Leu Leu Ser Leu Gly Ala Gln Ala Asn Thr Ser
85 90 95
Ala Leu Ile Leu Glu Gly Leu Gly Phe Asn Leu Thr Glu Thr Pro Glu
100 105 110
Ala Asp Ile His Gln Gly Phe Arg Ser Leu Leu His Thr Leu Ala Leu
115 120 125
Pro Ser Pro Lys Leu Glu Leu Lys Val Gly Asn Ser Leu Phe Leu Asp
130 135 140
Lys Arg Leu Lys Pro Arg Gln His Tyr Leu Asp Ser Ile Lys Glu Leu
145 150 155 160
Tyr Gly Ala Phe Ala Phe Ser Ala Asn Phe Thr Asp Ser Val Thr Thr
165 170 175
Gly Arg Gln Ile Asn Asp Tyr Leu Arg Arg Gln Thr Tyr Gly Gln Val
180 185 190
Val Asp Cys Leu Pro Glu Phe Ser Gln Asp Thr Phe Met Val Leu Ala
195 200 205
Asn Tyr Ile Phe Phe Lys Ala Lys Trp Lys His Pro Phe Ser Arg Tyr
210 215 220
Gln Thr Gln Lys Gln Glu Ser Phe Phe Val Asp Glu Arg Thr Ser Leu
225 230 235 240
Gln Val Pro Met Met His Gln Lys Glu Met His Arg Phe Leu Tyr Asp
245 250 255
Gln Asp Leu Ala Cys Thr Val Leu Gln Ile Glu Tyr Arg Gly Asn Ala
260 265 270
Leu Ala Leu Leu Val Leu Pro Asp Pro Gly Lys Met Lys Gln Val Glu
275 280 285
Ala Ala Leu Gln Pro Gln Thr Leu Arg Lys Trp Gly Gln Leu Leu Leu
290 295 300
Pro Ser Leu Leu Asp Leu His Leu Pro Arg Phe Ser Ile Ser Gly Thr
305 310 315 320
Tyr Asn Leu Glu Asp Ile Leu Pro Gln Ile Gly Leu Thr Asn Ile Leu
325 330 335
Asn Leu Glu Ala Asp Phe Ser Gly Val Thr Gly Gln Leu Asn Lys Thr

```
            340                 345                 350
Ile Ser Lys Val Ser His Lys Ala Met Val Asp Met Ser Glu Lys Gly
        355                 360                 365
Thr Glu Ala Gly Ala Ala Ser Gly Leu Leu Ser Gln Pro Pro Ser Leu
    370                 375                 380
Asn Thr Met Ser Asp Pro His Ala His Phe Asn Arg Pro Phe Leu Leu
385                 390                 395                 400
Leu Leu Trp Glu Val Thr Thr Gln Ser Leu Leu Phe Leu Gly Lys Val
                405                 410                 415
Val Asn Pro Val Ala Gly
            420
```

<210> 38
<211> 307
<212> PRT
<213> Homo sapiens

<220>
<223> Serpin A13 precursor SERPINA13

<400> 38

```
Met Glu Ala Ser Arg Trp Trp Leu Leu Val Thr Val Leu Met Ala Gly
 1               5                  10                  15
Ala His Cys Val Ala Leu Val Asp Gln Glu Ala Ser Asp Leu Ile His
            20                  25                  30
Ser Gly Pro Gln Asp Ser Ser Pro Gly Pro Ala Leu Pro Cys His Lys
        35                  40                  45
Ile Ser Val Ser Asn Ile Asp Phe Ala Phe Lys Leu Tyr Arg Gln Leu
    50                  55                  60
Ala Leu Asn Ala Pro Gly Glu Asn Ile Leu Phe Phe Pro Val Ser Ile
65                  70                  75                  80
Ser Leu Ala Leu Ala Met Leu Ser Trp Gly Ala Pro Val Ala Ser Arg
                85                  90                  95

Thr Gln Leu Leu Glu Gly Leu Gly Phe Thr Leu Thr Val Val Pro Glu
            100                 105                 110
Glu Glu Ile Gln Glu Gly Phe Trp Asp Leu Leu Ile Arg Leu Arg Gly
        115                 120                 125
Gln Gly Pro Arg Leu Leu Leu Thr Met Asp Gln Arg Arg Phe Ser Gly
    130                 135                 140
Leu Gly Ala Arg Ala Asn Gln Ser Leu Glu Glu Ala Gln Lys His Ile
145                 150                 155                 160
Asp Glu Tyr Thr Glu Gln Gln Thr Gln Gly Lys Leu Gly Ala Trp Glu
                165                 170                 175
Lys Asp Leu Gly Ser Glu Thr Thr Ala Val Leu Val Asn His Met Leu
            180                 185                 190
Leu Arg Ala Glu Trp Met Lys Pro Phe Asp Ser His Ala Thr Ser Pro
        195                 200                 205
Lys Glu Phe Phe Val Asp Glu His Ser Ala Val Trp Val Pro Met Met
    210                 215                 220
Lys Glu Lys Ala Ser His Arg Phe Leu His Asp Arg Glu Leu Gln Cys
225                 230                 235                 240
Ser Val Leu Arg Met Asp His Ala Gly Asn Thr Thr Thr Phe Phe Ile
                245                 250                 255
Phe Pro Asn Arg Gly Lys Met Arg His Leu Glu Asp Ala Leu Leu Pro
            260                 265                 270
```

```
Glu Thr Leu Ile Lys Trp Asp Ser Leu Leu Arg Thr Arg Glu Leu Asp
        275                 280                 285
Phe His Phe Pro Lys Phe Ser Ile Ser Arg Thr Cys Arg Leu Glu Met
    290                 295                 300
Leu Leu Pro
305
```

<210> 39
<211> 934
<212> DNA
<213> Homo sapiens

<220>
<223> granzyme B

<400> 39
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tgagaagatg caaccaatcc tgcttctgct ggccttcctc ctgctgccca gggcagatgc 60
aggggagatc atcgggggac atgaggccaa gccccactcc cgcccctaca tggcttatct 120
tatgatctgg gatcagaagt ctctgaagag gtgcggtggc ttcctgatac aagacgactt 180
cgtgctgaca gctgctcact gttggggaag ctccataaat gtcaccttgg gggcccacaa 240
tatcaaagaa caggagccga cccagcagtt tatccctgtg aaaagaccca tcccccatcc 300
agcctataat cctaagaact tctccaacga catcatgcta ctgcagctgg agagaaaggc 360
caagcggacc agagctgtgc agcccctcag gctacctagc aacaaggccc aggtgaagcc 420
agggcagaca tgcagtgtgg ccggctgggg gcagacggcc cccctgggaa aacactcaca 480
cacactacaa gaggtgaaga tgacagtgca ggaagatcga aagtgcgaat ctgacttacg 540
ccattattac gacagtacca ttgagttgtg cgtgggggac ccagagatta aaaagacttc 600
ctttaagggg gactctggag gccctcttgt gtgtaacaag gtggcccagg gcattgtctc 660
ctatggacga aacaatggca tgcctccacg agcctgcacc aaagtctcaa gctttgtaca 720
ctggataaag aaaaccatga aacgctacta actacaggaa gcaaactaag ccccgctgt 780
aatgaaacac cttctctgga gccaagtcca gatttacact gggagaggtg ccagcaactg 840
aataaatacc tctcccagtg taaatctgga gccaagtcca gatttacact gggagaggtg 900
ccagcaactg aataaatacc tcttagctga gtgg                          934
```

<210> 40
<211> 247
<212> PRT
<213> Homo sapiens

<220>
<223> granzyme B

<400> 40
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Met Gln Pro Ile Leu Leu Leu Leu Ala Phe Leu Leu Leu Pro Arg Ala
 1               5                  10                  15
Asp Ala Gly Glu Ile Ile Gly Gly His Glu Ala Lys Pro His Ser Arg
            20                  25                  30
Pro Tyr Met Ala Tyr Leu Met Ile Trp Asp Gln Lys Ser Leu Lys Arg
        35                  40                  45
Cys Gly Gly Phe Leu Ile Gln Asp Asp Phe Val Leu Thr Ala Ala His
    50                  55                  60
Cys Trp Gly Ser Ser Ile Asn Val Thr Leu Gly Ala His Asn Ile Lys
65                  70                  75                  80
Glu Gln Glu Pro Thr Gln Gln Phe Ile Pro Val Lys Arg Pro Ile Pro
                85                  90                  95
His Pro Ala Tyr Asn Pro Lys Asn Phe Ser Asn Asp Ile Met Leu Leu
            100                 105                 110
```

```
Gln Leu Glu Arg Lys Ala Lys Arg Thr Arg Ala Val Gln Pro Leu Arg
        115                 120                 125
Leu Pro Ser Asn Lys Ala Gln Val Lys Pro Gly Gln Thr Cys Ser Val
    130                 135                 140
Ala Gly Trp Gly Gln Thr Ala Pro Leu Gly Lys His Ser His Thr Leu
145                 150                 155                 160
Gln Glu Val Lys Met Thr Val Gln Glu Asp Arg Lys Cys Glu Ser Asp
                165                 170                 175
Leu Arg His Tyr Tyr Asp Ser Thr Ile Glu Leu Cys Val Gly Asp Pro
            180                 185                 190
Glu Ile Lys Lys Thr Ser Phe Lys Gly Asp Ser Gly Gly Pro Leu Val
        195                 200                 205
Cys Asn Lys Val Ala Gln Gly Ile Val Ser Tyr Gly Arg Asn Asn Gly
    210                 215                 220
Met Pro Pro Arg Ala Cys Thr Lys Val Ser Ser Phe Val His Trp Ile
225                 230                 235                 240
Lys Lys Thr Met Lys Arg Tyr
                245
```

<210> 41
<211> 1165
<212> DNA
<213> Homo sapiens

<220>
<223> Testisin transcript variant 1

<400> 41
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gctgggagta gagggcagag ctcccacccc gccccgcccc cagggggcgc cccgggcccg 60
gcgcgagagg aggcagaggg ggcgtcaggc cgcgggagag gaggccatgg gcgcgcgcgg 120
ggcgctgctg ctggcgctgc tgctggctcg ggctggactc aggaagccgg agtcgcagga 180
ggcggcgccg ttatcaggac catgcggccg acgggtcatc acgtcgcgca tcgtgggtgg 240
agaggacgcc gaactcgggc gttggccgtg gcaggggagc ctgcgcctgt gggattccca 300
cgtatgcgga gtgagcctgc tcagccaccg ctgggcactc acggcggcgc actgctttga 360
aacctatagt gaccttagtg atccctccgg gtggatggtc cagtttggcc agctgacttc 420
catgccatcc ttctggagcc tgcaggccta ctacacccgt tacttcgtat cgaatatcta 480
tctgagccct cgctacctgg ggaattcacc ctatgacatt gccttggtga agctgtctgc 540
acctgtcacc tacactaaac acatccagcc catctgtctc caggcctcca catttgagtt 600
tgagaaccgg acagactgct gggtgactgg ctgggggtac atcaaagagg atgaggcact 660
gccatctccc cacaccctcc aggaagttca ggtcgccatc ataaacaact ctatgtgcaa 720
ccacctcttc ctcaagtaca gtttccgcaa ggacatcttt ggagacatgg tttgtgctgg 780
caatgcccaa ggcgggaagg atgcctgctt cggtgactca ggtggaccct tggcctgtaa 840
caagaatgga ctgtggtatc agattggagt cgtgagctgg ggagtgggct gtggtcggcc 900
caatcggccc ggtgtctaca ccaatatcag ccaccacttt gagtggatcc agaagctgat 960
ggcccagagt ggcatgtccc agccagaccc ctcctggccg ctactctttt tccctcttct 1020
ctgggctctc ccactcctgg ggccggtctg agcctacctg agcccatgca gcctggggcc 1080
actgccaagt caggccctgg ttctcttctg tcttgtttgg taataaacac attccagttg 1140
atgccttgca gggcattctt caaaa                                      1165
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<210> 42
<211> 314
<212> PRT
<213> Homo sapiens

<220>

<223> Testisin isoform 1

<400> 42
Met Gly Ala Arg Gly Ala Leu Leu Leu Ala Leu Leu Leu Ala Arg Ala
 1   5   10   15
Gly Leu Arg Lys Pro Glu Ser Gln Glu Ala Ala Pro Leu Ser Gly Pro
            20   25   30
Cys Gly Arg Arg Val Ile Thr Ser Arg Ile Val Gly Gly Glu Asp Ala
        35   40   45
Glu Leu Gly Arg Trp Pro Trp Gln Gly Ser Leu Arg Leu Trp Asp Ser
    50   55   60
His Val Cys Gly Val Ser Leu Leu Ser His Arg Trp Ala Leu Thr Ala
65   70   75   80
Ala His Cys Phe Glu Thr Tyr Ser Asp Leu Ser Asp Pro Ser Gly Trp
                85   90   95
Met Val Gln Phe Gly Gln Leu Thr Ser Met Pro Ser Phe Trp Ser Leu
            100   105   110
Gln Ala Tyr Tyr Thr Arg Tyr Phe Val Ser Asn Ile Tyr Leu Ser Pro
        115   120   125
Arg Tyr Leu Gly Asn Ser Pro Tyr Asp Ile Ala Leu Val Lys Leu Ser
    130   135   140
Ala Pro Val Thr Tyr Thr Lys His Ile Gln Pro Ile Cys Leu Gln Ala
145   150   155   160
Ser Thr Phe Glu Phe Glu Asn Arg Thr Asp Cys Trp Val Thr Gly Trp
                165   170   175
Gly Tyr Ile Lys Glu Asp Glu Ala Leu Pro Ser Pro His Thr Leu Gln
            180   185   190
Glu Val Gln Val Ala Ile Ile Asn Asn Ser Met Cys Asn His Leu Phe
        195   200   205
Leu Lys Tyr Ser Phe Arg Lys Asp Ile Phe Gly Asp Met Val Cys Ala
    210   215   220
Gly Asn Ala Gln Gly Gly Lys Asp Ala Cys Phe Gly Asp Ser Gly Gly
225   230   235   240
Pro Leu Ala Cys Asn Lys Asn Gly Leu Trp Tyr Gln Ile Gly Val Val
                245   250   255
Ser Trp Gly Val Gly Cys Gly Arg Pro Asn Arg Pro Gly Val Tyr Thr
            260   265   270
Asn Ile Ser His His Phe Glu Trp Ile Gln Lys Leu Met Ala Gln Ser
        275   280   285
Gly Met Ser Gln Pro Asp Pro Ser Trp Pro Leu Leu Phe Phe Pro Leu
    290   295   300
Leu Trp Ala Leu Pro Leu Leu Gly Pro Val
305   310

<210> 43
<211> 1159
<212> DNA
<213> Homo sapiens

<220>
<223> Testisin transcript variant 2

<400> 43
gctgggagta gagggcagag ctcccacccc gccccgcccc caggggcgc cccgggcccg 60
gcgcgagagg aggcagaggg ggcgtcaggc cgcgggagag gaggccatgg gcgcgcgcgg 120
ggcgctgctg ctggcgctgc tgctggctcg ggctggactc aggaagccgg agtcgcagga 180

```
ggcggcgccg ttatcaggac catgcggccg acgggtcatc acgtcgcgca tcgtgggtgg 240
agaggacgcc gaactcgggc gttggccgtg gcaggggagc ctgcgcctgt gggattccca 300
cgtatgcgga gtgagcctgc tcagccaccg ctgggcactc acggcggcgc actgctttga 360
aactgacctt agtgatccct ccgggtggat ggtccagttt ggccagctga cttccatgcc 420
atccttctgg agcctgcagg cctactacac ccgttacttc gtatcgaata tctatctgag 480
ccctcgctac ctggggaatt caccctatga cattgccttg gtgaagctgt ctgcacctgt 540
cacctacact aaacacatcc agcccatctg tctccaggcc tccacatttg agtttgagaa 600
ccggacagac tgctgggtga ctggctgggg gtacatcaaa gaggatgagg cactgccatc 660
tccccacacc ctccaggaag ttcaggtcgc catcataaac aactctatgt gcaaccacct 720
cttcctcaag tacagtttcc gcaaggacat ctttggagac atggtttgtg ctggcaatgc 780
ccaaggcggg aaggatgcct gcttcggtga ctcaggtgga cccttggcct gtaacaagaa 840
tggactgtgg tatcagattg gagtcgtgag ctggggagtg ggctgtggtc ggcccaatcg 900
gcccggtgtc tacaccaata tcagccacca ctttgagtgg atccagaagc tgatggccca 960
gagtggcatg tcccagccag acccctcctg gccgctactc tttttccctc ttctctgggc 1020
tctcccactc ctggggccgg tctgagccta cctgagccca tgcagcctgg ggccactgcc 1080
aagtcaggcc ctggttctct tctgtcttgt ttggtaataa acacattcca gttgatgcct 1140
tgcagggcat tcttcaaaa                                           1159

<210> 44
<211> 312
<212> PRT
<213> Homo sapiens

<220>
<223> Testisin isoform 2

<400> 44
Met Gly Ala Arg Gly Ala Leu Leu Leu Ala Leu Leu Leu Ala Arg Ala
 1               5                  10                  15
Gly Leu Arg Lys Pro Glu Ser Gln Glu Ala Ala Pro Leu Ser Gly Pro
            20                  25                  30
Cys Gly Arg Arg Val Ile Thr Ser Arg Ile Val Gly Gly Glu Asp Ala
        35                  40                  45
Glu Leu Gly Arg Trp Pro Trp Gln Gly Ser Leu Arg Leu Trp Asp Ser
    50                  55                  60
His Val Cys Gly Val Ser Leu Leu Ser His Arg Trp Ala Leu Thr Ala
65                  70                  75                  80
Ala His Cys Phe Glu Thr Asp Leu Ser Asp Pro Ser Gly Trp Met Val
                85                  90                  95
Gln Phe Gly Gln Leu Thr Ser Met Pro Ser Phe Trp Ser Leu Gln Ala
            100                 105                 110
Tyr Tyr Thr Arg Tyr Phe Val Ser Asn Ile Tyr Leu Ser Pro Arg Tyr
        115                 120                 125
Leu Gly Asn Ser Pro Tyr Asp Ile Ala Leu Val Lys Leu Ser Ala Pro
    130                 135                 140
Val Thr Tyr Thr Lys His Ile Gln Pro Ile Cys Leu Gln Ala Ser Thr
145                 150                 155                 160
Phe Glu Phe Glu Asn Arg Thr Asp Cys Trp Val Thr Gly Trp Gly Tyr
                165                 170                 175
Ile Lys Glu Asp Glu Ala Leu Pro Ser Pro His Thr Leu Gln Glu Val
            180                 185                 190
Gln Val Ala Ile Ile Asn Asn Ser Met Cys Asn His Leu Phe Leu Lys
        195                 200                 205
Tyr Ser Phe Arg Lys Asp Ile Phe Gly Asp Met Val Cys Ala Gly Asn
    210                 215                 220
Ala Gln Gly Gly Lys Asp Ala Cys Phe Gly Asp Ser Gly Gly Pro Leu
225                 230                 235                 240
```

```
Ala Cys Asn Lys Asn Gly Leu Trp Tyr Gln Ile Gly Val Val Ser Trp
                245                 250                 255
Gly Val Gly Cys Gly Arg Pro Asn Arg Pro Gly Val Tyr Thr Asn Ile
            260                 265                 270
Ser His His Phe Glu Trp Ile Gln Lys Leu Met Ala Gln Ser Gly Met
        275                 280                 285
Ser Gln Pro Asp Pro Ser Trp Pro Leu Leu Phe Phe Pro Leu Leu Trp
    290                 295                 300
Ala Leu Pro Leu Leu Gly Pro Val
305                 310
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<210> 45
<211> 1135
<212> DNA
<213> Homo sapiens

<220>
<223> Testisin transcript variant 3

<400> 45
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ggcgctgctg ctggcgctgc tgctggctcg ggctggactc aggaagccgg agtcgcagga 180
ggcggcgccg ttatcaggac catgcggccg acgggtcatc acgtcgcgca tcgtgggtgg 240
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cgtatgcgga gtgagcctgc tcagccaccg ctgggcactc acggcggcgc actgctttga 360
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catgccatcc ttctggagcc tgcaggccta ctacacccgt tacttcgtat cgaatatcta 480
tctgagccct cgctacctgg ggaattcacc ctatgacatt gccttggtga agctgtctgc 540
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gccatctccc cacaccctcc aggaagttca ggtcgccatc ataaacaact ctatgtgcaa 720
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ataaacacat tccagttgat gccttgcagg gcattcttca aaaaaaaaaa aaaaa      1135
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<210> 46
<211> 300
<212> PRT
<213> Homo sapiens

<220>
<223> Testisin isoform 3

<400> 46
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 1               5                  10                  15
Gly Leu Arg Lys Pro Glu Ser Gln Glu Ala Ala Pro Leu Ser Gly Pro
            20                  25                  30
Cys Gly Arg Arg Val Ile Thr Ser Arg Ile Val Gly Gly Glu Asp Ala
        35                  40                  45
Glu Leu Gly Arg Trp Pro Trp Gln Gly Ser Leu Arg Leu Trp Asp Ser
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    50                  55                  60
His Val Cys Gly Val Ser Leu Leu Ser His Arg Trp Ala Leu Thr Ala
65                  70                  75                  80
Ala His Cys Phe Glu Thr Tyr Ser Asp Leu Ser Asp Pro Ser Gly Trp
                85                  90                  95
Met Val Gln Phe Gly Gln Leu Thr Ser Met Pro Ser Phe Trp Ser Leu
            100                 105                 110
Gln Ala Tyr Tyr Thr Arg Tyr Phe Val Ser Asn Ile Tyr Leu Ser Pro
        115                 120                 125
Arg Tyr Leu Gly Asn Ser Pro Tyr Asp Ile Ala Leu Val Lys Leu Ser
    130                 135                 140
Ala Pro Val Thr Tyr Thr Lys His Ile Gln Pro Ile Cys Leu Gln Ala
145                 150                 155                 160
Ser Thr Phe Glu Phe Glu Asn Arg Thr Asp Cys Trp Val Thr Gly Trp
                165                 170                 175
Gly Tyr Ile Lys Glu Asp Glu Ala Leu Pro Ser Pro His Thr Leu Gln
            180                 185                 190
Glu Val Gln Val Ala Ile Ile Asn Asn Ser Met Cys Asn His Leu Phe
        195                 200                 205
Leu Lys Tyr Ser Phe Arg Lys Asp Ile Phe Gly Asp Met Gly Asp Ser
    210                 215                 220
Gly Gly Pro Leu Ala Cys Asn Lys Asn Gly Leu Trp Tyr Gln Ile Gly
225                 230                 235                 240
Val Val Ser Trp Gly Val Gly Cys Gly Arg Pro Asn Arg Pro Gly Val
                245                 250                 255
Tyr Thr Asn Ile Ser His His Phe Glu Trp Ile Gln Lys Leu Met Ala
            260                 265                 270
Gln Ser Gly Met Ser Gln Pro Asp Pro Ser Trp Pro Leu Leu Phe Phe
        275                 280                 285
Pro Leu Leu Trp Ala Leu Pro Leu Leu Gly Pro Val
    290                 295                 300
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<210> 47
<211> 1194
<212> DNA
<213> Homo sapiens

<220>
<223> trypstase beta 1

<400> 47

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ccaggccctg cagcgagtgg gcatcgtcgg gggtcaggag gcccccagga gcaagtggcc 180
ctggcaggtg agcctgagag tccacggccc atactggatg cacttctgcg ggggctccct 240
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ggtcagcagg atcatcgtgc acccacagtt ctacaccgcc cagatcggag cggacatcgc 420
cctgctggag ctggaggagc cggtgaacgt ctccagccac gtccacacgg tcaccctgcc 480
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catcgtccgt gacgacatgc tgtgtgccgg gaacacccgg agggactcat gccagggcga 720
ctccggaggg cccctggtgt gcaaggtgaa tggcacctgg ctgcaggcgg gcgtggtcag 780
ctggggcgag ggctgtgccc agcccaaccg gcctggcatc tacacccgtg tcacctacta 840
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tgctctcttc tgagcccctt cccctgtcct gaggaccctt ccctatcctg agccccccttc 1080
cctgtcctaa gcctgacgcc tgcaccgggc cctccagccc tcccctgccc agatagctgg 1140
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<210> 48
<211> 275
<212> PRT
<213> Homo sapiens

<220>
<223> trypstase beta 1

<400> 48
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Tyr Ala Ala Pro Ala Pro Gly Gln Ala Leu Gln Arg Val Gly Ile Val
            20   25   30
Gly Gly Gln Glu Ala Pro Arg Ser Lys Trp Pro Trp Gln Val Ser Leu
        35   40   45
Arg Val His Gly Pro Tyr Trp Met His Phe Cys Gly Gly Ser Leu Ile
    50   55   60
His Pro Gln Trp Val Leu Thr Ala Ala His Cys Val Gly Pro Asp Val
65   70   75   80
Lys Asp Leu Ala Ala Leu Arg Val Gln Leu Arg Glu Gln His Leu Tyr
                85   90   95
Tyr Gln Asp Gln Leu Leu Pro Val Ser Arg Ile Ile Val His Pro Gln
            100   105   110
Phe Tyr Thr Ala Gln Ile Gly Ala Asp Ile Ala Leu Leu Glu Leu Glu
        115   120   125
Glu Pro Val Asn Val Ser Ser His Val His Thr Val Thr Leu Pro Pro
    130   135   140
Ala Ser Glu Thr Phe Pro Pro Gly Met Pro Cys Trp Val Thr Gly Trp
145   150   155   160
Gly Asp Val Asp Asn Asp Glu Arg Leu Pro Pro Pro Phe Pro Leu Lys
                165   170   175
Gln Val Lys Val Pro Ile Met Glu Asn His Ile Cys Asp Ala Lys Tyr
            180   185   190
His Leu Gly Ala Tyr Thr Gly Asp Asp Val Arg Ile Val Arg Asp Asp
        195   200   205
Met Leu Cys Ala Gly Asn Thr Arg Arg Asp Ser Cys Gln Gly Asp Ser
    210   215   220
Gly Gly Pro Leu Val Cys Lys Val Asn Gly Thr Trp Leu Gln Ala Gly
225   230   235   240
Val Val Ser Trp Gly Glu Gly Cys Ala Gln Pro Asn Arg Pro Gly Ile
                245   250   255
Tyr Thr Arg Val Thr Tyr Tyr Leu Asp Trp Ile His His Tyr Val Pro
            260   265   270
Lys Lys Pro
        275

<210> 49
<211> 1528
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hk5

<400> 49
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tctgtgcgtc ctgcacccac atctttctct gtcccctcct tgccctgtct ggaggctgct 180
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gtccttgtgg ttcctctcta cctggggaaa taaggtgcag cggccatggc tacagcaaga 300
ccccccctgga tgtgggtgct ctgtgctctg atcacagcct tgcttctggg ggtcacagag 360
catgttctcg ccaacaatga tgtttcctgt gaccacccct ctaacaccgt gccctctggg 420
agcaaccagg acctgggagc tggggccggg gaagacgccc ggtcggatga cagcagcagc 480
cgcatcatca atggatccga ctgcgatatg cacacccagc cgtggcaggc cgcgctgttg 540
ctaaggccca accagctcta ctgcggggcg gtgttggtgc atccacagtg gctgctcacg 600
gccgcccact gcaggaagaa agttttcaga gtccgtctcg gccactactc cctgtcacca 660
gtttatgaat ctgggcagca gatgttccag ggggtcaaat ccatccccca ccctggctac 720
tcccaccctg gccactctaa cgacctcatg ctcatcaaac tgaacagaag aattcgtccc 780
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tgcttgaata tcagcgtgct aagtcagaaa aggtgcgagg atgcttaccc gagacagata 960
gatgacacca tgttctgcgc cggtgacaaa gcaggtagag actcctgcca gggtgattct 1020
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tgtgcccggc ccaacagacc gggtgtctac acgaacctct gcaagttcac caagtggatc 1140
caggaaacca tccaggccaa ctcctgagtc atcccaggac tcagcacacc ggcatcccca 1200
cctgctgcag ggacagccct gacactcctt tcagaccctc attccttccc agagatgttg 1260
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gggcgggggt tgcgtctcaa tctccctggg gcactttcat cctcaagctc agggcccatc 1440
ccttctctgc agctctgacc caaatttagt cccagaaata aactgagaag tggaaaaaaa 1500
aaaaaaaaaa aaaaaaaaaa aaaaaaaa 1528

<210> 50
<211> 293
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hk5

<400> 50
Met Ala Thr Ala Arg Pro Pro Trp Met Trp Val Leu Cys Ala Leu Ile
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Thr Ala Leu Leu Leu Gly Val Thr Glu His Val Leu Ala Asn Asn Asp
            20   25   30
Val Ser Cys Asp His Pro Ser Asn Thr Val Pro Ser Gly Ser Asn Gln
        35   40   45
Asp Leu Gly Ala Gly Ala Gly Glu Asp Ala Arg Ser Asp Asp Ser Ser
    50   55   60
Ser Arg Ile Ile Asn Gly Ser Asp Cys Asp Met His Thr Gln Pro Trp
65   70   75   80
Gln Ala Ala Leu Leu Leu Arg Pro Asn Gln Leu Tyr Cys Gly Ala Val
                85   90   95
Leu Val His Pro Gln Trp Leu Leu Thr Ala Ala His Cys Arg Lys Lys
            100   105   110
Val Phe Arg Val Arg Leu Gly His Tyr Ser Leu Ser Pro Val Tyr Glu
        115   120   125

```
Ser Gly Gln Gln Met Phe Gln Gly Val Lys Ser Ile Pro His Pro Gly
    130                 135                 140
Tyr Ser His Pro Gly His Ser Asn Asp Leu Met Leu Ile Lys Leu Asn
145                 150                 155                 160
Arg Arg Ile Arg Pro Thr Lys Asp Val Arg Pro Ile Asn Val Ser Ser
                165                 170                 175
His Cys Pro Ser Ala Gly Thr Lys Cys Leu Val Ser Gly Trp Gly Thr
            180                 185                 190
Thr Lys Ser Pro Gln Val His Phe Pro Lys Val Leu Gln Cys Leu Asn
        195                 200                 205
Ile Ser Val Leu Ser Gln Lys Arg Cys Glu Asp Ala Tyr Pro Arg Gln
    210                 215                 220
Ile Asp Asp Thr Met Phe Cys Ala Gly Asp Lys Ala Gly Arg Asp Ser
225                 230                 235                 240
Cys Gln Gly Asp Ser Gly Gly Pro Val Val Cys Asn Gly Ser Leu Gln
                245                 250                 255
Gly Leu Val Ser Trp Gly Asp Tyr Pro Cys Ala Arg Pro Asn Arg Pro
            260                 265                 270
Gly Val Tyr Thr Asn Leu Cys Lys Phe Thr Lys Trp Ile Gln Glu Thr
        275                 280                 285
Ile Gln Ala Asn Ser
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<210> 51
<211> 4942
<212> DNA
<213> Homo sapiens

<220>
<223> Corin

<400> 51
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aaataaaatg gtaatggtct aa 4942

<210> 52
<211> 1042
<212> PRT
<213> Homo sapiens

<220>
<223> Corin

<400> 52
Met Lys Gln Ser Pro Ala Leu Ala Pro Glu Glu Arg Cys Arg Arg Ala
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Gly Ser Pro Lys Pro Val Leu Arg Ala Asp Asp Asn Asn Met Gly Asn
            20   25   30
Gly Cys Ser Gln Lys Leu Ala Thr Ala Asn Leu Leu Arg Phe Leu Leu
        35   40   45
Leu Val Leu Ile Pro Cys Ile Cys Ala Leu Val Leu Leu Leu Val Ile
    50   55   60
Leu Leu Ser Tyr Val Gly Thr Leu Gln Lys Val Tyr Phe Lys Ser Asn
65   70   75   80
Gly Ser Glu Pro Leu Val Thr Asp Gly Glu Ile Gln Gly Ser Asp Val
                85   90   95
Ile Leu Thr Asn Thr Ile Tyr Asn Gln Ser Thr Val Val Ser Thr Ala
            100   105   110
His Pro Asp Gln His Val Pro Ala Trp Thr Thr Asp Ala Ser Leu Pro
        115   120   125
Gly Asp Gln Ser His Arg Asn Thr Ser Ala Cys Met Asn Ile Thr His
    130   135   140
Ser Gln Cys Gln Met Leu Pro Tyr His Ala Thr Leu Thr Pro Leu Leu
145   150   155   160
Ser Val Val Arg Asn Met Glu Met Glu Lys Phe Leu Lys Phe Phe Thr
                165   170   175
Tyr Leu His Arg Leu Ser Cys Tyr Gln His Ile Met Leu Phe Gly Cys
            180   185   190
Thr Leu Ala Phe Pro Glu Cys Ile Ile Asp Gly Asp Asp Ser His Gly
        195   200   205
Leu Leu Pro Cys Arg Ser Phe Cys Glu Ala Ala Lys Glu Gly Cys Glu
    210   215   220
Ser Val Leu Gly Met Val Asn Tyr Ser Trp Pro Asp Phe Leu Arg Cys
225   230   235   240
Ser Gln Phe Arg Asn Gln Thr Glu Ser Ser Asn Val Ser Arg Ile Cys
                245   250   255
Phe Ser Pro Gln Gln Glu Asn Gly Lys Gln Leu Leu Cys Gly Arg Gly
            260   265   270
Glu Asn Phe Leu Cys Ala Ser Gly Ile Cys Ile Pro Gly Lys Leu Gln
        275   280   285
Cys Asn Gly Tyr Asn Asp Cys Asp Asp Trp Ser Asp Glu Ala His Cys
    290   295   300
Asn Cys Ser Glu Asn Leu Phe His Cys His Thr Gly Lys Cys Leu Asn
305   310   315   320
Tyr Ser Leu Val Cys Asp Gly Tyr Asp Asp Cys Gly Asp Leu Ser Asp
                325   330   335
Glu Gln Asn Cys Asp Cys Asn Pro Thr Thr Glu His Arg Cys Gly Asp
            340   345   350
Gly Arg Cys Ile Ala Met Glu Trp Val Cys Asp Gly Asp His Asp Cys

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        355                 360                 365
Val Asp Lys Ser Asp Glu Val Asn Cys Ser Cys His Ser Gln Gly Leu
    370                 375                 380
Val Glu Cys Arg Asn Gly Gln Cys Ile Pro Ser Thr Phe Gln Cys Asp
385                 390                 395                 400
Gly Asp Glu Asp Cys Lys Asp Gly Ser Asp Glu Glu Asn Cys Ser Val
                405                 410                 415
Ile Gln Thr Ser Cys Gln Glu Gly Asp Gln Arg Cys Leu Tyr Asn Pro
            420                 425                 430
Cys Leu Asp Ser Cys Gly Gly Ser Ser Leu Cys Asp Pro Asn Asn Ser
        435                 440                 445
Leu Asn Asn Cys Ser Gln Cys Glu Pro Ile Thr Leu Glu Leu Cys Met
    450                 455                 460
Asn Leu Pro Tyr Asn Ser Thr Ser Tyr Pro Asn Tyr Phe Gly His Arg
465                 470                 475                 480
Thr Gln Lys Glu Ala Ser Ile Ser Trp Glu Ser Ser Leu Phe Pro Ala
                485                 490                 495
Leu Val Gln Thr Asn Cys Tyr Lys Tyr Leu Met Phe Phe Ser Cys Thr
            500                 505                 510
Ile Leu Val Pro Lys Cys Asp Val Asn Thr Gly Glu His Ile Pro Pro
        515                 520                 525
Cys Arg Ala Leu Cys Glu His Ser Lys Glu Arg Cys Glu Ser Val Leu
    530                 535                 540
Gly Ile Val Gly Leu Gln Trp Pro Glu Asp Thr Asp Cys Ser Gln Phe
545                 550                 555                 560
Pro Glu Glu Asn Ser Asp Asn Gln Thr Cys Leu Met Pro Asp Glu Tyr
                565                 570                 575
Val Glu Glu Cys Ser Pro Ser His Phe Lys Cys Arg Ser Gly Gln Cys
            580                 585                 590
Val Leu Ala Ser Arg Arg Cys Asp Gly Gln Ala Asp Cys Asp Asp Asp
        595                 600                 605
Ser Asp Glu Glu Asn Cys Gly Cys Lys Glu Arg Asp Leu Trp Glu Cys
    610                 615                 620
Pro Ser Asn Lys Gln Cys Leu Lys His Thr Val Ile Cys Asp Gly Phe
625                 630                 635                 640
Pro Asp Cys Pro Asp Tyr Met Asp Glu Lys Asn Cys Ser Phe Cys Gln
                645                 650                 655
Asp Asp Glu Leu Glu Cys Ala Asn His Ala Cys Val Ser Arg Asp Leu
            660                 665                 670
Trp Cys Asp Gly Glu Ala Asp Cys Ser Asp Ser Ser Asp Glu Trp Asp
        675                 680                 685
Cys Val Thr Leu Ser Ile Asn Val Asn Ser Ser Ser Phe Leu Met Val
    690                 695                 700
His Arg Ala Ala Thr Glu His His Val Cys Ala Asp Gly Trp Gln Glu
705                 710                 715                 720
Ile Leu Ser Gln Leu Ala Cys Lys Gln Met Gly Leu Gly Glu Pro Ser
                725                 730                 735
Val Thr Lys Leu Ile Gln Glu Gln Glu Lys Glu Pro Arg Trp Leu Thr
            740                 745                 750
Leu His Ser Asn Trp Glu Ser Leu Asn Gly Thr Thr Leu His Glu Leu
        755                 760                 765
Leu Val Asn Gly Gln Ser Cys Glu Ser Arg Ser Lys Ile Ser Leu Leu
    770                 775                 780
Cys Thr Lys Gln Asp Cys Gly Arg Arg Pro Ala Ala Arg Met Asn Lys
785                 790                 795                 800
Arg Ile Leu Gly Gly Arg Thr Ser Arg Pro Gly Arg Trp Pro Trp Gln
                805                 810                 815
```

```
Cys Ser Leu Gln Ser Glu Pro Ser Gly His Ile Cys Gly Cys Val Leu
            820                 825                 830
Ile Ala Lys Lys Trp Val Leu Thr Val Ala His Cys Phe Glu Gly Arg
        835                 840                 845
Glu Asn Ala Ala Val Trp Lys Val Val Leu Gly Ile Asn Asn Leu Asp
    850                 855                 860
His Pro Ser Val Phe Met Gln Thr Arg Phe Val Lys Thr Ile Ile Leu
865                 870                 875                 880
His Pro Arg Tyr Ser Arg Ala Val Val Asp Tyr Asp Ile Ser Ile Val
                885                 890                 895
Glu Leu Ser Glu Asp Ile Ser Glu Thr Gly Tyr Val Arg Pro Val Cys
            900                 905                 910
Leu Pro Asn Pro Glu Gln Trp Leu Glu Pro Asp Thr Tyr Cys Tyr Ile
        915                 920                 925
Thr Gly Trp Gly His Met Gly Asn Lys Met Pro Phe Lys Leu Gln Glu
    930                 935                 940
Gly Glu Val Arg Ile Ile Ser Leu Glu His Cys Gln Ser Tyr Phe Asp
945                 950                 955                 960
Met Lys Thr Ile Thr Thr Arg Met Ile Cys Ala Gly Tyr Glu Ser Gly
                965                 970                 975
Thr Val Asp Ser Cys Met Gly Asp Ser Gly Gly Pro Leu Val Cys Glu
            980                 985                 990
Lys Pro Gly Gly Arg Trp Thr Leu Phe Gly Leu Thr Ser Trp Gly Ser
        995                 1000                1005
Val Cys Phe Ser Lys Val Leu Gly Pro Gly Val Tyr Ser Asn Val Ser
    1010                1015                1020
Tyr Phe Val Glu Trp Ile Lys Arg Gln Ile Tyr Ile Gln Thr Phe Leu
1025                1030                1035                1040
Leu Asn
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<210> 53
<211> 945
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 12 transcript variant 1

<400> 53

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gcaggtaggt ggacggagag atagcagcga cgaggacagg ccaaacagtg acagccacgt 60
agaggatctg gcagacaaag agacaaggtg agaaggagac tttggaagtg acccaccatg 120
gggctcagca tctttttgct cctgtgtgtt cttgggctca gccaggcagc cacaccgaag 180
attttcaatg gcactgagtg tgggcgtaac tcacagccgt ggcaggtggg gctgtttgag 240
ggcaccagcc tgcgctgcgg gggtgtcctt attgaccaca ggtgggtcct cacagcggct 300
cactgcagcg gcagcaggta ctgggtgcgc ctgggggaac acagcctcag ccagctcgac 360
tggaccgagc agatccggca cagcggcttc tctgtgaccc atcccggcta cctgggagcc 420
tcgacgagcc acgagcacga cctccggctg ctgcggctgc gcctgcccgt ccgcgtaacc 480
agcagcgttc aacccctgcc cctgcccaat gactgtgcaa ccgctggcac cgagtgccac 540
gtctcaggct ggggcatcac caaccaccca cggaacccat tcccggatct gctccagtgc 600
ctcaacctct ccatcgtctc ccatgccacc tgccatggtg tgtatcccgg gagaatcacg 660
agcaacatgg tgtgtgcagg cggcgtcccg gggcaggatg cctgccaggg tgattctggg 720
ggcccccctgg tgtgtggggg agtccttcaa ggtctggtgt cctgggggtc tgtggggccc 780
tgtggacaag atggcatccc tggagtctac acctatattt gcaactccac tcttgttggc 840
ctgggaactt cttggaactt taactcctgc cagcccttct aagacccacg agcggggtga 900
gagaagtgtg caatagtctg gaataaatat aaatgaagga ggggc                  945
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<210> 54
<211> 254
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 12 isoform 1

<400> 54
Met Gly Leu Ser Ile Phe Leu Leu Leu Cys Val Leu Gly Leu Ser Gln
 1   5   10   15
Ala Ala Thr Pro Lys Ile Phe Asn Gly Thr Glu Cys Gly Arg Asn Ser
            20   25   30
Gln Pro Trp Gln Val Gly Leu Phe Glu Gly Thr Ser Leu Arg Cys Gly
        35   40   45
Gly Val Leu Ile Asp His Arg Trp Val Leu Thr Ala Ala His Cys Ser
    50   55   60
Gly Ser Arg Tyr Trp Val Arg Leu Gly Glu His Ser Leu Ser Gln Leu
65   70   75   80
Asp Trp Thr Glu Gln Ile Arg His Ser Gly Phe Ser Val Thr His Pro
                85   90   95
Gly Tyr Leu Gly Ala Ser Thr Ser His Glu His Asp Leu Arg Leu Leu
            100   105   110
Arg Leu Arg Leu Pro Val Arg Val Thr Ser Ser Val Gln Pro Leu Pro
        115   120   125
Leu Pro Asn Asp Cys Ala Thr Ala Gly Thr Glu Cys His Val Ser Gly
    130   135   140
Trp Gly Ile Thr Asn His Pro Arg Asn Pro Phe Pro Asp Leu Leu Gln
145   150   155   160
Cys Leu Asn Leu Ser Ile Val Ser His Ala Thr Cys His Gly Val Tyr
                165   170   175
Pro Gly Arg Ile Thr Ser Asn Met Val Cys Ala Gly Gly Val Pro Gly
            180   185   190
Gln Asp Ala Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Gly Gly
        195   200   205
Val Leu Gln Gly Leu Val Ser Trp Gly Ser Val Gly Pro Cys Gly Gln
    210   215   220
Asp Gly Ile Pro Gly Val Tyr Thr Tyr Ile Cys Asn Ser Thr Leu Val
225   230   235   240
Gly Leu Gly Thr Ser Trp Asn Phe Asn Ser Cys Gln Pro Phe
                245   250

<210> 55
<211> 1074
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 12 transcript variant 2

<400> 55
gcaggtaggt ggacggagag atagcagcga cgaggacagg ccaaacagtg acagccacgt 60
agaggatctg gcagacaaag agacaaggtg agaaggagac tttggaagtg acccaccatg 120
gggctcagca tctttttgct cctgtgtgtt cttgggctca gccaggcagc cacaccgaag 180
attttcaatg gcactgagtg tgggcgtaac tcacagccgt ggcaggtggg gctgtttgag 240

```
ggcaccagcc tgcgctgcgg gggtgtcctt attgaccaca ggtgggtcct cacagcggct 300
cactgcagcg gcagcaggta ctgggtgcgc ctgggggaac acagcctcag ccagctcgac 360
tggaccgagc agatccggca cagcggcttc tctgtgaccc atcccggcta cctgggagcc 420
tcgacgagcc acgagcacga cctccggctg ctgcggctgc gcctgcccgt ccgcgtaacc 480
agcagcgttc aacccctgcc cctgcccaat gactgtgcaa ccgctggcac cgagtgccac 540
gtctcaggct ggggcatcac caaccaccca cggaacccat tcccggatct gctccagtgc 600
ctcaacctct ccatcgtctc ccatgccacc tgccatggtg tgtatcccgg gagaatcacg 660
agcaacatgg tgtgtgcagg cggcgtcccg gggcaggatg cctgccaggg tgattctggg 720
ggcccctgg tgtgtggggg agtccttcaa ggtctggtgt cctgggggtc tgtggggccc 780
tgtggacaag atggcatccc tggagtctac acctatattt gcaagtatgt ggactggatc 840
cggatgatca tgaggaacaa ctgacctgtt tcctccacct ccacccccac cccttaactt 900
gggtacccct ctggccctca gagcaccaat atctcctcca tcacttcccc tagctccact 960
cttgttggcc tgggaacttc ttggaacttt aactcctgcc agcccttcta agacccacga 1020
gcggggtgag agaagtgtgc aatagtctgg aataaatata aatgaaggag gggc       1074
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<210> 56
<211> 248
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 12 isoform 2

<400> 56

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Met Gly Leu Ser Ile Phe Leu Leu Leu Cys Val Leu Gly Leu Ser Gln
 1               5                  10                  15
Ala Ala Thr Pro Lys Ile Phe Asn Gly Thr Glu Cys Gly Arg Asn Ser
            20                  25                  30
Gln Pro Trp Gln Val Gly Leu Phe Glu Gly Thr Ser Leu Arg Cys Gly
        35                  40                  45
Gly Val Leu Ile Asp His Arg Trp Val Leu Thr Ala Ala His Cys Ser
    50                  55                  60
Gly Ser Arg Tyr Trp Val Arg Leu Gly Glu His Ser Leu Ser Gln Leu
65                  70                  75                  80
Asp Trp Thr Glu Gln Ile Arg His Ser Gly Phe Ser Val Thr His Pro
                85                  90                  95
Gly Tyr Leu Gly Ala Ser Thr Ser His Glu His Asp Leu Arg Leu Leu
            100                 105                 110
Arg Leu Arg Leu Pro Val Arg Val Thr Ser Ser Val Gln Pro Leu Pro
        115                 120                 125
Leu Pro Asn Asp Cys Ala Thr Ala Gly Thr Glu Cys His Val Ser Gly
    130                 135                 140
Trp Gly Ile Thr Asn His Pro Arg Asn Pro Phe Pro Asp Leu Leu Gln
145                 150                 155                 160
Cys Leu Asn Leu Ser Ile Val Ser His Ala Thr Cys His Gly Val Tyr
                165                 170                 175
Pro Gly Arg Ile Thr Ser Asn Met Val Cys Ala Gly Gly Val Pro Gly
            180                 185                 190
Gln Asp Ala Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Gly Gly
        195                 200                 205
Val Leu Gln Gly Leu Val Ser Trp Gly Ser Val Gly Pro Cys Gly Gln
    210                 215                 220
Asp Gly Ile Pro Gly Val Tyr Thr Tyr Ile Cys Lys Tyr Val Asp Trp
225                 230                 235                 240
Ile Arg Met Ile Met Arg Asn Asn
                245
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<210> 57
<211> 814
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 12 transcript variant 3

<400> 57
gcaggtaggt ggacggagag atagcagcga cgaggacagg ccaaacagtg acagccacgt 60
agaggatctg gcagacaaag agacaaggtg agaaggagac tttggaagtg acccaccatg 120
gggctcagca tctttttgct cctgtgtgtt cttgggctca gccaggcagc cacaccgaag 180
attttcaatg gcactgagtg tgggcgtaac tcacagccgt ggcaggtggg gctgtttgag 240
ggcaccagcc tgcgctgcgg gggtgtcctt attgaccaca ggtgggtcct cacagcggct 300
cactgcagcg gcagacccat tcccggatct gctccagtgc ctcaacctct ccatcgtctc 360
ccatgccacc tgccatggtg tgtatcccgg gagaatcacg agcaacatgg tgtgtgcagg 420
cggcgtcccg gggcaggatg cctgccaggg tgattctggg ggccccctgg tgtgtggggg 480
agtccttcaa ggtctggtgt cctgggggtc tgtggggccc tgtggacaag atggcatccc 540
tggagtctac acctatattt gcaagtatgt ggactggatc cggatgatca tgaggaacaa 600
ctgacctgtt tcctccacct ccacccccac cccttaactt gggtacccct ctggccctca 660
gagcaccaat atctcctcca tcacttcccc tagctccact cttgttggcc tgggaacttc 720
ttggaacttt aactcctgcc agcccttcta agacccacga gcggggtgag agaagtgtgc 780
aatagtctgg aataaatata aatgaaggag gggc 814

<210> 58
<211> 111
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 12 isoform 3

<400> 58
Met Gly Leu Ser Ile Phe Leu Leu Leu Cys Val Leu Gly Leu Ser Gln
1 5 10 15
Ala Ala Thr Pro Lys Ile Phe Asn Gly Thr Glu Cys Gly Arg Asn Ser
20 25 30
Gln Pro Trp Gln Val Gly Leu Phe Glu Gly Thr Ser Leu Arg Cys Gly
35 40 45
Gly Val Leu Ile Asp His Arg Trp Val Leu Thr Ala Ala His Cys Ser
50 55 60
Gly Arg Pro Ile Pro Gly Ser Ala Pro Val Pro Gln Pro Leu His Arg
65 70 75 80
Leu Pro Cys His Leu Pro Trp Cys Val Ser Arg Glu Asn His Glu Gln
85 90 95
His Gly Val Cys Arg Arg Arg Pro Gly Ala Gly Cys Leu Pro Gly
100 105 110

<210> 59
<211> 1471
<212> DNA
<213> Homo sapiens

<220>
<223> DESC1 oritease

<400> 59
tgacttggat gtagacctcg accttcacag gactcttcat tgctggttgg caatgatgta 60
tcggccagat gtggtgaggg ctaggaaaag agtttgttgg gaaccctggg ttatcggcct 120
cgtcatcttc atatccctga ttgtcctggc agtgtgcatt ggactcactg ttcattatgt 180
gagatataat caaaagaaga cctacaatta ctatagcaca ttgtcattta caactgacaa 240
actatatgct gagtttggca gagaggcttc taacaatttt acagaaatga gccagagact 300
tgaatcaatg gtgaaaaatg cattttataa atctccatta agggaagaat ttgtcaagtc 360
tcaggttatc aagttcagtc aacagaagca tggagtgttg gctcatatgc tgttgatttg 420
tagatttcac tctactgagg atcctgaaac tgtagataaa attgttcaac ttgttttaca 480
tgaaaagctg caagatgctg taggaccccc taaagtagat cctcactcag ttaaaattaa 540
aaaaatcaac aagacagaaa cagacagcta tctaaaccat tgctgcggaa cacgaagaag 600
taaaactcta ggtcagagtc tcaggatcgt tggtgggaca gaagtagaag agggtgaatg 660
gccctggcag gctagcctgc agtgggatgg gagtcatcgc tgtggagcaa ccttaattaa 720
tgccacatgg cttgtgagtg ctgctcactg ttttacaaca tataagaacc ctgccagatg 780
gactgcttcc tttggagtaa caataaaacc ttcgaaaatg aaacggggtc tccggagaat 840
aattgtccat gaaaaatata aacacccatc acatgactat gatatttctc ttgcagagct 900
ttctagccct gttccctaca caaatgcagt acatagagtt tgtctccctg atgcatccta 960
tgagtttcaa ccaggtgatg tgatgtttgt gacaggattt ggagcactga aaaatgatgg 1020
ttacagtcaa aatcatcttc gacaagcaca ggtgactctc atagacgcta caacttgcaa 1080
tgaacctcaa gcttacaatg acgccataac tcctagaatg ttatgtgctg gctccttaga 1140
aggaaaaaca gatgcatgcc agggtgactc tggaggacca ctggttagtt cagatgctag 1200
agatatctgg taccttgctg gaatagtgag ctggggagat gaatgtgcga aacccaacaa 1260
gcctggtgtt tatactagag ttacggcctt gcgggactgg attacttcaa aaactggtat 1320
ctaagagaga aaagcctcat ggaacagata acatttttt ttgtttttg ggtgtggagg 1380
ccatttttag agatacagaa ttggagaaga cttgcaaaac agctagattt gactgatctc 1440
aataaactgt ttgcttgatg caaaaaaaaa a 1471

<210> 60
<211> 422
<212> PRT
<213> Homo sapiens

<220>
<223> DESC1 oritease

<400> 60
Met Tyr Arg Pro Asp Val Val Arg Ala Arg Lys Arg Val Cys Trp Glu
 1   5   10   15
Pro Trp Val Ile Gly Leu Val Ile Phe Ile Ser Leu Ile Val Leu Ala
            20   25   30
Val Cys Ile Gly Leu Thr Val His Tyr Val Arg Tyr Asn Gln Lys Lys
        35   40   45
Thr Tyr Asn Tyr Tyr Ser Thr Leu Ser Phe Thr Thr Asp Lys Leu Tyr
    50   55   60
Ala Glu Phe Gly Arg Glu Ala Ser Asn Asn Phe Thr Glu Met Ser Gln
65   70   75   80
Arg Leu Glu Ser Met Val Lys Asn Ala Phe Tyr Lys Ser Pro Leu Arg
                85   90   95
Glu Glu Phe Val Lys Ser Gln Val Ile Lys Phe Ser Gln Gln Lys His
            100   105   110
Gly Val Leu Ala His Met Leu Leu Ile Cys Arg Phe His Ser Thr Glu
        115   120   125
Asp Pro Glu Thr Val Asp Lys Ile Val Gln Leu Val Leu His Glu Lys
    130   135   140
Leu Gln Asp Ala Val Gly Pro Pro Lys Val Asp Pro His Ser Val Lys
145   150   155   160

```
Ile Lys Lys Ile Asn Lys Thr Glu Thr Asp Ser Tyr Leu Asn His Cys
                165                 170                 175
Cys Gly Thr Arg Arg Ser Lys Thr Leu Gly Gln Ser Leu Arg Ile Val
            180                 185                 190
Gly Gly Thr Glu Val Glu Glu Gly Glu Trp Pro Trp Gln Ala Ser Leu
        195                 200                 205
Gln Trp Asp Gly Ser His Arg Cys Gly Ala Thr Leu Ile Asn Ala Thr
    210                 215                 220
Trp Leu Val Ser Ala Ala His Cys Phe Thr Thr Tyr Lys Asn Pro Ala
225                 230                 235                 240
Arg Trp Thr Ala Ser Phe Gly Val Thr Ile Lys Pro Ser Lys Met Lys
                245                 250                 255
Arg Gly Leu Arg Arg Ile Ile Val His Glu Lys Tyr Lys His Pro Ser
            260                 265                 270
His Asp Tyr Asp Ile Ser Leu Ala Glu Leu Ser Ser Pro Val Pro Tyr
        275                 280                 285
Thr Asn Ala Val His Arg Val Cys Leu Pro Asp Ala Ser Tyr Glu Phe
    290                 295                 300
Gln Pro Gly Asp Val Met Phe Val Thr Gly Phe Gly Ala Leu Lys Asn
305                 310                 315                 320
Asp Gly Tyr Ser Gln Asn His Leu Arg Gln Ala Gln Val Thr Leu Ile
                325                 330                 335
Asp Ala Thr Thr Cys Asn Glu Pro Gln Ala Tyr Asn Asp Ala Ile Thr
            340                 345                 350
Pro Arg Met Leu Cys Ala Gly Ser Leu Glu Gly Lys Thr Asp Ala Cys
        355                 360                 365
Gln Gly Asp Ser Gly Gly Pro Leu Val Ser Ser Asp Ala Arg Asp Ile
    370                 375                 380
Trp Tyr Leu Ala Gly Ile Val Ser Trp Gly Asp Glu Cys Ala Lys Pro
385                 390                 395                 400
Asn Lys Pro Gly Val Tyr Thr Arg Val Thr Ala Leu Arg Asp Trp Ile
                405                 410                 415
Thr Ser Lys Thr Gly Ile
            420
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<210> 61
<211> 1124
<212> DNA
<213> Homo sapiens

<220>
<223> tryptase gamma 1

<400> 61
ccatggccct tggggcctgt ggcctcctgc tgctcctggc tgtgcccggt gtgtccctca 60
ggactttgca gccagggtgt ggccggccgc aggtttcgga tgcaggcggc cggatcgtgg 120
ggggtcacgc tgccccggcc ggcgcatggc catggcaggc cagcctccgc ctgcggagga 180
tgcacgtgtg cggcgggtca ctgctcagcc cccagtgggt gctcacagct gcccactgct 240
tctccgggtc cctgaactca tccgactacc aggtgcacct gggggaactg gagatcactt 300
tgtctcccca cttctccacc gtgaggcaga tcatcctgca ctccagcccc tcaggacagc 360
cggggaccag cggggacatc gccctggtgg agctcagtgt ccccgtgacc ctctccagcc 420
ggatcctgcc cgtctgcctc ccggaggcct cagatgactt ctgccctggg atccggtgct 480
gggtgaccgg ctggggctat acgcgggagg gagagcctct gccacccccg tacagcctgc 540
gggaggtgaa agtctccgtg gtggacacag agacctgccg ccgggactat cccggccccg 600
ggggcagcat ccttcagccc gacatgctgt gtgcccgggg ccccggggat gcctgccagg 660
acgactccgg ggggcctctg gtctgccagg tgaacggtgc ctgggtgcag gctggcattg 720

tgagctgggg tgagggctgc ggccgcccca acaggccggg agtctacact cgtgtccctg 780
cctacgtgaa ctggatccgc cgccacatca cagcatcagg gggctcagag tctgggtacc 840
ccaggctccc cctcctggct ggcttcttcc tccccggcct cttccttctg ctagtctcct 900
gtgtcctgct ggccaagtgc ctgctgcacc catctgcgga tggtactccc ttccccgccc 960
ctgactgatg gcaggaatcc aagtgcattt cttaaataag ttactattta ttccgctccg 1020
ccccctccct ctcccttgag aagctgagtc ttctgcatca gattattgca acatttaacc 1080
tgaatttaaa agcacacgaa acaaaaaaaa aaaaaaaaaa aaaa 1124

<210> 62
<211> 321
<212> PRT
<213> Homo sapiens

<220>
<223> tryptase gamma 1

<400> 62
Met Ala Leu Gly Ala Cys Gly Leu Leu Leu Leu Leu Ala Val Pro Gly
1 5 10 15
Val Ser Leu Arg Thr Leu Gln Pro Gly Cys Gly Arg Pro Gln Val Ser
20 25 30
Asp Ala Gly Gly Arg Ile Val Gly Gly His Ala Ala Pro Ala Gly Ala
35 40 45
Trp Pro Trp Gln Ala Ser Leu Arg Leu Arg Arg Met His Val Cys Gly
50 55 60
Gly Ser Leu Leu Ser Pro Gln Trp Val Leu Thr Ala Ala His Cys Phe
65 70 75 80
Ser Gly Ser Leu Asn Ser Ser Asp Tyr Gln Val His Leu Gly Glu Leu
85 90 95
Glu Ile Thr Leu Ser Pro His Phe Ser Thr Val Arg Gln Ile Ile Leu
100 105 110
His Ser Ser Pro Ser Gly Gln Pro Gly Thr Ser Gly Asp Ile Ala Leu
115 120 125
Val Glu Leu Ser Val Pro Val Thr Leu Ser Ser Arg Ile Leu Pro Val
130 135 140
Cys Leu Pro Glu Ala Ser Asp Asp Phe Cys Pro Gly Ile Arg Cys Trp
145 150 155 160
Val Thr Gly Trp Gly Tyr Thr Arg Glu Gly Glu Pro Leu Pro Pro Pro
165 170 175
Tyr Ser Leu Arg Glu Val Lys Val Ser Val Val Asp Thr Glu Thr Cys
180 185 190
Arg Arg Asp Tyr Pro Gly Pro Gly Gly Ser Ile Leu Gln Pro Asp Met
195 200 205
Leu Cys Ala Arg Gly Pro Gly Asp Ala Cys Gln Asp Asp Ser Gly Gly
210 215 220
Pro Leu Val Cys Gln Val Asn Gly Ala Trp Val Gln Ala Gly Ile Val
225 230 235 240
Ser Trp Gly Glu Gly Cys Gly Arg Pro Asn Arg Pro Gly Val Tyr Thr
245 250 255
Arg Val Pro Ala Tyr Val Asn Trp Ile Arg Arg His Ile Thr Ala Ser
260 265 270
Gly Gly Ser Glu Ser Gly Tyr Pro Arg Leu Pro Leu Leu Ala Gly Phe
275 280 285
Phe Leu Pro Gly Leu Phe Leu Leu Leu Val Ser Cys Val Leu Leu Ala
290 295 300
Lys Cys Leu Leu His Pro Ser Ala Asp Gly Thr Pro Phe Pro Ala Pro
305 310 315 320

Asp

<210> 63
<211> 1459
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK14

<400> 63
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ctggggcctc tgctccccca tctctcagga gtcgaaagtg agaaagcaag acatcaagga 120
gggacctgtg ccctgctcca catcctccca cctgccgccc gcagagcctg caggccccgc 180
ccccctcgtc tctggtccct acctctctgc tgtgtcttca tgtccctgag ggtcttgggc 240
tctgggacct ggccctcagc ccctaaaatg ttcctcctgc tgacagcact tcaagtcctg 300
gctatagcca tgacacagag ccaagaggat gagaacaaga taattggtgg ccatacgtgc 360
acccggagct cccagccgtg gcaggcggcc ctgctggcgg gtcccaggcg ccgcttcctc 420
tgcggaggcg ccctgctttc aggccagtgg gtcatcactg ctgctcactg cggccgcccg 480
atccttcagg ttgccctggg caagcacaac ctgaggaggt gggaggccac ccagcaggtg 540
ctgcgcgtgg ttcgtcaggt gacgcacccc aactacaact cccggaccca cgacaacgac 600
ctcatgctgc tgcagctaca gcagcccgca cggatcggga gggcagtcag gcccattgag 660
gtcacccagg cctgtgccag ccccgggacc tcctgccgag tgtcaggctg gggaactata 720
tccagcccca tcgccaggta ccccgcctct ctgcaatgcg tgaacatcaa catctccccg 780
gatgaggtgt gccagaaggc ctatcctaga accatcacgc ctggcatggt ctgtgcagga 840
gttccccagg gcgggaagga ctcttgtcag ggtgactctg ggggacccct ggtgtgcaga 900
ggacagctcc agggcctcgt gtcttgggga atggagcgct gcgccctgcc tggctacccc 960
ggtgtctaca ccaacctgtg caagtacaga agctggattg aggaaacgat gcgggacaaa 1020
tgatggtctt cacggtggga tggacctcgt cagctgccca ggccctcctc tctctactca 1080
ggacccagga gtccaggccc cagcccctcc tccctcagac ccaggagtcc aggcccccag 1140
cccctcctcc ctcagacccg ggagtccagg cccccagccc ctcctccctc agacccagga 1200
gccccagtcc ccagcatcct gatctttact ccggctctga tctctccttt cccagagcag 1260
ttgcttcagg cgttttctcc ccaccaagcc cccacccttg ctgtgtcacc atcactactc 1320
aagaccggag gcacagaggg caggagcaca gacccccttaa accggcattg tattccaaag 1380
acgacaattt ttaacacgct tagtgtctct aaaaaccgaa taaataatga caataaaaat 1440
ggaatcatcc taaattgta 1459

<210> 64
<211> 251
<212> PRT
<213> Homo sapiens

<220>
<223> Kallikrein-14 precursor S01.029

<400> 64
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1 5 10 15
Gln Ser Gln Glu Asp Glu Asn Lys Ile Ile Gly Gly His Thr Cys Thr
20 25 30
Arg Ser Ser Gln Pro Trp Gln Ala Ala Leu Leu Ala Gly Pro Arg Arg
35 40 45
Arg Phe Leu Cys Gly Gly Ala Leu Leu Ser Gly Gln Trp Val Ile Thr

50 55 60

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Ala Ala His Cys Gly Arg Pro Ile Leu Gln Val Ala Leu Gly Lys His
65                  70                  75                  80
Asn Leu Arg Arg Trp Glu Ala Thr Gln Gln Val Leu Arg Val Val Arg
                85                  90                  95
Gln Val Thr His Pro Asn Tyr Asn Ser Arg Thr His Asp Asn Asp Leu
            100                 105                 110
Met Leu Leu Gln Leu Gln Gln Pro Ala Arg Ile Gly Arg Ala Val Arg
        115                 120                 125
Pro Ile Glu Val Thr Gln Ala Cys Ala Ser Pro Gly Thr Ser Cys Arg
    130                 135                 140
Val Ser Gly Trp Gly Thr Ile Ser Ser Pro Ile Ala Arg Tyr Pro Ala
145                 150                 155                 160
Ser Leu Gln Cys Val Asn Ile Asn Ile Ser Pro Asp Glu Val Cys Gln
                165                 170                 175
Lys Ala Tyr Pro Arg Thr Ile Thr Pro Gly Met Val Cys Ala Gly Val
            180                 185                 190
Pro Gln Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu
        195                 200                 205
Val Cys Arg Gly Gln Leu Gln Gly Leu Val Ser Trp Gly Met Glu Arg
    210                 215                 220
Cys Ala Leu Pro Gly Tyr Pro Gly Val Tyr Thr Asn Leu Cys Lys Tyr
225                 230                 235                 240
Arg Ser Trp Ile Glu Glu Thr Met Arg Asp Lys
                245                 250
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<210> 65
<211> 3008
<212> DNA
<213> Homo sapiens

<220>
<223> hyaluronan-binding serine protease (HGF activator-like protein)

<400> 65
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cctgaatcct tggagactga cattttccc ccctaaaggc atagacaaca aaagaaattt 60
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catgttctgc tgttaatggc tctggtggga aagacagcct gtgggttctc cctgatgtct 180
ttattggaaa gcctggaccc agactggacc cctgaccagt atgattacag ctacgaggat 240
tataatcagg aagagaacac cagtagcaca cttacccacg ctgagaatcc tgactggtac 300
tacactgagg accaagctga tccatgccag cccaacccct gtgaacacgg tggggactgc 360
ctcgtccatg ggagcacctt cacatgcagc tgcctggctc ctttctctgg gaataagtgt 420
cagaaagtgc aaaatacgtg caaggacaac ccatgtggcc ggggccaatg tctcattacc 480
cagagtcctc cctactaccg ctgtgtctgt aaacacccct acacaggtcc cagctgctcc 540
caagtggttc ctgtatgcag gccaaacccc tgccagaatg gggctacctg ctcccggcat 600
aagcggagat ccaagttcac ctgtgcctgt cccgaccagt tcaaggggaa attctgtgaa 660
ataggttctg atgactgcta tgttggcgat ggctactctt accgagggaa aatgaatagg 720
acagtcaacc agcatgcgtg cctttactgg aactcccacc tcctcttgca ggagaattac 780
aacatgttta tggaggatgc tgaaacccat gggattgggg aacacaattt ctgcagaaac 840
ccagatgcgg acgaaaagcc ctggtgcttt attaaagtta ccaatgacaa ggtgaaatgg 900
gaatactgtg atgtctcagc ctgctcagcc caggacgttg cctacccaga ggaaagcccc 960
actgagccat caaccaagct tccggggttt gactcctgtg gaaagactga gatagcagag 1020
aggaagatca agagaatcta tggaggcttt aagagcacgg cgggcaagca cccatggcag 1080
gcgtccctcc agtcctcgct gcctctgacc atctccatgc cccagggcca cttctgtggt 1140
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agacatctaa aggtggtgct aggggaccag gacctgaaga aagaagaatt tcatgagcag 1260
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aaatacgtga agactgtgtg cttgcctgat gggtcctttc cctctgggag tgagtgccac 1440
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gtcaagctga ttgccaacac tttgtgcaac tcccgccaac tctatgacca catgattgat 1560
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tctggaggcc ccctgacctg tgagaaggac ggcacctact acgtctatgg gatagtgagc 1680
tggggcctgg agtgtgggaa gaggccaggg gtctacaccc aagttaccaa attcctgaat 1740
tggatcaaag ccaccatcaa aagtgaaagt ggcttctaag gtactgtctt ctggacctca 1800
gagcccactc tccttggcac cctgacaccg ggaggcctca tggccaacaa tggacacctc 1860
cagagcctcc aggggaccac acagtagact atccctactc taagcagaga caactgccac 1920
ccagcctggg ccttcccaga ccagcatttg cacaatatca ccaggcttct tctgcctccc 1980
ttggtaaccc aaggaatgat ggaatcaaca caacatagta tgtttgcttt ccttacccaa 2040
ttgtaccttc tagaaaatca gtgttcacag agactgcctc caccacaggc atcctgcaaa 2100
tgcagactcc agaatcccca gcatcagcgg gaaccaccat cacatcttta ttcctcagcc 2160
cagacactcg aggcactcaa cagaatcagc catccacgtc taggtatcag agaggaccac 2220
aaatacaaca ttctccatct gctttcagag ttattatttt aataaaggaa gatctgggat 2280
gggctggtgg gccattccag cttgccgaaa tcaaagccat ctgaagcctg tctctggtga 2340
acaaacttcc tctctggcct ctcaggaatc agggtggcat ggctcacaac agcagggcct 2400
tcttcttttt gacgtgcaga atctcagtgg catctgggtt cacctcccca ctctgatgat 2460
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gagcatttaa caggctcacc ctccctttcc ttttcccctc ttctaccctc cccaagaaaa 2640
agggccttca aggcaggaat gagaaagcaa agccaatctc tcatttagac ctggcttctt 2700
tcttctgaac aaagtagggt tcaaaatgca gactgtcata tccagcgagt ccctgaccct 2760
ttctgcgaat gtaacgagca agcagtcagc acagcctggg ctgccctggc ccgggattga 2820
tgtagccccg gtaggtttgc ctctgcagaa ctaatggctg tgacttcaga gaaagccctg 2880
caggaagttt aacctgcgtg tcatctgcct ggtcatctca gacccatgaa attaggcgcc 2940
ttgtttgagc tgcgtttcac acttctttag agctagctga cctttggcca aaaataaact 3000
ttgaaaag 3008

<210> 66
<211> 560
<212> PRT
<213> Homo sapiens

<220>
<223> hyaluronan-binding serine protease (HGF activator-like protein)

<400> 66
Met Phe Ala Arg Met Ser Asp Leu His Val Leu Leu Leu Met Ala Leu
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Val Gly Lys Thr Ala Cys Gly Phe Ser Leu Met Ser Leu Leu Glu Ser
            20   25   30
Leu Asp Pro Asp Trp Thr Pro Asp Gln Tyr Asp Tyr Ser Tyr Glu Asp
        35   40   45
Tyr Asn Gln Glu Glu Asn Thr Ser Ser Thr Leu Thr His Ala Glu Asn
    50   55   60
Pro Asp Trp Tyr Tyr Thr Glu Asp Gln Ala Asp Pro Cys Gln Pro Asn
65   70   75   80
Pro Cys Glu His Gly Gly Asp Cys Leu Val His Gly Ser Thr Phe Thr
                85   90   95
Cys Ser Cys Leu Ala Pro Phe Ser Gly Asn Lys Cys Gln Lys Val Gln
            100   105   110
Asn Thr Cys Lys Asp Asn Pro Cys Gly Arg Gly Gln Cys Leu Ile Thr
        115   120   125
Gln Ser Pro Pro Tyr Tyr Arg Cys Val Cys Lys His Pro Tyr Thr Gly

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    130                 135                 140
Pro Ser Cys Ser Gln Val Val Pro Val Cys Arg Pro Asn Pro Cys Gln
145                 150                 155                 160
Asn Gly Ala Thr Cys Ser Arg His Lys Arg Arg Ser Lys Phe Thr Cys
                165                 170                 175
Ala Cys Pro Asp Gln Phe Lys Gly Lys Phe Cys Glu Ile Gly Ser Asp
            180                 185                 190
Asp Cys Tyr Val Gly Asp Gly Tyr Ser Tyr Arg Gly Lys Met Asn Arg
        195                 200                 205
Thr Val Asn Gln His Ala Cys Leu Tyr Trp Asn Ser His Leu Leu Leu
    210                 215                 220
Gln Glu Asn Tyr Asn Met Phe Met Glu Asp Ala Glu Thr His Gly Ile
225                 230                 235                 240
Gly Glu His Asn Phe Cys Arg Asn Pro Asp Ala Asp Glu Lys Pro Trp
                245                 250                 255
Cys Phe Ile Lys Val Thr Asn Asp Lys Val Lys Trp Glu Tyr Cys Asp
            260                 265                 270
Val Ser Ala Cys Ser Ala Gln Asp Val Ala Tyr Pro Glu Glu Ser Pro
        275                 280                 285
Thr Glu Pro Ser Thr Lys Leu Pro Gly Phe Asp Ser Cys Gly Lys Thr
    290                 295                 300
Glu Ile Ala Glu Arg Lys Ile Lys Arg Ile Tyr Gly Gly Phe Lys Ser
305                 310                 315                 320
Thr Ala Gly Lys His Pro Trp Gln Ala Ser Leu Gln Ser Ser Leu Pro
                325                 330                 335
Leu Thr Ile Ser Met Pro Gln Gly His Phe Cys Gly Gly Ala Leu Ile
            340                 345                 350
His Pro Cys Trp Val Leu Thr Ala Ala His Cys Thr Asp Ile Lys Thr
        355                 360                 365
Arg His Leu Lys Val Val Leu Gly Asp Gln Asp Leu Lys Lys Glu Glu
    370                 375                 380
Phe His Glu Gln Ser Phe Arg Val Glu Lys Ile Phe Lys Tyr Ser His
385                 390                 395                 400
Tyr Asn Glu Arg Asp Glu Ile Pro His Asn Asp Ile Ala Leu Leu Lys
                405                 410                 415
Leu Lys Pro Val Asp Gly His Cys Ala Leu Glu Ser Lys Tyr Val Lys
            420                 425                 430
Thr Val Cys Leu Pro Asp Gly Ser Phe Pro Ser Gly Ser Glu Cys His
        435                 440                 445
Ile Ser Gly Trp Gly Val Thr Glu Thr Gly Lys Gly Ser Arg Gln Leu
    450                 455                 460
Leu Asp Ala Lys Val Lys Leu Ile Ala Asn Thr Leu Cys Asn Ser Arg
465                 470                 475                 480
Gln Leu Tyr Asp His Met Ile Asp Asp Ser Met Ile Cys Ala Gly Asn
                485                 490                 495
Leu Gln Lys Pro Gly Gln Asp Thr Cys Gln Gly Asp Ser Gly Gly Pro
            500                 505                 510
Leu Thr Cys Glu Lys Asp Gly Thr Tyr Tyr Val Tyr Gly Ile Val Ser
        515                 520                 525
Trp Gly Leu Glu Cys Gly Lys Arg Pro Gly Val Tyr Thr Gln Val Thr
    530                 535                 540
Lys Phe Leu Asn Trp Ile Lys Ala Thr Ile Lys Ser Glu Ser Gly Phe
545                 550                 555                 560
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<210> 67
<211> 2124

<212> DNA
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 4 transcript variant 1

<400> 67
aatcaagctg cccaaagtcc cccaatcact cctggaatac acagagagag gcagcagctt 60
gctcagcgga caaggatgct gggcgtgagg gaccaaggcc tgccctgcac tcgggcctcc 120
tccagccagt gctgaccagg gacttctgac ctgctggcca gccaggacct gtgtggggag 180
gccctcctgc tgccttgggg tgacaatctc agctccaggc tacagggaga ccgggaggat 240
cacagagcca gcatgttaca ggatcctgac agtgatcaac ctctgaacag cctcgatgtc 300
aaaccccctgc gcaaaccccg tatccccatg gagaccttca gaaaggtggg gatccccatc 360
atcatagcac tactgagcct ggcgagtatc atcattgtgg ttgtcctcat caaggtgatt 420
ctggataaat actacttcct ctgcgggcag cctctccact tcatcccgag gaagcagctg 480
tgtgacggag agctggactg tcccttgggg gaggacgagg agcactgtgt caagagcttc 540
cccgaagggc ctgcagtggc agtccgcctc tccaaggacc gatccacact gcaggtgctg 600
gactcggcca cagggaactg gttctctgcc tgtttcgaca acttcacaga agctctcgct 660
gagacagcct gtaggcagat gggctacagc agcaaaccca ctttcagagc tgtggagatt 720
ggcccagacc aggatctgga tgttgttgaa atcacagaaa acagccagga gcttcgcatg 780
cggaactcaa gtgggccctg tctctcaggc tccctggtct ccctgcactg tcttgcctgt 840
gggaagagcc tgaagacccc ccgtgtggtg ggtggggagg aggcctctgt ggattcttgg 900
ccttggcagg tcagcatcca gtacgacaaa cagcacgtct gtggagggag catcctggac 960
ccccactggg tcctcacggc agcccactgc ttcaggaaac ataccgatgt gttcaactgg 1020
aaggtgcggg caggctcaga caaactgggc agcttcccat ccctggctgt ggccaagatc 1080
atcatcattg aattcaaccc catgtacccc aaagacaatg acatcgccct catgaagctg 1140
cagttcccac tcactttctc aggcacagtc aggcccatct gtctgccctt ctttgatgag 1200
gagctcactc cagccacccc actctggatc attggatggg gctttacgaa gcagaatgga 1260
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aatgcagacg atgcgtacca gggggaagtc accgagaaga tgatgtgtgc aggcatcccg 1380
gaaggggtg tggacacctg ccagggtgac agtggtgggc ccctgatgta ccaatctgac 1440
cagtggcatg tggtgggcat cgttagctgg ggctatggct gcgggggccc gagcacccca 1500
ggagtataca ccaaggtctc agcctatctc aactggatct acaatgtctg gaaggctgag 1560
ctgtaatgct gctgcccctt tgcagtgctg ggagccgctt ccttcctgcc ctgcccacct 1620
ggggatcccc caaagtcaga cacagagcaa gagtcccctt gggtacaccc ctctgcccac 1680
agcctcagca tttcttggag cagcaaaggg cctcaattcc tgtaagagac cctcgcagcc 1740
cagaggcgcc cagaggaagt cagcagccct agctcggcca cacttggtgc tcccagcatc 1800
ccagggagag acacagccca ctgaacaagg tctcaggggt attgctaagc caagaaggaa 1860
ctttcccaca ctactgaatg gaagcaggct gtcttgtaaa agcccagatc actgtgggct 1920
ggagaggaga aggaaagggt ctgcgccagc cctgtccgtc ttcacccatc cccaagccta 1980
ctagagcaag aaaccagttg taatataaaa tgcactgccc tactgttggt atgactaccg 2040
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atctctggaa aaaaaaaaaa aaaa 2124

<210> 68
<211> 437
<212> PRT
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 4 isoform 1

<400> 68
Met Leu Gln Asp Pro Asp Ser Asp Gln Pro Leu Asn Ser Leu Asp Val
 1   5   10   15
Lys Pro Leu Arg Lys Pro Arg Ile Pro Met Glu Thr Phe Arg Lys Val
            20   25   30

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Gly Ile Pro Ile Ile Ile Ala Leu Leu Ser Leu Ala Ser Ile Ile Ile
        35                  40                  45
Val Val Val Leu Ile Lys Val Ile Leu Asp Lys Tyr Tyr Phe Leu Cys
    50                  55                  60
Gly Gln Pro Leu His Phe Ile Pro Arg Lys Gln Leu Cys Asp Gly Glu
65                  70                  75                  80
Leu Asp Cys Pro Leu Gly Glu Asp Glu Glu His Cys Val Lys Ser Phe
                85                  90                  95
Pro Glu Gly Pro Ala Val Ala Val Arg Leu Ser Lys Asp Arg Ser Thr
            100                 105                 110
Leu Gln Val Leu Asp Ser Ala Thr Gly Asn Trp Phe Ser Ala Cys Phe
        115                 120                 125
Asp Asn Phe Thr Glu Ala Leu Ala Glu Thr Ala Cys Arg Gln Met Gly
    130                 135                 140
Tyr Ser Ser Lys Pro Thr Phe Arg Ala Val Glu Ile Gly Pro Asp Gln
145                 150                 155                 160
Asp Leu Asp Val Val Glu Ile Thr Glu Asn Ser Gln Glu Leu Arg Met
                165                 170                 175
Arg Asn Ser Ser Gly Pro Cys Leu Ser Gly Ser Leu Val Ser Leu His
            180                 185                 190
Cys Leu Ala Cys Gly Lys Ser Leu Lys Thr Pro Arg Val Val Gly Gly
        195                 200                 205
Glu Glu Ala Ser Val Asp Ser Trp Pro Trp Gln Val Ser Ile Gln Tyr
    210                 215                 220
Asp Lys Gln His Val Cys Gly Gly Ser Ile Leu Asp Pro His Trp Val
225                 230                 235                 240
Leu Thr Ala Ala His Cys Phe Arg Lys His Thr Asp Val Phe Asn Trp
                245                 250                 255
Lys Val Arg Ala Gly Ser Asp Lys Leu Gly Ser Phe Pro Ser Leu Ala
            260                 265                 270
Val Ala Lys Ile Ile Ile Ile Glu Phe Asn Pro Met Tyr Pro Lys Asp
        275                 280                 285
Asn Asp Ile Ala Leu Met Lys Leu Gln Phe Pro Leu Thr Phe Ser Gly
    290                 295                 300
Thr Val Arg Pro Ile Cys Leu Pro Phe Phe Asp Glu Glu Leu Thr Pro
305                 310                 315                 320
Ala Thr Pro Leu Trp Ile Ile Gly Trp Gly Phe Thr Lys Gln Asn Gly
                325                 330                 335
Gly Lys Met Ser Asp Ile Leu Leu Gln Ala Ser Val Gln Val Ile Asp
            340                 345                 350
Ser Thr Arg Cys Asn Ala Asp Asp Ala Tyr Gln Gly Glu Val Thr Glu
        355                 360                 365
Lys Met Met Cys Ala Gly Ile Pro Glu Gly Gly Val Asp Thr Cys Gln
    370                 375                 380
Gly Asp Ser Gly Gly Pro Leu Met Tyr Gln Ser Asp Gln Trp His Val
385                 390                 395                 400
Val Gly Ile Val Ser Trp Gly Tyr Gly Cys Gly Gly Pro Ser Thr Pro
                405                 410                 415
Gly Val Tyr Thr Lys Val Ser Ala Tyr Leu Asn Trp Ile Tyr Asn Val
            420                 425                 430
Trp Lys Ala Glu Leu
        435
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<210> 69
<211> 1983
<212> DNA

<213> Homo sapiens

<220>
<223> transmembrane protease, serine 4 transcript variant 2

<400> 69
aatcaagctg cccaaagtcc cccaatcact cctggaatac acagagagag gcagcagctt 60
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tccagccagt gctgaccagg gacttctgac ctgctggcca gccaggacct gtgtggggag 180
gccctcctgc tgccttgggg tgacaatctc agctccaggc tacagggaga ccgggaggat 240
cacagagcca gcatggatcc tgacagtgat caacctctga acagcctcga tgtcaaaccc 300
ctgcgcaaac cccgtatccc catggagacc ttcagaaagg tggggatccc catcatcata 360
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gccacaggga actggttctc tgcctgtttc gacaacttca cagaagctct cgctgagaca 660
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caggtcagca tccagtacga caaacagcac gtctgtggag ggagcatcct ggacccccac 960
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cgggcaggct cagacaaact gggcagcttc ccatccctgg ctgtggccaa gatcatcatc 1080
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ccactcactt tctcaggcac agtcaggccc atctgtctgc ccttctttga tgaggagctc 1200
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tagctcggcc acacttggtg ctcccagcat cccagggaga gacacagccc actgaacaag 1680
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tgtcttgtaa aagcccagat cactgtgggc tggagaggag aaggaaaggg tctgcgccag 1800
ccctgtccgt cttcacccat ccccaagcct actagagcaa gaaaccagtt gtaatataaa 1860
atgcactgcc ctactgttgg tatgactacc gttacctact gttgtcattg ttattacagc 1920
tatggccact attattaaag agctgtgtaa catctctgga aaaaaaaaaa aaaaaaaaaa 1980
aaa 1983

<210> 70
<211> 335
<212> PRT
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 4 isoform 2

<400> 70
Met Asp Pro Asp Ser Asp Gln Pro Leu Asn Ser Leu Asp Val Lys Pro
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Leu Arg Lys Pro Arg Ile Pro Met Glu Thr Phe Arg Lys Val Gly Ile
            20   25   30
Pro Ile Ile Ile Ala Leu Leu Ser Leu Ala Ser Ile Ile Ile Val Val
        35   40   45
Val Leu Ile Lys Val Ile Leu Asp Lys Tyr Tyr Phe Leu Cys Gly Gln

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    50                  55                  60
Pro Leu His Phe Ile Pro Arg Lys Gln Leu Cys Asp Gly Glu Leu Asp
65                  70                  75                  80
Cys Pro Leu Gly Glu Asp Glu Glu His Cys Val Lys Ser Phe Pro Glu
                85                  90                  95
Gly Pro Ala Val Ala Val Arg Leu Ser Lys Asp Arg Ser Thr Leu Gln
            100                 105                 110
Val Leu Asp Ser Ala Thr Gly Asn Trp Phe Ser Ala Cys Phe Asp Asn
        115                 120                 125
Phe Thr Glu Ala Leu Ala Glu Thr Ala Cys Arg Gln Met Gly Tyr Ser
    130                 135                 140
Ser Lys Pro Thr Phe Arg Ala Val Glu Ile Gly Pro Asp Gln Asp Leu
145                 150                 155                 160
Asp Val Val Glu Ile Thr Glu Asn Ser Gln Glu Leu Arg Met Arg Asn
                165                 170                 175
Ser Ser Gly Pro Cys Leu Ser Gly Ser Leu Val Ser Leu His Cys Leu
            180                 185                 190
Ala Cys Gly Lys Ser Leu Lys Thr Pro Arg Val Val Gly Gly Glu Glu
        195                 200                 205
Ala Ser Val Asp Ser Trp Pro Trp Gln Val Ser Ile Gln Tyr Asp Lys
    210                 215                 220
Gln His Val Cys Gly Gly Ser Ile Leu Asp Pro His Trp Val Leu Thr
225                 230                 235                 240
Ala Ala His Cys Phe Arg Lys His Thr Asp Val Phe Asn Trp Lys Val
                245                 250                 255
Arg Ala Gly Ser Asp Lys Leu Gly Ser Phe Pro Ser Leu Ala Val Ala
            260                 265                 270
Lys Ile Ile Ile Ile Glu Phe Asn Pro Met Tyr Pro Lys Asp Asn Asp
        275                 280                 285
Ile Ala Leu Met Lys Leu Gln Phe Pro Leu Thr Phe Ser Gly Thr Val
    290                 295                 300
Arg Pro Ile Cys Leu Pro Phe Phe Asp Glu Glu Leu Thr Pro Ala Thr
305                 310                 315                 320
Pro Leu Trp Ile Ile Gly Trp Gly Phe Thr Lys Gln Asn Gly Gly
                325                 330                 335
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<210> 71
<211> 855
<212> DNA
<213> Homo sapiens

<220>
<223> tryptase delta 1

<400> 71
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gtcctggcga gcccggccta cgtggccccc gccccaggcc aggccctgca gcaaacgggc 120
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cgcggcccat actggatgca cttctgcggg ggctccctca tccacccca gtgggtgcta 240
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ccggggatgc cgtgctgggt cactggctgg ggcgacgtgg acaataatgt gcacctgccg 540
ccgccatacc cgctgaagga ggtggaagtc cccgtagtgg aaaaccacct ttgcaacgcg 600
gaatatcaca ccggcctcca tacgggccac agctttcaaa tcgtccgcga tgacatgctg 660

tgtgcgggga gcgaaaatca cgactcctgc cagggtgact ctggagggcc cctggtctgc 720
aaggtgaatg gcacctaact gcaggcgggc gtggtcagct gggaggagag ctgtgcccag 780
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gtccccaaga agccc 855

<210> 72
<211> 242
<212> PRT
<213> Homo sapiens

<220>
<223> tryptase delta 1

<400> 72
Met Leu Leu Leu Ala Pro Gln Met Leu Ser Leu Leu Leu Leu Ala Leu
 1   5   10   15
Pro Val Leu Ala Ser Pro Ala Tyr Val Ala Pro Ala Pro Gly Gln Ala
            20   25   30
Leu Gln Gln Thr Gly Ile Val Gly Gly Gln Glu Ala Pro Arg Ser Lys
        35   40   45
Trp Pro Trp Gln Val Ser Leu Arg Val Arg Gly Pro Tyr Trp Met His
    50   55   60
Phe Cys Gly Gly Ser Leu Ile His Pro Gln Trp Val Leu Thr Ala Ala
65   70   75   80
His Cys Val Glu Pro Asp Ile Lys Asp Leu Ala Ala Leu Arg Val Gln
                85   90   95
Leu Arg Glu Gln His Leu Tyr Tyr Gln Asp Gln Leu Leu Pro Val Ser
            100   105   110
Arg Ile Ile Val His Pro Gln Phe Tyr Ile Ile Gln Thr Gly Ala Asp
        115   120   125
Ile Ala Leu Leu Glu Leu Glu Glu Pro Val Asn Ile Ser Ser His Ile
    130   135   140
His Thr Val Thr Leu Pro Pro Ala Ser Glu Thr Phe Pro Pro Gly Met
145   150   155   160
Pro Cys Trp Val Thr Gly Trp Gly Asp Val Asp Asn Asn Val His Leu
                165   170   175
Pro Pro Pro Tyr Pro Leu Lys Glu Val Glu Val Pro Val Val Glu Asn
            180   185   190
His Leu Cys Asn Ala Glu Tyr His Thr Gly Leu His Thr Gly His Ser
        195   200   205
Phe Gln Ile Val Arg Asp Asp Met Leu Cys Ala Gly Ser Glu Asn His
    210   215   220
Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Lys Val Asn
225   230   235   240
Gly Thr

<210> 73
<211> 1462
<212> DNA
<213> Homo sapiens

<220>
<223> Marapsin

<400> 73

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accgaggcca acggcacccc gtgctgcgct ggggtgaggg gtctgccctg gggtctcggg 180
gttcagggct aggtcacgga ggagtcggct ctgggcgctt ccttcctgag gagaggagct 240
gggcaggccg ggccgacggg ttgggccgca tagccgggcc tgtgctcatc tccagcataa 300
aactccactt catggagcct gcacctcgct cgtgctccaa cgcttctgcc accgccgacc 360
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gctgctgctg tgttttgggt ctcagagggc caaggcagca acagcctgtg gtcgccccag 480
gatgctgaac cgaatggtgg gcgggcagga cacgcaggag ggcgagtggc cctggcaagt 540
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cctcctgccc gaaccgcgga tcctgcagaa actcgctgtg cccatcatcg acacacccaa 960
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taaaaaccca gcctgtgtgc ca                                          1462

<210> 74
<211> 290
<212> PRT
<213> Homo sapiens

<220>
<223> Marapsin

<400> 74
Met Arg Arg Pro Ala Ala Val Pro Leu Leu Leu Leu Leu Cys Phe Gly
 1               5                  10                  15
Ser Gln Arg Ala Lys Ala Ala Thr Ala Cys Gly Arg Pro Arg Met Leu
            20                  25                  30
Asn Arg Met Val Gly Gly Gln Asp Thr Gln Glu Gly Glu Trp Pro Trp
        35                  40                  45
Gln Val Ser Ile Gln Arg Asn Gly Ser His Phe Cys Gly Gly Ser Leu
    50                  55                  60
Ile Ala Glu Gln Trp Val Leu Thr Ala Ala His Cys Phe Arg Asn Thr
65                  70                  75                  80
Ser Glu Thr Ser Leu Tyr Gln Val Leu Leu Gly Ala Arg Gln Leu Val
                85                  90                  95
Gln Pro Gly Pro His Ala Met Tyr Ala Arg Val Arg Gln Val Glu Ser
            100                 105                 110
Asn Pro Leu Tyr Gln Gly Thr Ala Ser Ser Ala Asp Val Ala Leu Val
        115                 120                 125
Glu Leu Glu Ala Pro Val Pro Phe Thr Asn Tyr Ile Leu Pro Val Cys
    130                 135                 140
Leu Pro Asp Pro Ser Val Ile Phe Glu Thr Gly Met Asn Cys Trp Val
145                 150                 155                 160
Thr Gly Trp Gly Ser Pro Ser Glu Glu Asp Leu Leu Pro Glu Pro Arg
                165                 170                 175
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Ile Leu Gln Lys Leu Ala Val Pro Ile Ile Asp Thr Pro Lys Cys Asn
            180                 185                 190
Leu Leu Tyr Ser Lys Asp Thr Glu Phe Gly Tyr Gln Pro Lys Thr Ile
        195                 200                 205
Lys Asn Asp Met Leu Cys Ala Gly Phe Glu Glu Gly Lys Lys Asp Ala
    210                 215                 220
Cys Lys Gly Asp Ser Gly Gly Pro Leu Val Cys Leu Val Gly Gln Ser
225                 230                 235                 240
Trp Leu Gln Ala Gly Val Ile Ser Trp Gly Glu Gly Cys Ala Arg Gln
                245                 250                 255
Asn Arg Pro Gly Val Tyr Ile Arg Val Thr Ala His His Asn Trp Ile
            260                 265                 270
His Arg Ile Ile Pro Lys Leu Gln Phe Gln Pro Ala Arg Leu Gly Gly
        275                 280                 285
Gln Lys
    290
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<210> 75
<211> 1755
<212> DNA
<213> Homo sapiens

<220>
<223> Tryptase homologue 2

<400> 75

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ccagcccagc cttgaagaca gaatgagagg ggtttcctgt ctccaggtcc tgctccttct 180
ggtgctggga gctgctggga ctcagggaag gaagtctgca gcctgcgggc agccccgcat 240
gtccagtcgg atcgttgggg gccgggatgg ccgggacgga gagtggccgt ggcaggcgag 300
catccagcat cgtggggcac acgtgtgcgg ggggtcgctc atcgcccccc agtgggtgct 360
gacagcggcg cactgcttcc ccaggagggc actgccagct gagtaccgcg tgcgcctggg 420
ggcgctgcgt ctgggctcca cctcgccccg cacgctctcg gtgcccgtgc gacgggtgct 480
gctgcccccg gactactccg aggacggggc ccgcggcgac ctggcactgc tgcagctgcg 540
tcgcccggtg cccctgagcg ctcgcgtcca acccgtctgc ctgcccgtgc ccggcgcccg 600
cccgccgccc ggcacaccat gccgggtcac cggctggggc agcctccgcc caggagtgcc 660
cctcccagag tggcgaccgc tacaaggagt aagggtgccg ctgctggact cgcgcacctg 720
cgacggcctc taccacgtgg gcgcggacgt gccccaggct gagcgcattg tgctgcctgg 780
gagtctgtgt gccggctacc cccagggcca caaggacgcc tgccagggtg attctggggg 840
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cctcctctcc tctttgggga tcaccagctc tgactccacc aaccctcatc caggaatctg 1200
ccatgagtcc cagggagtca cactccccac tcccttcctg gcttgtattt acttttcttg 1260
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agagccccgc cggccaatcc cttcatttca acctaaagag accctaagca gagaacctag 1620
ctgagccact cctgacctac aaagttgtga cttaataaat gtgtgctttg aacccaaaaa 1680
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aaaaaaaaaa aaaaa                                                  1755
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<210> 76
<211> 284
<212> PRT
<213> Homo sapiens

<220>
<223> Tryptase homologue 2

<400> 76
Met Arg Gly Val Ser Cys Leu Gln Val Leu Leu Leu Leu Val Leu Gly
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Ala Ala Gly Thr Gln Gly Arg Lys Ser Ala Ala Cys Gly Gln Pro Arg
            20   25   30
Met Ser Ser Arg Ile Val Gly Gly Arg Asp Gly Arg Asp Gly Glu Trp
        35   40   45
Pro Trp Gln Ala Ser Ile Gln His Pro Gly Ala His Val Cys Gly Gly
    50   55   60
Ser Leu Ile Ala Pro Gln Trp Val Leu Thr Ala Ala His Cys Phe Pro
65   70   75   80
Arg Arg Ala Leu Pro Ala Glu Tyr Arg Val Arg Leu Gly Ala Leu Arg
                85   90   95
Leu Gly Ser Thr Ser Pro Arg Thr Leu Ser Val Pro Val Arg Arg Val
            100   105   110
Leu Leu Pro Pro Asp Tyr Ser Glu Asp Gly Ala Arg Gly Asp Leu Ala
        115   120   125
Leu Leu Gln Leu Arg Arg Pro Val Pro Leu Ser Ala Arg Val Gln Pro
    130   135   140
Val Cys Leu Pro Val Pro Gly Ala Arg Pro Pro Pro Gly Thr Pro Cys
145   150   155   160
Arg Val Thr Gly Trp Gly Ser Leu Arg Pro Gly Val Pro Leu Pro Glu
                165   170   175
Trp Arg Pro Leu Gln Gly Val Arg Val Pro Leu Leu Asp Ser Arg Thr
            180   185   190
Cys Asp Gly Leu Tyr His Val Gly Ala Asp Val Pro Gln Ala Glu Arg
        195   200   205
Ile Val Leu Pro Gly Ser Leu Cys Ala Gly Tyr Pro Gln Gly His Lys
    210   215   220
Asp Ala Cys Gln Gly Asp Ser Gly Gly Pro Leu Thr Cys Leu Gln Ser
225   230   235   240
Gly Ser Trp Val Leu Val Gly Val Val Ser Trp Gly Lys Gly Cys Ala
                245   250   255
Leu Pro Asn Arg Pro Gly Val Tyr Thr Ser Val Ala Thr Tyr Ser Pro
            260   265   270
Trp Ile Gln Ala Arg Val Thr Ser Asn Ala Ser Arg
        275   280

<210> 77
<211> 321
<212> DNA
<213> Homo sapiens

<220>
<223> Tryptase homologue 3

<400> 77

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gctgcgcact gcttcgctcc ccagggtgac tcaggtggac ccttggtctg tgacaaggat 180
ggactgtggt atcaggttgg aatcgtgagc tggggaatgg actgcggtca acccaatcgg 240
cctggtgtct acaccaacat cagtgtgtac ttccactgga tccggagggt gatgtcccac 300
agtacaccca ggccaaaccc c 321

<210> 78
<211> 107
<212> PRT
<213> Homo sapiens

<220>
<223> Tryptase homologue 3

<400> 78
Ala Leu Val Ala Gly Gly Val Glu Ser Ala Arg Gly Arg Trp Pro Trp
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Gln Ala Ser Leu Arg Leu Arg Arg Arg His Arg Cys Gly Gly Ser Leu
20 25 30
Leu Ser Arg Arg Trp Val Leu Ser Ala Ala His Cys Phe Ala Pro Gln
35 40 45
Gly Asp Ser Gly Gly Pro Leu Val Cys Asp Lys Asp Gly Leu Trp Tyr
50 55 60
Gln Val Gly Ile Val Ser Trp Gly Met Asp Cys Gly Gln Pro Asn Arg
65 70 75 80
Pro Gly Val Tyr Thr Asn Ile Ser Val Tyr Phe His Trp Ile Arg Arg
85 90 95
Val Met Ser His Ser Thr Pro Arg Pro Asn Pro
100 105

<210> 79
<211> 2468
<212> DNA
<213> Homo sapiens

<220>

<223> transmembrane protease, serine 3 transcript variant A

<400> 79
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ccatctacat ttttgggact cgggaattat gaggtagagg tggaggcgga gccggatgtc 180
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gatgctgttg ctgcacagat cctgtcactg ctgccattga agtttttcc aatcatcgtc 360
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aaaaaaaa 2468

<210> 80
<211> 454
<212> PRT
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 3 isoform 1

<400> 80
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Ser Leu Phe Gly Leu Asp Asp Leu Lys Ile Ser Pro Val Ala Pro Asp
            20   25   30
Ala Asp Ala Val Ala Ala Gln Ile Leu Ser Leu Leu Pro Leu Lys Phe
        35   40   45
Phe Pro Ile Ile Val Ile Gly Ile Ile Ala Leu Ile Leu Ala Leu Ala
    50   55   60
Ile Gly Leu Gly Ile His Phe Asp Cys Ser Gly Lys Tyr Arg Cys Arg
65   70   75   80
Ser Ser Phe Lys Cys Ile Glu Leu Ile Ala Arg Cys Asp Gly Val Ser
                85   90   95
Asp Cys Lys Asp Gly Glu Asp Glu Tyr Arg Cys Val Arg Val Gly Gly
            100   105   110
Gln Asn Ala Val Leu Gln Val Phe Thr Ala Ala Ser Trp Lys Thr Met
        115   120   125
Cys Ser Asp Asp Trp Lys Gly His Tyr Ala Asn Val Ala Cys Ala Gln
    130   135   140
Leu Gly Phe Pro Ser Tyr Val Ser Ser Asp Asn Leu Arg Val Ser Ser

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145                 150                 155                 160
Leu Glu Gly Gln Phe Arg Glu Glu Phe Val Ser Ile Asp His Leu Leu
                165                 170                 175
Pro Asp Asp Lys Val Thr Ala Leu His His Ser Val Tyr Val Arg Glu
            180                 185                 190
Gly Cys Ala Ser Gly His Val Val Thr Leu Gln Cys Thr Ala Cys Gly
        195                 200                 205
His Arg Arg Gly Tyr Ser Ser Arg Ile Val Gly Gly Asn Met Ser Leu
    210                 215                 220
Leu Ser Gln Trp Pro Trp Gln Ala Ser Leu Gln Phe Gln Gly Tyr His
225                 230                 235                 240
Leu Cys Gly Gly Ser Val Ile Thr Pro Leu Trp Ile Ile Thr Ala Ala
                245                 250                 255
His Cys Val Tyr Asp Leu Tyr Leu Pro Lys Ser Trp Thr Ile Gln Val
            260                 265                 270
Gly Leu Val Ser Leu Leu Asp Asn Pro Ala Pro Ser His Leu Val Glu
        275                 280                 285
Lys Ile Val Tyr His Ser Lys Tyr Lys Pro Lys Arg Leu Gly Asn Asp
    290                 295                 300
Ile Ala Leu Met Lys Leu Ala Gly Pro Leu Thr Phe Asn Glu Met Ile
305                 310                 315                 320
Gln Pro Val Cys Leu Pro Asn Ser Glu Glu Asn Phe Pro Asp Gly Lys
                325                 330                 335
Val Cys Trp Thr Ser Gly Trp Gly Ala Thr Glu Asp Gly Ala Gly Asp
            340                 345                 350
Ala Ser Pro Val Leu Asn His Ala Ala Val Pro Leu Ile Ser Asn Lys
        355                 360                 365
Ile Cys Asn His Arg Asp Val Tyr Gly Gly Ile Ile Ser Pro Ser Met
    370                 375                 380
Leu Cys Ala Gly Tyr Leu Thr Gly Gly Val Asp Ser Cys Gln Gly Asp
385                 390                 395                 400
Ser Gly Gly Pro Leu Val Cys Gln Glu Arg Arg Leu Trp Lys Leu Val
                405                 410                 415
Gly Ala Thr Ser Phe Gly Ile Gly Cys Ala Glu Val Asn Lys Pro Gly
            420                 425                 430
Val Tyr Thr Arg Val Thr Ser Phe Leu Asp Trp Ile His Glu Gln Met
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Glu Arg Asp Leu Lys Thr
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<210> 81
<211> 2554
<212> DNA
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 3 transcript variant B

<400> 81
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tgtctttctg ggggatacta ttcaacccat agcacatccc ctcatccccc atggaataac 180
cgggtcagag gtggagcagg taggactgaa ctagagaatg tgccccttgg tgggtggccc 240
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aaggatagtt aaatttgtaa gtttcatggc actccaagtc aggttctggg gctttctgct 360
cttccttttt ctggttatca gatgcagatg ctgttgctgc acagatcctg tcactgctgc 420
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ggaagaccat gtgctccgat gactggaagg gtcactacgc aaatgttgcc tgtgcccaac 720
tgggtttccc aagctatgtg agttcagata acctcagagt gagctcgctg gaggggcagt 780
tccgggagga gtttgtgtcc atcgatcacc tcttgccaga tgacaaggtg actgcattac 840
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cagcctgtgg tcatagaagg ggctacagct cacgcatcgt gggtggaaac atgtccttgc 960
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tgcccaactc tgaagagaac ttccccgatg gaaaagtgtg ctggacgtca ggatgggggg 1320
ccacagagga tggagcaggt gacgcctccc ctgtcctgaa ccacgcggcc gtccctttga 1380
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tggtgtgtca agagaggagg ctgtggaagt tagtgggagc gaccagcttt ggcatcggct 1560
gcgcagaggt gaacaagcct ggggtgtaca cccgtgtcac ctccttcctg gactggatcc 1620
acgagcagat ggagagagac ctaaaaacct gaagaggaag gggacaagta gccacctgag 1680
ttcctgaggt gatgaagaca gcccgatcct cccctggact cccgtgtagg aacctgcaca 1740
cgagcagaca cccttggagc tctgagttcc ggcaccagta gcaggcccga aagaggcacc 1800
cttccatctg attccagcac aaccttcaag ctgctttttg ttttttgttt ttttgaggtg 1860
gagtctcgct ctgttgccca ggctggagtg cagtggcgaa atccctgctc actgcagcct 1920
ccgcttccct ggttcaagcg attctcttgc ctcagcttcc ccagtagctg ggaccacagg 1980
tgcccgccac cacacccaac taatttttgt atttttagta gagacagggt ttcaccatgt 2040
tggccaggct gctctcaaac ccctgacctc aaatgatgtg cctgcttcag cctcccacag 2100
tgctgggatt acaggcatgg gccaccacgc ctagcctcac gctcctttct gatcttcact 2160
aagaacaaaa gaagcagcaa cttgcaaggg cggcctttcc cactggtcca tctggttttc 2220
tctccagggg tcttgcaaaa ttcctgacga gataagcagt tatgtgacct cacgtgcaaa 2280
gccaccaaca gccactcaga aaagacgcac cagcccagaa gtgcagaact gcagtcactg 2340
cacgttttca tctctaggga ccagaaccaa acccaccctt tctacttcca agacttattt 2400
tcacatgtgg ggaggttaat ctaggaatga ctcgtttaag gcctattttc atgatttctt 2460
tgtagcattt ggtgcttgac gtattattgt cctttgattc caaataatat gtttccttcc 2520
ctcaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa                              2554
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<210> 82
<211> 327
<212> PRT
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 3 isoform 2

<400> 82

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Met Cys Ser Asp Asp Trp Lys Gly His Tyr Ala Asn Val Ala Cys Ala
 1               5                  10                  15
Gln Leu Gly Phe Pro Ser Tyr Val Ser Ser Asp Asn Leu Arg Val Ser
            20                  25                  30
Ser Leu Glu Gly Gln Phe Arg Glu Glu Phe Val Ser Ile Asp His Leu
        35                  40                  45
Leu Pro Asp Asp Lys Val Thr Ala Leu His His Ser Val Tyr Val Arg
    50                  55                  60
Glu Gly Cys Ala Ser Gly His Val Val Thr Leu Gln Cys Thr Ala Cys
65                  70                  75                  80
Gly His Arg Arg Gly Tyr Ser Ser Arg Ile Val Gly Gly Asn Met Ser
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                85                  90                  95
Leu Leu Ser Gln Trp Pro Trp Gln Ala Ser Leu Gln Phe Gln Gly Tyr
            100                 105                 110
His Leu Cys Gly Gly Ser Val Ile Thr Pro Leu Trp Ile Ile Thr Ala
        115                 120                 125
Ala His Cys Val Tyr Asp Leu Tyr Leu Pro Lys Ser Trp Thr Ile Gln
    130                 135                 140
Val Gly Leu Val Ser Leu Leu Asp Asn Pro Ala Pro Ser His Leu Val
145                 150                 155                 160
Glu Lys Ile Val Tyr His Ser Lys Tyr Lys Pro Lys Arg Leu Gly Asn
                165                 170                 175
Asp Ile Ala Leu Met Lys Leu Ala Gly Pro Leu Thr Phe Asn Glu Met
            180                 185                 190
Ile Gln Pro Val Cys Leu Pro Asn Ser Glu Glu Asn Phe Pro Asp Gly
        195                 200                 205
Lys Val Cys Trp Thr Ser Gly Trp Gly Ala Thr Glu Asp Gly Ala Gly
    210                 215                 220
Asp Ala Ser Pro Val Leu Asn His Ala Ala Val Pro Leu Ile Ser Asn
225                 230                 235                 240
Lys Ile Cys Asn His Arg Asp Val Tyr Gly Gly Ile Ile Ser Pro Ser
                245                 250                 255
Met Leu Cys Ala Gly Tyr Leu Thr Gly Gly Val Asp Ser Cys Gln Gly
            260                 265                 270
Asp Ser Gly Gly Pro Leu Val Cys Gln Glu Arg Arg Leu Trp Lys Leu
        275                 280                 285
Val Gly Ala Thr Ser Phe Gly Ile Gly Cys Ala Glu Val Asn Lys Pro
    290                 295                 300
Gly Val Tyr Thr Arg Val Thr Ser Phe Leu Asp Trp Ile His Glu Gln
305                 310                 315                 320
Met Glu Arg Asp Leu Lys Thr
                325
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<210> 83
<211> 2135
<212> DNA
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 3 transcript variant C

<400> 83
gcaggggac agttgttagt gttgcactct gaaagagctg ttggttaatt cctgccttcc 60
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tgtatcgagc tgatagctcg atgtgacgga gtctcggatt gcaaagacgg ggaggacgag 180
taccgctgtg tccgggtggg tggtcagaat gccgtgctcc aggtgttcac agctgcttcg 240
tggaagacca tgtgctccga tgactggaag ggtcactacg caaatgttgc ctgtgcccaa 300
ctgggtttcc caagctatgt gagttcagat aacctcagag tgagctcgct ggaggggcag 360
ttccgggagg agtttgtgtc catcgatcac ctcttgccag atgacaaggt gactgcatta 420
caccactcag tatatgtgag ggagggatgt gcctctggcc acgtggttac cttgcagtgc 480
acagcctgtg gtcatagaag gggctacagc tcacgcatcg tgggtggaaa catgtccttg 540
ctctcgcagt ggccctggca ggccagcctt cagttccagg gctaccacct gtgcgggggc 600
tctgtcatca cgcccctgtg gatcatcact gctgcacact gtgtttatga cttgtacctc 660
cccaagtcat ggaccatcca ggtgggtcta gtttccctgt tggacaatcc agccccatcc 720
cacttggtgg agaagattgt ctaccacagc aagtacaagc caaagaggct gggcaatgac 780
atcgccctta tgaagctggc cgggccactc acgttcaatg aaatgatcca gcctgtgtgc 840
ctgcccaact ctgaagagaa cttccccgat ggaaaagtgt gctggacgtc aggatggggg 900

gccacagagg atggagcagg tgacgcctcc cctgtcctga accacgcggc cgtccctttg 960
atttccaaca agatctgcaa ccacagggac gtgtacggtg gcatcatctc cccctccatg 1020
ctctgcgcgg gctacctgac gggtggcgtg gacagctgcc agggggacag cgggggccc 1080
ctggtgtgtc aagagaggag gctgtggaag ttagtgggag cgaccagctt tggcatcggc 1140
tgcgcagagg tgaacaagcc tggggtgtac acccgtgtca cctccttcct ggactggatc 1200
cacgagcaga tggagagaga cctaaaaacc tgaagaggaa ggggacaagt agccacctga 1260
gttcctgagg tgatgaagac agcccgatcc tcccctggac tcccgtgtag gaacctgcac 1320
acgagcagac acccttggag ctctgagttc cggcaccagt agcaggcccg aaagaggcac 1380
ccttccatct gattccagca caaccttcaa gctgcttttt gtttttttgtt tttttgaggt 1440
ggagtctcgc tctgttgccc aggctggagt gcagtggcga aatccctgct cactgcagcc 1500
tccgcttccc tggttcaagc gattctcttg cctcagcttc cccagtagct gggaccacag 1560
gtgcccgcca ccacacccaa ctaatttttg tatttttagt agagacaggg tttcaccatg 1620
ttggccaggc tgctctcaaa cccctgacct caaatgatgt gcctgcttca gcctcccaca 1680
gtgctgggat tacaggcatg ggccaccacg cctagcctca cgctcctttc tgatcttcac 1740
taagaacaaa agaagcagca acttgcaagg gcggcctttc ccactggtcc atctggtttt 1800
ctctccaggg gtcttgcaaa attcctgacg agataagcag ttatgtgacc tcacgtgcaa 1860
agccaccaac agccactcag aaaagacgca ccagcccaga agtgcagaac tgcagtcact 1920
gcacgttttc atctctaggg accagaacca aacccaccct ttctacttcc aagacttatt 1980
ttcacatgtg gggaggttaa tctaggaatg actcgtttaa ggcctatttt catgatttct 2040
ttgtagcatt tggtgcttga cgtattattg tcctttgatt ccaaataata tgtttccttc 2100
cctcaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 2135

<210> 84
<211> 327
<212> PRT
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 3 isoform 2

<400> 84
Met Cys Ser Asp Asp Trp Lys Gly His Tyr Ala Asn Val Ala Cys Ala
1 5 10 15
Gln Leu Gly Phe Pro Ser Tyr Val Ser Ser Asp Asn Leu Arg Val Ser
20 25 30
Ser Leu Glu Gly Gln Phe Arg Glu Glu Phe Val Ser Ile Asp His Leu
35 40 45
Leu Pro Asp Asp Lys Val Thr Ala Leu His His Ser Val Tyr Val Arg
50 55 60
Glu Gly Cys Ala Ser Gly His Val Val Thr Leu Gln Cys Thr Ala Cys
65 70 75 80
Gly His Arg Arg Gly Tyr Ser Ser Arg Ile Val Gly Gly Asn Met Ser
85 90 95
Leu Leu Ser Gln Trp Pro Trp Gln Ala Ser Leu Gln Phe Gln Gly Tyr
100 105 110
His Leu Cys Gly Gly Ser Val Ile Thr Pro Leu Trp Ile Ile Thr Ala
115 120 125
Ala His Cys Val Tyr Asp Leu Tyr Leu Pro Lys Ser Trp Thr Ile Gln
130 135 140
Val Gly Leu Val Ser Leu Leu Asp Asn Pro Ala Pro Ser His Leu Val
145 150 155 160
Glu Lys Ile Val Tyr His Ser Lys Tyr Lys Pro Lys Arg Leu Gly Asn
165 170 175
Asp Ile Ala Leu Met Lys Leu Ala Gly Pro Leu Thr Phe Asn Glu Met
180 185 190
Ile Gln Pro Val Cys Leu Pro Asn Ser Glu Glu Asn Phe Pro Asp Gly
195 200 205

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Lys Val Cys Trp Thr Ser Gly Trp Gly Ala Thr Glu Asp Gly Ala Gly
    210                 215                 220
Asp Ala Ser Pro Val Leu Asn His Ala Ala Val Pro Leu Ile Ser Asn
225                 230                 235                 240
Lys Ile Cys Asn His Arg Asp Val Tyr Gly Gly Ile Ile Ser Pro Ser
                245                 250                 255
Met Leu Cys Ala Gly Tyr Leu Thr Gly Gly Val Asp Ser Cys Gln Gly
            260                 265                 270
Asp Ser Gly Gly Pro Leu Val Cys Gln Glu Arg Arg Leu Trp Lys Leu
        275                 280                 285
Val Gly Ala Thr Ser Phe Gly Ile Gly Cys Ala Glu Val Asn Lys Pro
    290                 295                 300
Gly Val Tyr Thr Arg Val Thr Ser Phe Leu Asp Trp Ile His Glu Gln
305                 310                 315                 320
Met Glu Arg Asp Leu Lys Thr
                325
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<210> 85
<211> 1359
<212> DNA
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 3 transcript variant D

<400> 85
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ggaaagggct gtgtttatgg gaagccagta acactgtggc ctactatctc ttccgtggtg 120
ccatctacat ttttgggact cgggaattat gaggtagagg tggaggcgga gccggatgtc 180
agaggtcctg aaatagtcac catgggggaa aatgatccgc ctgctgttga agcccccttc 240
tcattccgat cgctttttgg ccttgatgat ttgaaaataa gtcctgttgc accagatgca 300
gatgctgttg ctgcacagat cctgtcactg ctgccattga agtttttttcc aatcatcgtc 360
attgggatca ttgcattgat attagcactg gccattggtc tgggcatcca cttcgactgc 420
tcagggaagt acagatgtcg ctcatccttt aagtgtatcg agctgatagc tcgatgtgac 480
ggagtctcgg attgcaaaga cggggaggac gagtaccgct gtgtccgggt gggtggtcag 540
aatgccgtgc tccaggtgtt cacagctgct tcgtggaaga ccatgtgctc cgatgactgg 600
aagggtcact acgcaaatgt tgcctgtgcc caactgggtt tcccaagcta tgtgagttca 660
gataacctca gagtgagctc gctggagggg cagttccggg aggagtttgt gtccatcgat 720

cacctcttgc cagatgacaa ggtgactgca ttacaccact cagtatatgt gagggaggga 780
tgtgcctctg gccacgtggt taccttgcag tgcacagcct gtggtcatag aaggggctac 840
agctcacgca tcgtgggtgg aaacatgtcc ttgctctcgc agtggccctg gcaggccagc 900
cttcagttcc agggctacca cctgtgcggg ggctctgtca tcacgcccct gtggatcatc 960
actgctgcac actgtgttta tgacttgtac ctccccaagt catggaccat ccaggtgggt 1020
ctagtttccc tgttggacaa tccagcccca tcccacttgg tggagaagat tgtctaccac 1080
agcaagtaca agccaaagag gctgggcaat gacatcgccc ttatgaagct ggccgggcca 1140
ctcacgttca atggtacatc tgggtctcta tgtggttctg cagctcttcc tttgtttcaa 1200
gaggatttgc aattgctcat tgaagcattc ttatgatggc tgctttataa tccttgtcag 1260
atattaataa ttccaactcc tgattcatgt tggtgttggc atcagttgat tatcttttct 1320
cattaaaatt gtgatgctcc taaaaaaaaa aaaaaaaaa                        1359
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<210> 86
<211> 344
<212> PRT
<213> Homo sapiens

<220>
<223> transmembrane protease, serine 3 isoform 3

<400> 86
Met Gly Glu Asn Asp Pro Pro Ala Val Glu Ala Pro Phe Ser Phe Arg
1 5 10 15
Ser Leu Phe Gly Leu Asp Asp Leu Lys Ile Ser Pro Val Ala Pro Asp
20 25 30
Ala Asp Ala Val Ala Ala Gln Ile Leu Ser Leu Leu Pro Leu Lys Phe
35 40 45
Phe Pro Ile Ile Val Ile Gly Ile Ile Ala Leu Ile Leu Ala Leu Ala
50 55 60
Ile Gly Leu Gly Ile His Phe Asp Cys Ser Gly Lys Tyr Arg Cys Arg
65 70 75 80
Ser Ser Phe Lys Cys Ile Glu Leu Ile Ala Arg Cys Asp Gly Val Ser
85 90 95
Asp Cys Lys Asp Gly Glu Asp Glu Tyr Arg Cys Val Arg Val Gly Gly
100 105 110
Gln Asn Ala Val Leu Gln Val Phe Thr Ala Ala Ser Trp Lys Thr Met
115 120 125
Cys Ser Asp Asp Trp Lys Gly His Tyr Ala Asn Val Ala Cys Ala Gln
130 135 140
Leu Gly Phe Pro Ser Tyr Val Ser Ser Asp Asn Leu Arg Val Ser Ser
145 150 155 160
Leu Glu Gly Gln Phe Arg Glu Glu Phe Val Ser Ile Asp His Leu Leu
165 170 175
Pro Asp Asp Lys Val Thr Ala Leu His His Ser Val Tyr Val Arg Glu
180 185 190
Gly Cys Ala Ser Gly His Val Val Thr Leu Gln Cys Thr Ala Cys Gly
195 200 205
His Arg Arg Gly Tyr Ser Ser Arg Ile Val Gly Gly Asn Met Ser Leu
210 215 220
Leu Ser Gln Trp Pro Trp Gln Ala Ser Leu Gln Phe Gln Gly Tyr His
225 230 235 240
Leu Cys Gly Gly Ser Val Ile Thr Pro Leu Trp Ile Ile Thr Ala Ala
245 250 255
His Cys Val Tyr Asp Leu Tyr Leu Pro Lys Ser Trp Thr Ile Gln Val
260 265 270
Gly Leu Val Ser Leu Leu Asp Asn Pro Ala Pro Ser His Leu Val Glu
275 280 285
Lys Ile Val Tyr His Ser Lys Tyr Lys Pro Lys Arg Leu Gly Asn Asp
290 295 300
Ile Ala Leu Met Lys Leu Ala Gly Pro Leu Thr Phe Asn Gly Thr Ser
305 310 315 320
Gly Ser Leu Cys Gly Ser Ala Ala Leu Pro Leu Phe Gln Glu Asp Leu
325 330 335
Gln Leu Leu Ile Glu Ala Phe Leu
340

<210> 87
<211> 1191
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK15 transcript variant 1

<400> 87
actgcagccg aaccctggtc cctcctccac aatgtggctt ctcctcactc tctccttcct 60
gctggcatcc acagcagccc aggatggtga caagttgctg gaaggtgacg agtgtgcacc 120
ccactcccag ccatggcaag tggctctcta cgagcgtgga cgctttaact gtggcgcttc 180
cctcatctcc ccacactggg tgctgtctgc ggcccactgc caaagccgct tcatgagagt 240
gcgcctggga gagcacaacc tgcgcaagcg cgatggccca gagcaactac ggaccacgtc 300
tcgggtcatt ccacacccgc gctacgaagc gcgcagccac cgcaacgaca tcatgttgct 360
gcgcctagtc cagcccgcac gcctgaaccc ccagtgagtc tcccagatac gttgcattgt 420
gccaacatca gcattatctc ggacacatct tgtgacaaga gctacccagg gcgcctgaca 480
aacaccatgg tgtgtgcagg cgcggagggc agaggcgcag aatcctgtga gggtgactct 540
gggggacccc tggtctgtgg gggcatcctg cagggcattg tgtcctgggg tgacgtccct 600
tgtgacaaca ccaccaagcc tggtgtctat accaaagtct gccactactt ggagtggatc 660
agggaaacca tgaagaggaa ctgactattc tagcctatct cctgtgcccc tgactgagca 720
gaagccccca cagctggcca gcagccccgc ctgacatgga acagaacgga gccatccccc 780
aagaccctgt ccaaggccca gatgttagcc aaggacttgt cccacctgag gacaaagctg 840
gcgctcaagg tcacctgttt aatgccaaga taacaaagcg ctgatccaag ttgctctgta 900
ggaatttctg tgacttttt ctggggtcaa agagaaaccc cgagacactg tacactgttc 960
cttttcaccc accaccccga tccctaggtg aggagaagcg gcttgaagca gggctccatt 1020
cattcaacac acatgaccac ccgtgtgatc ttgaacaaga ggcccaatct cacttcgcct 1080
tggtttcctt atctgtaaaa tgagaccatc ttattgctga cttcaaaggg ctgttgtgag 1140
gattaaatga gatgattcgt ctgaactgat taaaatcgtg tctggcactg a 1191

<210> 88
<211> 121
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK15 isoform 1

<400> 88
Met Trp Leu Leu Leu Thr Leu Ser Phe Leu Leu Ala Ser Thr Ala Ala
 1   5   10   15
Gln Asp Gly Asp Lys Leu Leu Glu Gly Asp Glu Cys Ala Pro His Ser
            20   25   30
Gln Pro Trp Gln Val Ala Leu Tyr Glu Arg Gly Arg Phe Asn Cys Gly
        35   40   45
Ala Ser Leu Ile Ser Pro His Trp Val Leu Ser Ala Ala His Cys Gln
    50   55   60
Ser Arg Phe Met Arg Val Arg Leu Gly Glu His Asn Leu Arg Lys Arg
65   70   75   80
Asp Gly Pro Glu Gln Leu Arg Thr Thr Ser Arg Val Ile Pro His Pro
                85   90   95
Arg Tyr Glu Ala Arg Ser His Arg Asn Asp Ile Met Leu Leu Arg Leu
            100   105   110
Val Gln Pro Ala Arg Leu Asn Pro Gln
        115   120

<210> 89
<211> 1172
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK15 transcript variant 2

<400> 89
actgcagccg aaccctggtc cctcctccac aatgtggctt ctcctcactc tctccttcct 60
gctggcatcc acagcagccc aggatggtga caagttgctg gaaggtgacg agtgtgcacc 120
ccactcccag ccatggcaag tggctctcta cgagcgtgga cgctttaact gtggcgcttc 180
cctcatctcc ccacactggg tgctgtctgc ggcccactgc caaagccgct tcatgagagt 240
gcgcctggga gagcacaacc tgcgcaagcg cgatggccca gagcaactac ggaccacgtc 300
tcgggtcatt ccacacccgc gctacgaagc gcgcagccac cgcaacgaca tcatgttgct 360
gcgcctagtc cagcccgcac gcctgaaccc ccaggtgcgc cccgcggtgc tacccacgcg 420
ttgcccccac ccgggggagg cctgtgtggt gtctggctgg ggcctggtgt cccacaacga 480
gcctgggacc gctgggagcc cccggtcaca agggtgactc tgggggaccc ctggtctgtg 540
ggggcatcct gcagggcatt gtgtcctggg gtgacgtccc ttgtgacaac accaccaagc 600
ctggtgtcta taccaaagtc tgccactact tggagtggat cagggaaacc atgaagagga 660
actgactatt ctagcctatc tcctgtgccc ctgactgagc agaagccccc acagctggcc 720
agcagccccg cctgacatgg aacagaacgg agccatcccc caagaccctg tccaaggccc 780
agatgttagc caaggacttg tcccacctga ggacaaagct ggcgctcaag gtcacctgtt 840
taatgccaag ataacaaagc gctgatccaa gttgctctgt aggaatttct gtgacttttt 900
tctggggtca aagagaaacc ccgagacact gtacactgtt ccttttcacc caccaccccg 960
atccctaggt gaggagaagc ggcttgaagc agggctccat tcattcaaca cacatgacca 1020
cccgtgtgat cttgaacaag aggcccaatc tcacttcgcc ttggtttcct tatctgtaaa 1080
atgagaccat cttattgctg acttcaaagg gctgttgtga ggattaaatg agatgattcg 1140
tctgaactga ttaaaatcgt gtctggcact ga 1172

<210> 90
<211> 161
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK15 isoform 2

<400> 90
Met Trp Leu Leu Leu Thr Leu Ser Phe Leu Leu Ala Ser Thr Ala Ala
 1   5   10   15
Gln Asp Gly Asp Lys Leu Leu Glu Gly Asp Glu Cys Ala Pro His Ser
            20   25   30
Gln Pro Trp Gln Val Ala Leu Tyr Glu Arg Gly Arg Phe Asn Cys Gly
        35   40   45
Ala Ser Leu Ile Ser Pro His Trp Val Leu Ser Ala Ala His Cys Gln
    50   55   60
Ser Arg Phe Met Arg Val Arg Leu Gly Glu His Asn Leu Arg Lys Arg
65   70   75   80
Asp Gly Pro Glu Gln Leu Arg Thr Thr Ser Arg Val Ile Pro His Pro
                85   90   95
Arg Tyr Glu Ala Arg Ser His Arg Asn Asp Ile Met Leu Leu Arg Leu
            100   105   110
Val Gln Pro Ala Arg Leu Asn Pro Gln Val Arg Pro Ala Val Leu Pro
        115   120   125
Thr Arg Cys Pro His Pro Gly Glu Ala Cys Val Val Ser Gly Trp Gly
    130   135   140
Leu Val Ser His Asn Glu Pro Gly Thr Ala Gly Ser Pro Arg Ser Gln
145   150   155   160
Gly

<210> 91

<211> 1054
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK15 transcript variant 3

<400> 91

actgcagccg aaccctggtc cctcctccac aatgtggctt ctcctcactc tctccttcct 60
gctggcatcc acagcagccc aggatggtga caagttgctg gaaggtgacg agtgtgcacc 120
ccactcccag ccatggcaag tggctctcta cgagcgtgga cgctttaact gtggcgcttc 180
cctcatctcc ccacactggg tgctgtctgc ggcccactgc caaagccgct tcatgagagt 240
gcgcctggga gagcacaacc tgcgcaagcg cgatggccca gagcaactac ggaccacgtc 300
tcgggtcatt ccacacccgc gctacgaagc gcgcagccac cgcaacgaca tcatgttgct 360
gcgcctagtc cagcccgcac gcctgaaccc ccagggtgac tctgggggac ccctggtctg 420
tgggggcatc ctgcagggca ttgtgtcctg gggtgacgtc ccttgtgaca acaccaccaa 480
gcctggtgtc tataccaaag tctgccacta cttggagtgg atcagggaaa ccatgaagag 540
gaactgacta ttctagccta tctcctgtgc ccctgactga gcagaagccc ccacagctgg 600
ccagcagccc cgcctgacat ggaacagaac ggagccatcc cccaagaccc tgtccaaggc 660
ccagatgtta gccaaggact tgtcccacct gaggacaaag ctggcgctca aggtcacctg 720
tttaatgcca agataacaaa gcgctgatcc aagttgctct gtaggaattt ctgtgacttt 780
tttctggggt caaagagaaa ccccgagaca ctgtacactg ttccttttca cccaccaccc 840
cgatccctag gtgaggagaa gcggcttgaa gcagggctcc attcattcaa cacacatgac 900
cacccgtgtg atcttgaaca agaggcccaa tctcacttcg ccttggtttc cttatctgta 960
aaatgagacc atcttattgc tgacttcaaa gggctgttgt gaggattaaa tgagatgatt 1020
cgtctgaact gattaaaatc gtgtctggca ctga 1054

<210> 92
<211> 171
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK15 isoform 3

<400> 92
Met Trp Leu Leu Leu Thr Leu Ser Phe Leu Leu Ala Ser Thr Ala Ala
 1   5   10   15
Gln Asp Gly Asp Lys Leu Leu Glu Gly Asp Glu Cys Ala Pro His Ser
            20   25   30
Gln Pro Trp Gln Val Ala Leu Tyr Glu Arg Gly Arg Phe Asn Cys Gly
        35   40   45
Ala Ser Leu Ile Ser Pro His Trp Val Leu Ser Ala Ala His Cys Gln
    50   55   60
Ser Arg Phe Met Arg Val Arg Leu Gly Glu His Asn Leu Arg Lys Arg
65   70   75   80
Asp Gly Pro Glu Gln Leu Arg Thr Thr Ser Arg Val Ile Pro His Pro
                85   90   95
Arg Tyr Glu Ala Arg Ser His Arg Asn Asp Ile Met Leu Leu Arg Leu
            100   105   110

Val Gln Pro Ala Arg Leu Asn Pro Gln Gly Asp Ser Gly Gly Pro Leu
        115   120   125
Val Cys Gly Gly Ile Leu Gln Gly Ile Val Ser Trp Gly Asp Val Pro
    130   135   140
Cys Asp Asn Thr Thr Lys Pro Gly Val Tyr Thr Lys Val Cys His Tyr

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145                 150                 155                 160
Leu Glu Trp Ile Arg Glu Thr Met Lys Arg Asn
                165                 170
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<210> 93
<211> 1309
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK15 transcript variant 4

<400> 93

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gctggcatcc acagcagccc aggatggtga caagttgctg gaaggtgacg agtgtgcacc 120
ccactcccag ccatggcaag tggctctcta cgagcgtgga cgctttaact gtggcgcttc 180
cctcatctcc ccacactggg tgctgtctgc ggcccactgc caaagccgct tcatgagagt 240
gcgcctggga gagcacaacc tgcgcaagcg cgatggccca gagcaactac ggaccacgtc 300
tcgggtcatt ccacacccgc gctacgaagc gcgcagccac cgcaacgaca tcatgttgct 360
gcgcctagtc cagcccgcac gcctgaaccc ccaggtgcgc cccgcggtgc tacccacgcg 420
ttgcccccac ccgggggagg cctgtgtggt gtctggctgg ggcctggtgt cccacaacga 480
gcctgggacc gctgggagcc cccggtcaca agtgagtctc ccagatacgt tgcattgtgc 540
caacatcagc attatctcgg acacatcttg tgacaagagc tacccagggc gcctgacaaa 600
caccatggtg tgtgcaggcg cggagggcag aggcgcagaa tcctgtgagg gtgactctgg 660
gggacccctg gtctgtgggg gcatcctgca gggcattgtg tcctggggtg acgtcccttg 720
tgacaacacc accaagcctg gtgtctatac caaagtctgc cactacttgg agtggatcag 780
ggaaaccatg aagaggaact gactattcta gcctatctcc tgtgcccctg actgagcaga 840
agcccccaca gctggccagc agccccgcct gacatggaac agaacggagc catcccccaa 900
gaccctgtcc aaggcccaga tgttagccaa ggacttgtcc cacctgagga caaagctggc 960
gctcaaggtc acctgtttaa tgccaagata acaaagcgct gatccaagtt gctctgtagg 1020
aatttctgtg actttttct ggggtcaaag agaaaccccg agacactgta cactgttcct 1080
tttcacccac caccccgatc cctaggtgag gagaagcggc ttgaagcagg gctccattca 1140
ttcaacacac atgaccaccc gtgtgatctt gaacaagagg cccaatctca cttcgccttg 1200
gtttccttat ctgtaaaatg agaccatctt attgctgact tcaaagggct gttgtgagga 1260
ttaaatgaga tgattcgtct gaactgatta aaatcgtgtc tggcactga              1309
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<210> 94
<211> 256
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK15 isoform 4

<400> 94

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Met Trp Leu Leu Leu Thr Leu Ser Phe Leu Leu Ala Ser Thr Ala Ala
 1               5                  10                  15
Gln Asp Gly Asp Lys Leu Leu Glu Gly Asp Glu Cys Ala Pro His Ser
            20                  25                  30
Gln Pro Trp Gln Val Ala Leu Tyr Glu Arg Gly Arg Phe Asn Cys Gly
        35                  40                  45
Ala Ser Leu Ile Ser Pro His Trp Val Leu Ser Ala Ala His Cys Gln
    50                  55                  60
Ser Arg Phe Met Arg Val Arg Leu Gly Glu His Asn Leu Arg Lys Arg
65                  70                  75                  80
Asp Gly Pro Glu Gln Leu Arg Thr Thr Ser Arg Val Ile Pro His Pro
```

```
                85                  90                  95
Arg Tyr Glu Ala Arg Ser His Arg Asn Asp Ile Met Leu Leu Arg Leu
            100                 105                 110
Val Gln Pro Ala Arg Leu Asn Pro Gln Val Arg Pro Ala Val Leu Pro
        115                 120                 125
Thr Arg Cys Pro His Pro Gly Glu Ala Cys Val Val Ser Gly Trp Gly
    130                 135                 140
Leu Val Ser His Asn Glu Pro Gly Thr Ala Gly Ser Pro Arg Ser Gln
145                 150                 155                 160
Val Ser Leu Pro Asp Thr Leu His Cys Ala Asn Ile Ser Ile Ile Ser
                165                 170                 175
Asp Thr Ser Cys Asp Lys Ser Tyr Pro Gly Arg Leu Thr Asn Thr Met
            180                 185                 190
Val Cys Ala Gly Ala Glu Gly Arg Gly Ala Glu Ser Cys Glu Gly Asp
        195                 200                 205
Ser Gly Gly Pro Leu Val Cys Gly Gly Ile Leu Gln Gly Ile Val Ser
    210                 215                 220
Trp Gly Asp Val Pro Cys Asp Asn Thr Thr Lys Pro Gly Val Tyr Thr
225                 230                 235                 240
Lys Val Cys His Tyr Leu Glu Trp Ile Arg Glu Thr Met Lys Arg Asn
                245                 250                 255
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<210> 95
<211> 920
<212> DNA
<213> Homo sapiens

<220>
<223> Mername-AA031 peptidase

<400> 95
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cagacaggag gcgtctgtag agatatcatg aacttcaact tagctttgtt ttccagagac 60
tggagctaaa ctgggctttc aacatcatca tgaagtttat cctcctctgg gccctcttga 120
atctgactgt tgctttggcc tttaatccag attacacagt cagctccact ccccttact 180
tggtctattt gaaatctgac tacttgccct gcgctggagt cctgatccac ccgctttggg 240
tgatcacagc tgcacactgc aatttaccaa agcttcgggt gatattgggg gttacaatcc 300
cagcagactc taatgaaaag catctgcaag tgattggcta tgagaagatg attcatcatc 360
cacacttctc agtcacttct attgatcatg acatcatgct aatcaagctg aaaacagagg 420
ctgaactcaa tgactatgtg aaattagcca acctgcccta ccaaactatc tctgaaaata 480
ccatgtgctc tgtctctacc tggagctaca atgtgtgtga tatctacaaa gagcccgatt 540
cactgcaaac tgtgaacatc tctgtaatct ccaagcctca gtgtcgcgat gcctataaaa 600
cctacaacat cacggaaaat atgctgtgtg tgggcattgt gccaggaagg aggcagccct 660
gcaaggaagt ttctgctgcc ccggcaatct gcaatgggat gcttcaagga atcctgtctt 720
ttgcggatgg atgtgttttg agagccgatg ttggcatcta tgccaaaatt ttttactata 780
taccctggat tgaaaatgta atccaaaata actgagctgt ggcagttgtg gaccatatga 840
cacagcttgt ccccatcgtt cacctttaga attaaatata aattaactcc tcaaaaaaaa 900
aaaaaaaaaa aaaaaaaaaa                                          920
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<210> 96

<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mername-AA031 peptidase

<400> 96
Met Lys Phe Ile Leu Leu Trp Ala Leu Leu Asn Leu Thr Val Ala Leu
1 5 10 15
Ala Phe Asn Pro Asp Tyr Thr Val Ser Ser Thr Pro Pro Tyr Leu Val
20 25 30
Tyr Leu Lys Ser Asp Tyr Leu Pro Cys Ala Gly Val Leu Ile His Pro
35 40 45
Leu Trp Val Ile Thr Ala Ala His Cys Asn Leu Pro Lys Leu Arg Val
50 55 60
Ile Leu Gly Val Thr Ile Pro Ala Asp Ser Asn Glu Lys His Leu Gln
65 70 75 80
Val Ile Gly Tyr Glu Lys Met Ile His His Pro His Phe Ser Val Thr
85 90 95
Ser Ile Asp His Asp Ile Met Leu Ile Lys Leu Lys Thr Glu Ala Glu
100 105 110
Leu Asn Asp Tyr Val Lys Leu Ala Asn Leu Pro Tyr Gln Thr Ile Ser
115 120 125
Glu Asn Thr Met Cys Ser Val Ser Thr Trp Ser Tyr Asn Val Cys Asp
130 135 140
Ile Tyr Lys Glu Pro Asp Ser Leu Gln Thr Val Asn Ile Ser Val Ile
145 150 155 160
Ser Lys Pro Gln Cys Arg Asp Ala Tyr Lys Thr Tyr Asn Ile Thr Glu
165 170 175
Asn Met Leu Cys Val Gly Ile Val Pro Gly Arg Arg Gln Pro Cys Lys
180 185 190
Glu Val Ser Ala Ala Pro Ala Ile Cys Asn Gly Met Leu Gln Gly Ile
195 200 205
Leu Ser Phe Ala Asp Gly Cys Val Leu Arg Ala Asp Val Gly Ile Tyr
210 215 220
Ala Lys Ile Phe Tyr Tyr Ile Pro Trp Ile Glu Asn Val Ile Gln Asn
225 230 235 240
Asn

<210> 97
<211> 2393
<212> DNA
<213> Homo sapiens

<220>
<223> membrane-type mosaic serine protease

<400> 97
cgcccgggca ggttgagaag ccaggggcca agatggatct tctcctcgac atcagctaag 60
cctggaggac tcttcccctc agagaccatg gagagggaca gccacgggaa tgcatctcca 120
gcaagaacac cttcagctgg agcatctcca gcccaggcat ctccagctgg gacacctcca 180
ggccgggcat ctccagccca ggcatctcca gcccaggcat ctccagctgg gacacctccg 240
ggccgggcat ctccagccca ggcatctcca gctggtacac ctccaggccg ggcatctcca 300
ggccgggcat ctccagccca ggcatctcca gcccgggcat ctccggctct ggcatcactt 360
tccaggtcct catccggcag gtcatcatcc gccaggtcag cctcggtgac aacctcccca 420
accagagtgt accttgttag agcaacacca gtgggggctg tacccatccg atcatctcct 480
gccaggtcag caccagcaac cagggccacc agggagagcc caggtacgag cctgcccaag 540
ttcacctggc gggagggcca gaagcagcta ccgctcatcg ggtgcgtgct cctcctcatt 600
gccctggtgg tttcgctcat catcctcttc cagttctggc agggccacac agggatcagg 660
cacaaggagc agagggagag ctgtcccaag cacgctgttc gctgtgacgg ggtggtggac 720

tgcaagctga agagtgacga gctgggctgc gtgaggtttg actgggacaa gtctctgctt 780
aaaatctact ctgggtcctc ccatcagtgg cttcccatct gtagcagcaa ctggaatgac 840
tcctactcag agaagacctg ccagcagctg ggtttcgaga gtgctcaccg gacaaccgag 900
gttgcccaca gggattttgc caacagcttc tcaatcttga gatacaactc caccatccag 960
gaaagcctcc acaggtctga atgcccttcc cagcggtata tctccctcca gtgttcccac 1020
tgcggactga gggccatgac cgggcggatc gtgggagggg cgctggcctc ggatagcaag 1080
tggccttggc aagtgagtct gcacttcggc accacccaca tctgtggagg cacgctcatt 1140
gacgcccagt gggtgctcac tgccgcccac tgcttcttcg tgacccggga gaaggtcctg 1200
gagggctgga aggtgtacgc gggcaccagc aacctgcacc agttgcctga ggcagcctcc 1260
attgccgaga tcatcatcaa cagcaattac accgatgagg aggacgacta tgacatcgcc 1320
ctcatgcggc tgtccaagcc cctgaccctg tccgctcaca tccaccctgc ttgcctcccc 1380
atgcatggac agacctttag cctcaatgag acctgctgga tcacaggctt tggcaagacc 1440
agggagacag atgacaagac atccccccttc ctccgggagg tgcaggtcaa tctcatcgac 1500
ttcaagaaat gcaatgacta cttggtctat gacagttacc ttaccccaag gatgatgtgt 1560
gctggggacc ttcgtggggg cagagactcc tgccagggag acagcggggg gcctcttgtc 1620
tgtgagcaga acaaccgctg gtacctggca ggtgtcacca gctggggcac aggctgtggc 1680
cagagaaaca aacctggtgt gtacaccaaa gtgacagaag ttcttccctg gatttacagc 1740
aagatggagg taagatccct gcagcaggac actgcaccca gcaggctggg aacttcctca 1800
ggtggggacc ctggaggagc acccagggtg taggcagagg tcccctcagc gtccccatat 1860
tcgggggtg ttctggacag ggtcaaatgt gatgcctggg gtcaatccca gctgtctgtg 1920
tttctttccc tgcttttctt ccctcagaac agagctcagc gggttgaaaa agggtggacc 1980
tacaggccag gcaggcagtt gctgggcaga tgttctccca gaagtatttt tttgtgtaag 2040
gttgcaatgg actttgaaaa cgtttcagtt tctgcagagg attttgtgat agtctttgtt 2100
atcaagcatt tatgcatggg aatccgctct tcatggcctt tcccagctct gtttgtttta 2160
gtctttttga ttttcttttt gttgttgttg ttgtcttttt ttaaaaacac aagtgactcc 2220
attttaactc tgacaacttt cacagctgtc accagaatgc tccctgagaa ctaccattct 2280
ttccctttcc cacttaaaat atttcatcag aacctcacca ctatcataaa agagtataaa 2340
gtaataaaat aataaaaagc gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 2393

<210> 98
<211> 581
<212> PRT
<213> Homo Sapiens

<220>
<223> membrane-type mosaic serine protease

<400> 98
Met Glu Arg Asp Ser His Gly Asn Ala Ser Pro Ala Arg Thr Pro Ser
1 5 10 15
Ala Gly Ala Ser Pro Ala Gln Ala Ser Pro Ala Gly Thr Pro Pro Gly
20 25 30
Arg Ala Ser Pro Ala Gln Ala Ser Pro Ala Gln Ala Ser Pro Ala Gly
35 40 45
Thr Pro Pro Gly Arg Ala Ser Pro Ala Gln Ala Ser Pro Ala Gly Thr

50 55 60
Pro Pro Gly Arg Ala Ser Pro Gly Arg Ala Ser Pro Ala Gln Ala Ser
65 70 75 80
Pro Ala Arg Ala Ser Pro Ala Leu Ala Ser Leu Ser Arg Ser Ser Ser
85 90 95
Gly Arg Ser Ser Ser Ala Arg Ser Ala Ser Val Thr Thr Ser Pro Thr
100 105 110
Arg Val Tyr Leu Val Arg Ala Thr Pro Val Gly Ala Val Pro Ile Arg
115 120 125
Ser Ser Pro Ala Arg Ser Ala Pro Ala Thr Arg Ala Thr Arg Glu Ser
130 135 140

```
Pro Gly Thr Ser Leu Pro Lys Phe Thr Trp Arg Glu Gly Gln Lys Gln
145                 150                 155                 160
Leu Pro Leu Ile Gly Cys Val Leu Leu Leu Ile Ala Leu Val Val Ser
                165                 170                 175
Leu Ile Ile Leu Phe Gln Phe Trp Gln Gly His Thr Gly Ile Arg His
            180                 185                 190
Lys Glu Gln Arg Glu Ser Cys Pro Lys His Ala Val Arg Cys Asp Gly
        195                 200                 205
Val Val Asp Cys Lys Leu Lys Ser Asp Glu Leu Gly Cys Val Arg Phe
    210                 215                 220
Asp Trp Asp Lys Ser Leu Leu Lys Ile Tyr Ser Gly Ser Ser His Gln
225                 230                 235                 240
Trp Leu Pro Ile Cys Ser Ser Asn Trp Asn Asp Ser Tyr Ser Glu Lys
                245                 250                 255
Thr Cys Arg Gln Leu Gly Phe Glu Ser Ala His Arg Thr Thr Glu Val
            260                 265                 270
Ala His Arg Asp Phe Ala Asn Ser Phe Ser Ile Leu Arg Tyr Asn Ser
        275                 280                 285
Thr Ile Gln Glu Ser Leu His Arg Ser His Cys Pro Ser Gln Arg Tyr
    290                 295                 300
Ile Ser Leu Gln Cys Ser His Cys Gly Leu Arg Ala Met Thr Gly Arg
305                 310                 315                 320
Ile Val Gly Gly Ala Leu Ala Ser Asp Ser Lys Trp Pro Trp Gln Val
                325                 330                 335
Ser Leu His Phe Gly Thr Thr His Ile Cys Gly Gly Thr Leu Ile Asp
            340                 345                 350
Ala Gln Trp Val Leu Thr Ala Ala His Cys Phe Phe Val Thr Arg Glu
        355                 360                 365
Lys Val Leu Glu Gly Trp Lys Val Tyr Ala Gly Thr Ser Asn Leu His
    370                 375                 380
Gln Leu Pro Glu Ala Ala Ser Ile Ala Glu Ile Ile Ile Asn Ser Asn
385                 390                 395                 400
Tyr Thr Asp Glu Glu Asp Asp Tyr Asp Ile Ala Leu Met Arg Leu Ser
                405                 410                 415
Lys Pro Leu Thr Leu Ser Ala His Ile His Pro Ala Cys Leu Pro Met
            420                 425                 430
His Gly Gln Thr Phe Ser Leu Asn Glu Thr Cys Trp Ile Thr Gly Phe
        435                 440                 445
Gly Lys Thr Arg Glu Thr Asp Asp Lys Thr Ser Pro Phe Leu Arg Glu
    450                 455                 460
Val Gln Val Asn Leu Ile Asp Phe Lys Lys Cys Asn Asp Tyr Leu Val
465                 470                 475                 480
Tyr Asp Ser Tyr Leu Thr Pro Arg Met Met Cys Ala Gly Asp Leu His
                485                 490                 495
Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys
            500                 505                 510
Glu Gln Asn Asn Arg Trp Tyr Leu Ala Gly Val Thr Ser Trp Gly Thr
        515                 520                 525
Gly Cys Gly Gln Arg Asn Lys Pro Gly Val Tyr Thr Lys Val Thr Glu
    530                 535                 540
Val Leu Pro Trp Ile Tyr Ser Lys Met Glu Val Arg Ser Leu Gln Gln
545                 550                 555                 560
Asp Thr Ala Pro Ser Arg Leu Gly Thr Ser Ser Gly Gly Asp Pro Gly
                565                 570                 575
Gly Ala Pro Arg Val
            580
```

<210> 99
<211> 148
<212> PRT
<213> Homo sapiens

<220>
<223> mername-AA038 peptidase

<400> 99
Cys Gly Lys Pro Lys Val Val Gly Lys Ile Tyr Gly Gly Arg Asp Ala
 1   5   10   15
Ala Ala Gly Gln Trp Pro Trp Gln Ala Ser Leu Leu Tyr Trp Gly Ser
            20   25   30
His Leu Cys Gly Ala Val Leu Ile Asp Ser Cys Trp Leu Val Ser Thr
        35   40   45
Thr His Cys Phe Leu Asn Lys Ser Gln Ala Pro Lys Asn Tyr Gln Val
    50   55   60
Leu Leu Gly Asn Ile Gln Leu Tyr His Gln Thr Gln His Thr Gln Lys
65   70   75   80
Met Ser Val His Arg Ile Ile Thr His Pro Asp Phe Glu Lys Leu His
                85   90   95
Pro Phe Gly Ser Asp Ile Ala Met Leu Gln Leu His Leu Pro Met Asn
            100   105   110
Phe Thr Ser Tyr Ile Val Pro Val Cys Leu Pro Ser Arg Asp Met Gln
        115   120   125
Leu Pro Ser Asn Val Ser Cys Trp Ile Thr Gly Trp Gly Met Ala Ile
    130   135   140
Leu Gly Gly Leu
145

<210> 100
<211> 712
<212> DNA
<213> Homo sapiens

<220>
<223> mername-AA128 peptidase

<400> 100
cacagagggc tccagcgtga ttgccactgg ttaatgacct gccacccccg ccccccccaac 60
ctctggtgcc gtccaaggac tctgacccca gtgcagtgtc tgtagggaag aggagccatg 120
gggcttcggg caggccccat cctgcttctg ctgctgtggc tgctgccaga atgcggccac 180
tccaaggagg ccgggaggat tgtgggaggc caagacaccc aggaaggacg ctggccgtgg 240
caggttggcc tgtggttgac ctcagtgggg catgtatgtg ggggcttcct catccaccca 300
cgctgggtgc tcacagccgc ccactgcttc ctgagggtga ctccgggggg ccgctggtct 360
gccccatcaa tgatacgtgg atccaggccg gcattgtgag ctggggattc ggctgtgccc 420
ggcctttccg gcctggtgtc tacacccagg tgctaagcta cacagactgg attcagagaa 480
ccctggctga atctcactca ggcatgtctg gggcccgccc aggtgcccca ggatcccact 540
caggcacctc cagatcccac ccagtgctgc tgcttgagct gttgaccgta tgcttgcttg 600
ggtccctgtg aaccatgagc catggagtcc gggatcccct ttctggtagg attgatggaa 660
tctaataata aaaactgtag gtttttttatg tgaaaaaaaa aaaaaaaaaa aa   712

<210> 101
<211> 146
<212> PRT

<213> Homo sapiens

<220>
<223> mername-AA128 peptidase

<400> 101
Met Arg Pro Leu Gln Gly Gly Arg Glu Asp Cys Gly Arg Pro Arg His
 1   5   10   15
Pro Gly Arg Thr Leu Ala Val Ala Gly Trp Pro Val Val Asp Leu Ser
            20   25   30
Gly Ala Cys Met Trp Gly Leu Pro His Pro Pro Thr Leu Gly Ala His
        35   40   45
Ser Arg Pro Leu Leu Pro Glu Gly Asp Ser Gly Gly Pro Leu Val Cys
    50   55   60
Pro Ile Asn Asp Thr Trp Ile Gln Ala Gly Ile Val Ser Trp Gly Phe
65   70   75   80
Gly Cys Ala Arg Pro Phe Arg Pro Gly Val Tyr Thr Gln Val Leu Ser
                85   90   95
Tyr Thr Asp Trp Ile Gln Arg Thr Leu Ala Glu Ser His Ser Gly Met
            100   105   110
Ser Gly Ala Arg Pro Gly Ala Pro Gly Ser His Ser Gly Thr Ser Arg
        115   120   125
Ser His Pro Val Leu Leu Leu Glu Leu Leu Thr Val Cys Leu Leu Gly
    130   135   140
Ser Leu
145

<210> 102
<211> 800
<212> DNA
<213> Homo sapiens

<220>
<223> cationic trypsin (Homo sapiens-type 1) (cationic)

<400> 102
accaccatga atccactcct gatccttacc tttgtggcag ctgctcttgc tgccccctttt 60
gatgatgatg acaagatcgt tgggggctac aactgtgagg agaattctgt cccctaccag 120
gtgtccctga attctggcta ccacttctgt ggtggctccc tcatcaacga acagtgggtg 180
gtatcagcag gccactgcta caagtcccgc atccaggtga gactgggaga gcacaacatc 240
gaagtcctgg aggggaatga gcagttcatc aatgcagcca agatcatccg ccacccccaa 300
tacgacagga agactctgaa caatgacatc atgttaatca agctctcctc acgtgcagta 360
atcaacgccc gcgtgtccac catctctctg cccaccgccc ctccagccac tggcacgaag 420
tgcctcatct ctggctgggg caacactgcg agctctggcg ccgactaccc agacgagctg 480
cagtgcctgg acgctcctgt gctgagccag gctaagtgtg aagcctccta ccctggaaag 540
attaccagca acatgttctg tgtgggcttc cttgagggag gcaaggattc atgtcagggt 600
gattctggtg gccctgtggt ctgcaatgga cagctccaag gagttgtctc ctggggtgat 660
ggctgtgccc agaagaacaa gcctggagtc tacaccaagg tctacaacta tgtgaaatgg 720
attaagaaca ccatagctgc caatagctaa agcccccagt atctcttcag tctctatacc 780
aataaagtga ccctgttctc   800

<210> 103
<211> 247
<212> PRT
<213> Homo sapiens

<220>
<223> cationic trypsin (Homo sapiens-type 1) (cationic)

<400> 103
Met Asn Pro Leu Leu Ile Leu Thr Phe Val Ala Ala Ala Leu Ala Ala
 1   5   10   15
Pro Phe Asp Asp Asp Asp Lys Ile Val Gly Gly Tyr Asn Cys Glu Glu
            20   25   30
Asn Ser Val Pro Tyr Gln Val Ser Leu Asn Ser Gly Tyr His Phe Cys
        35   40   45
Gly Gly Ser Leu Ile Asn Glu Gln Trp Val Val Ser Ala Gly His Cys
    50   55   60
Tyr Lys Ser Arg Ile Gln Val Arg Leu Gly Glu His Asn Ile Glu Val
65   70   75   80
Leu Glu Gly Asn Glu Gln Phe Ile Asn Ala Ala Lys Ile Ile Arg His
                85   90   95
Pro Gln Tyr Asp Arg Lys Thr Leu Asn Asn Asp Ile Met Leu Ile Lys
            100   105   110
Leu Ser Ser Arg Ala Val Ile Asn Ala Arg Val Ser Thr Ile Ser Leu
        115   120   125
Pro Thr Ala Pro Pro Ala Thr Gly Thr Lys Cys Leu Ile Ser Gly Trp
    130   135   140
Gly Asn Thr Ala Ser Ser Gly Ala Asp Tyr Pro Asp Glu Leu Gln Cys
145   150   155   160
Leu Asp Ala Pro Val Leu Ser Gln Ala Lys Cys Glu Ala Ser Tyr Pro
                165   170   175
Gly Lys Ile Thr Ser Asn Met Phe Cys Val Gly Phe Leu Glu Gly Gly
            180   185   190
Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Val Val Cys Asn Gly
        195   200   205
Gln Leu Gln Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln Lys Asn
    210   215   220
Lys Pro Gly Val Tyr Thr Lys Val Tyr Asn Tyr Val Lys Trp Ile Lys
225   230   235   240
Asn Thr Ile Ala Ala Asn Ser
                245

<210> 104
<211> 938
<212> DNA
<213> Homo sapiens

<220>
<223> Neutrophil elastase

<400> 104
gcacggaggg gcagagaccc cggagcccca gccccaccat gaccctcggc cgccgactcg 60
cgtgtctttt cctcgcctgt gtcctgccgg ccttgctgct gggggggcacc gcgctggcct 120
cggagattgt gggggggccgg cgagcgcggc cccacgcgtg gcccttcatg gtgtccctgc 180
agctgcgcgg aggccacttc tgcggcgcca ccctgattgc gcccaacttc gtcatgtcgg 240
ccgcgcactg cgtggcgaat gtaaacgtcc gcgcggtgcg ggtggtcctg ggagcccata 300
acctctcgcg gcgggagccc acccggcagg tgttcgccgt gcagcgcatc ttcgaaaacg 360
gctacgaccc cgtaaacttg ctcaacgaca tcgtgattct ccagctcaac gggtcggcca 420
ccatcaacgc caacgtgcag gtggcccagc tgccggctca gggacgccgc ctgggcaacg 480
gggtgcagtg cctggccatg ggctggggcc ttctgggcag gaaccgtggg atcgccagcg 540
tcctgcagga gctcaacgtg acggtggtga cgtccctctg ccgtcgcagc aacgtctgca 600

ctctcgtgag gggccggcag gccggcgtct gtttcgggga ctccggcagc cccttggtct 660
gcaacgggct aatccacgga attgcctcct tcgtccgggg aggctgcgcc tcagggctct 720
accccgatgc ctttgccccg gtggcacagt ttgtaaactg gatcgactct atcatccaac 780
gctccgagga caacccctgt ccccaccccc gggacccgga cccggccagc aggacccact 840
gagaagggct gcccgggtca cctcagctgc ccacacccac actctccagc atctggcaca 900
ataaacattc tctgttttgt agaaaaaaaa aaaaaaaa 938

<210> 105
<211> 267
<212> PRT
<213> Homo sapiens

<220>
<223> Neutrophil elastase

<400> 105
Met Thr Leu Gly Arg Arg Leu Ala Cys Leu Phe Leu Ala Cys Val Leu
1 5 10 15
Pro Ala Leu Leu Leu Gly Gly Thr Ala Leu Ala Ser Glu Ile Val Gly
20 25 30
Gly Arg Arg Ala Arg Pro His Ala Trp Pro Phe Met Val Ser Leu Gln
35 40 45
Leu Arg Gly Gly His Phe Cys Gly Ala Thr Leu Ile Ala Pro Asn Phe
50 55 60
Val Met Ser Ala Ala His Cys Val Ala Asn Val Asn Val Arg Ala Val
65 70 75 80
Arg Val Val Leu Gly Ala His Asn Leu Ser Arg Arg Glu Pro Thr Arg
85 90 95
Gln Val Phe Ala Val Gln Arg Ile Phe Glu Asn Gly Tyr Asp Pro Val
100 105 110
Asn Leu Leu Asn Asp Ile Val Ile Leu Gln Leu Asn Gly Ser Ala Thr
115 120 125
Ile Asn Ala Asn Val Gln Val Ala Gln Leu Pro Ala Gln Gly Arg Arg
130 135 140
Leu Gly Asn Gly Val Gln Cys Leu Ala Met Gly Trp Gly Leu Leu Gly
145 150 155 160
Arg Asn Arg Gly Ile Ala Ser Val Leu Gln Glu Leu Asn Val Thr Val
165 170 175
Val Thr Ser Leu Cys Arg Arg Ser Asn Val Cys Thr Leu Val Arg Gly
180 185 190
Arg Gln Ala Gly Val Cys Phe Gly Asp Ser Gly Ser Pro Leu Val Cys
195 200 205
Asn Gly Leu Ile His Gly Ile Ala Ser Phe Val Arg Gly Gly Cys Ala
210 215 220
Ser Gly Leu Tyr Pro Asp Ala Phe Ala Pro Val Ala Gln Phe Val Asn
225 230 235 240
Trp Ile Asp Ser Ile Ile Gln Arg Ser Glu Asp Asn Pro Cys Pro His
245 250 255
Pro Arg Asp Pro Asp Pro Ala Ser Arg Thr His
260 265

<210> 106
<211> 3895
<212> DNA
<213> Homo sapiens

<220>
<223> mannan-binding lectin-associated serine protease-3

<400> 106
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tgcttctccc tgtcaaaggc ttcagcccac accgtggagc taaacaatat gtttggccag 180
atccagtcgc ctggttatcc agactcctat cccagtgatt cagaggtgac ttggaatatc 240
actgtcccag atgggtttcg gatcaagctt tacttcatgc acttcaactt ggaatcctcc 300
tacctttgtg aatatgacta tgtgaaggta gaaactgagg accaggtgct ggcaaccttc 360
tgtggcaggg agaccacaga cacagagcag actcccggcc aggaggtggt cctctcccct 420
ggctccttca tgtccatcac tttccggtca gatttctcca atgaggagcg tttcacaggc 480
tttgatgccc actacatggc tgtggatgtg gacgagtgca aggagaggga ggacgaggag 540
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actcaaagga ctggggtgat caccagccct gacttcccaa acccttaccc caagagctct 720
gaatgcctgt ataccatcga gctggaggag ggtttcatgg tcaacctgca gtttgaggac 780
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gtgtgggagc agatgggctt accacaaagt gttgtggagc cccaggtgga acggtgagct 2280
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attacctgga aaaagaaaag acccacactg tgtcctgctg tgcttttggg caggaaaatg 3240
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caaggcagcc agagaagccc ctgagaggga atgattggga agtgtccact ttctcaaccg 3720
gctcatcaaa cacactcctt tgtctatgaa tggcacatgt aaatgatgtt atattttgta 3780
tcttttatat catatgcttc accattctgt aaagggcctc tgcattgttg ctcccatcag 3840
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<210> 107
<211> 728
<212> PRT
<213> Homo sapiens

<220>
<223> mannan-binding lectin-associated serine protease-3

<400> 107
Met Arg Trp Leu Leu Leu Tyr Tyr Ala Leu Cys Phe Ser Leu Ser Lys
1 5 10 15
Ala Ser Ala His Thr Val Glu Leu Asn Asn Met Phe Gly Gln Ile Gln
20 25 30
Ser Pro Gly Tyr Pro Asp Ser Tyr Pro Ser Asp Ser Glu Val Thr Trp
35 40 45
Asn Ile Thr Val Pro Asp Gly Phe Arg Ile Lys Leu Tyr Phe Met His
50 55 60
Phe Asn Leu Glu Ser Ser Tyr Leu Cys Glu Tyr Asp Tyr Val Lys Val
65 70 75 80
Glu Thr Glu Asp Gln Val Leu Ala Thr Phe Cys Gly Arg Glu Thr Thr
85 90 95
Asp Thr Glu Gln Thr Pro Gly Gln Glu Val Val Leu Ser Pro Gly Ser
100 105 110
Phe Met Ser Ile Thr Phe Arg Ser Asp Phe Ser Asn Glu Glu Arg Phe
115 120 125
Thr Gly Phe Asp Ala His Tyr Met Ala Val Asp Val Asp Glu Cys Lys
130 135 140
Glu Arg Glu Asp Glu Glu Leu Ser Cys Asp His Tyr Cys His Asn Tyr
145 150 155 160
Ile Gly Gly Tyr Tyr Cys Ser Cys Arg Phe Gly Tyr Ile Leu His Thr
165 170 175
Asp Asn Arg Thr Cys Arg Val Glu Cys Ser Asp Asn Leu Phe Thr Gln
180 185 190
Arg Thr Gly Val Ile Thr Ser Pro Asp Phe Pro Asn Pro Tyr Pro Lys
195 200 205
Ser Ser Glu Cys Leu Tyr Thr Ile Glu Leu Glu Glu Gly Phe Met Val
210 215 220
Asn Leu Gln Phe Glu Asp Ile Phe Asp Ile Glu Asp His Pro Glu Val
225 230 235 240
Pro Cys Pro Tyr Asp Tyr Ile Lys Ile Lys Val Gly Pro Lys Val Leu
245 250 255
Gly Pro Phe Cys Gly Glu Lys Ala Pro Glu Pro Ile Ser Thr Gln Ser
260 265 270
His Ser Val Leu Ile Leu Phe His Ser Asp Asn Ser Gly Glu Asn Arg

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         275                 280                 285
Gly Trp Arg Leu Ser Tyr Arg Ala Ala Gly Asn Glu Cys Pro Glu Leu
     290                 295                 300
Gln Pro Pro Val His Gly Lys Ile Glu Pro Ser Gln Ala Lys Tyr Phe
305                 310                 315                 320
Phe Lys Asp Gln Val Leu Val Ser Cys Asp Thr Gly Tyr Lys Val Leu
                325                 330                 335
Lys Asp Asn Val Glu Met Asp Thr Phe Gln Ile Glu Cys Leu Lys Asp
            340                 345                 350
Gly Thr Trp Ser Asn Lys Ile Pro Thr Cys Lys Ile Val Asp Cys Arg
        355                 360                 365
Ala Pro Gly Glu Leu Glu His Gly Leu Ile Thr Phe Ser Thr Arg Asn
    370                 375                 380
Asn Leu Thr Thr Tyr Lys Ser Glu Ile Lys Tyr Ser Cys Gln Glu Pro
385                 390                 395                 400
Tyr Tyr Lys Met Leu Asn Asn Asn Thr Gly Ile Tyr Thr Cys Ser Ala
                405                 410                 415
Gln Gly Val Trp Met Asn Lys Val Leu Gly Arg Ser Leu Pro Thr Cys
            420                 425                 430
Leu Pro Glu Cys Gly Gln Pro Ser Arg Ser Leu Pro Ser Leu Val Lys
        435                 440                 445
Arg Ile Ile Gly Gly Arg Asn Ala Glu Pro Gly Leu Phe Pro Trp Gln
    450                 455                 460
Ala Leu Ile Val Val Glu Asp Thr Ser Arg Val Pro Asn Asp Lys Trp
465                 470                 475                 480
Phe Gly Ser Gly Ala Leu Leu Ser Ala Ser Trp Ile Leu Thr Ala Ala
                485                 490                 495
His Val Leu Arg Ser Gln Arg Arg Asp Thr Thr Val Ile Pro Val Ser
            500                 505                 510
Lys Glu His Val Thr Val Tyr Leu Gly Leu His Asp Val Arg Asp Lys
        515                 520                 525
Ser Gly Ala Val Asn Ser Ser Ala Ala Arg Val Val Leu His Pro Asp
    530                 535                 540
Phe Asn Ile Gln Asn Tyr Asn His Asp Ile Ala Leu Val Gln Leu Gln
545                 550                 555                 560
Glu Pro Val Pro Leu Gly Pro His Val Met Pro Val Cys Leu Pro Arg
                565                 570                 575
Leu Glu Pro Glu Gly Pro Ala Pro His Met Leu Gly Leu Val Ala Gly
            580                 585                 590
Trp Gly Ile Ser Asn Pro Asn Val Thr Val Asp Glu Ile Ile Ser Ser
        595                 600                 605
Gly Thr Arg Thr Leu Ser Asp Val Leu Gln Tyr Val Lys Leu Pro Val
    610                 615                 620
Val Pro His Ala Glu Cys Lys Thr Ser Tyr Glu Ser Arg Ser Gly Asn
625                 630                 635                 640
Tyr Ser Val Thr Glu Asn Met Phe Cys Ala Gly Tyr Tyr Glu Gly Gly
                645                 650                 655
Lys Asp Thr Cys Leu Gly Asp Ser Gly Gly Ala Phe Val Ile Phe Asp
            660                 665                 670
Asp Leu Ser Gln Arg Trp Val Val Gln Gly Leu Val Ser Trp Gly Gly
        675                 680                 685
Pro Glu Glu Cys Gly Ser Lys Gln Val Tyr Gly Val Tyr Thr Lys Val
    690                 695                 700
Ser Asn Tyr Val Asp Trp Val Trp Glu Gln Met Gly Leu Pro Gln Ser
705                 710                 715                 720
Val Val Glu Pro Gln Val Glu Arg
                725
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<210> 108
<211> 924
<212> DNA
<213> Homo sapiens

<220>
<223> cathepsin G

<400> 108
gcacagcagc aactgactgg gcagcctttc aggaaagatg cagccactcc tgcttctgct 60
ggcctttctc ctacccactg gggctgaggc aggggagatc atcggaggcc gggagagcag 120
gccccactcc cgcccctaca tggcgtatct tcagatccag agtccagcag gtcagagcag 180
atgtggaggg ttcctggtgc gagaagactt tgtgctgaca gcagctcatt gctggggaag 240
caatataaat gtcaccctgg gcgcccacaa tatccagaga cgggaaaaca cccagcaaca 300
catcactgcg cgcagagcca tccgccaccc tcaatataat cagcggacca tccagaatga 360
catcatgtta ttgcagctga gcagaagagt cagacggaat cgaaacgtga acccagtggc 420
tctgcctaga gcccaggagg gactgagacc cgggacgctg tgcactgtgg ccggctgggg 480
cagggtcagc atgaggaggg gaacagatac actccgagag gtgcagctga gagtgcagag 540
ggataggcag tgcctccgca tcttcggttc ctacgacccc cgaaggcaga tttgtgtggg 600
ggaccggcgg gaacggaagg ctgccttcaa gggggattcc ggaggccccc tgctgtgtaa 660
caatgtggcc cacggcatcg tctcctatgg aaagtcgtca ggggttcctc cagaagtctt 720
caccagggtc tcaagtttcc tgccctggat aaggacaaca atgagaagct tcaaactgct 780
ggatcagatg gagacccccc tgtgactgac tcttcttctc ggggacacag gccagctcca 840
cagtgttgcc agagccttaa taaacgtcca cagagtataa ataaccaatt cctcatttgt 900
tcattaaacg tcattcagta ctta 924

<210> 109
<211> 255
<212> PRT
<213> Homo sapiens

<220>
<223> cathepsin G

<400> 109
Met Gln Pro Leu Leu Leu Leu Leu Ala Phe Leu Leu Pro Thr Gly Ala
 1   5   10   15
Glu Ala Gly Glu Ile Ile Gly Gly Arg Glu Ser Arg Pro His Ser Arg
            20   25   30
Pro Tyr Met Ala Tyr Leu Gln Ile Gln Ser Pro Ala Gly Gln Ser Arg
        35   40   45
Cys Gly Gly Phe Leu Val Arg Glu Asp Phe Val Leu Thr Ala Ala His
    50   55   60
Cys Trp Gly Ser Asn Ile Asn Val Thr Leu Gly Ala His Asn Ile Gln
65   70   75   80
Arg Arg Glu Asn Thr Gln Gln His Ile Thr Ala Arg Arg Ala Ile Arg
                85   90   95
His Pro Gln Tyr Asn Gln Arg Thr Ile Gln Asn Asp Ile Met Leu Leu
            100   105   110
Gln Leu Ser Arg Arg Val Arg Arg Asn Arg Asn Val Asn Pro Val Ala
        115   120   125
Leu Pro Arg Ala Gln Glu Gly Leu Arg Pro Gly Thr Leu Cys Thr Val
    130   135   140
Ala Gly Trp Gly Arg Val Ser Met Arg Arg Gly Thr Asp Thr Leu Arg
145   150   155   160

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Glu Val Gln Leu Arg Val Gln Arg Asp Arg Gln Cys Leu Arg Ile Phe
                165                 170                 175
Gly Ser Tyr Asp Pro Arg Arg Gln Ile Cys Val Gly Asp Arg Arg Glu
            180                 185                 190
Arg Lys Ala Ala Phe Lys Gly Asp Ser Gly Gly Pro Leu Leu Cys Asn
        195                 200                 205
Asn Val Ala His Gly Ile Val Ser Tyr Gly Lys Ser Ser Gly Val Pro
    210                 215                 220
Pro Glu Val Phe Thr Arg Val Ser Ser Phe Leu Pro Trp Ile Arg Thr
225                 230                 235                 240
Thr Met Arg Ser Phe Lys Leu Leu Asp Gln Met Glu Thr Pro Leu
                245                 250                 255
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<210> 110
<211> 1001
<212> DNA
<213> Homo sapiens

<220>
<223> myeloblastin (proteinase 3)

<400> 110
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gtgctgctgg ccttgctgct gagcggtgct gcccgagctg cggagatcgt gggcgggcac 120
gaggcgcagc cacactcccg gccctacatg gcctccctgc agatgcgggg gaacccgggc 180
agccacttct gcggaggcac cttgatccac cccagcttcg tgctgacggc cgcgcactgc 240
ctgcgggaca taccccagcg cctggtgaac gtggtgctcg gagcccacaa cgtgcggacg 300
caggagccca cccagcagca cttctcggtg gctcaggtgt ttctgaacaa ctacgacgcg 360
gagaacaaac tgaacgacgt tctcctcatc cagctgagca gcccagccaa cctcagtgcc 420
tccgtcgcca cagtccagct gccacagcag gaccagccag tgccccacgg cacccagtgc 480
ctggccatgg gctggggccg cgtgggtgcc cacgaccccc cagcccaggt cctgcaggag 540
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cgccgcaagg ccggcatctg cttcggagac tcaggtggcc ccctgatctg tgatggcatc 660
atccaaggaa tagactcctt cgtgatctgg ggatgtgcca cccgcctttt ccctgacttc 720
ttcacgcggg tagccctcta cgtggactgg atccgttcca cgctgcgccg tgtggaggcc 780
aagggccgcc cctgaaccgc ccctcccaca gcgctggccg ggaccccgag cctggctcca 840
aaccctcgag gcggatcttt ggacagaagc agctcttccc cgaacactgt ggcgtccggg 900
acggccccac ccgtcccccc acactccctc ccacggggct ccgggagaca ggccggccct 960
gcacctcacc ccaccgtgac ctcaataaac gttgaaactc c                    1001
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<210> 111
<211> 256
<212> PRT
<213> Homo sapiens

<220>
<223> myeloblastin (proteinase 3)

<400> 111
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Met Ala His Arg Pro Pro Ser Pro Ala Leu Ala Ser Val Leu Leu Ala
 1               5                  10                  15
Leu Leu Leu Ser Gly Ala Ala Arg Ala Ala Glu Ile Val Gly Gly His
            20                  25                  30

Glu Ala Gln Pro His Ser Arg Pro Tyr Met Ala Ser Leu Gln Met Arg
        35                  40                  45
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Gly Asn Pro Gly Ser His Phe Cys Gly Gly Thr Leu Ile His Pro Ser
    50                  55                  60
Phe Val Leu Thr Ala Ala His Cys Leu Arg Asp Ile Pro Gln Arg Leu
65                  70                  75                  80
Val Asn Val Val Leu Gly Ala His Asn Val Arg Thr Gln Glu Pro Thr
                85                  90                  95
Gln Gln His Phe Ser Val Ala Gln Val Phe Leu Asn Asn Tyr Asp Ala
            100                 105                 110
Glu Asn Lys Leu Asn Asp Val Leu Leu Ile Gln Leu Ser Ser Pro Ala
        115                 120                 125
Asn Leu Ser Ala Ser Val Ala Thr Val Gln Leu Pro Gln Gln Asp Gln
    130                 135                 140
Pro Val Pro His Gly Thr Gln Cys Leu Ala Met Gly Trp Gly Arg Val
145                 150                 155                 160
Gly Ala His Asp Pro Pro Ala Gln Val Leu Gln Glu Leu Asn Val Thr
                165                 170                 175
Val Val Thr Phe Phe Cys Arg Pro His Asn Ile Cys Thr Phe Val Pro
            180                 185                 190
Arg Arg Lys Ala Gly Ile Cys Phe Gly Asp Ser Gly Gly Pro Leu Ile
        195                 200                 205
Cys Asp Gly Ile Ile Gln Gly Ile Asp Ser Phe Val Ile Trp Gly Cys
    210                 215                 220
Ala Thr Arg Leu Phe Pro Asp Phe Phe Thr Arg Val Ala Leu Tyr Val
225                 230                 235                 240
Asp Trp Ile Arg Ser Thr Leu Arg Arg Val Glu Ala Lys Gly Arg Pro
                245                 250                 255
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<210> 112
<211> 878
<212> DNA
<213> Homo sapiens

<220>
<223> granzyme A

<400> 112
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aaattattgg aggaaatgaa gtaactcctc attcaagacc ctacatggtc ctacttagtc 180
ttgacagaaa aaccatctgt gctggggctt tgattgcaaa agactgggtg ttgactgcag 240
ctcactgtaa cttgaacaaa aggtcccagg tcattcttgg ggctcactca ataaccaggg 300
aagagccaac aaaacagata atgcttgtta agaaagagtt tccctatcca tgctatgacc 360
cagccacacg cgaaggtgac cttaaacttt tacagctgac ggaaaaagca aaaattaaca 420
aatatgtgac tatccttcat ctacctaaaa aggggggatga tgtgaaacca ggaaccatgt 480
gccaagttgc agggtggggg aggactcaca atagtgcatc ttggtccgat actctgagag 540
aagtcaatat caccatcata gacagaaaag tctgcaatga tcgaaatcac tataatttta 600
accctgtgat tggaatgaat atggtttgtg ctggaagcct ccgaggtgga agagactcgt 660
gcaatggaga ttctggaagc cctttgttgt gcgagggtgt tttccgaggg gtcacttcct 720
ttggccttga aaataaatgc ggagaccctc gtgggcctgg tgtctatatt cttctctcaa 780
agaaacacct caactggata attatgacta tcaagggagc agtttaaata accgtttcct 840
ttcatttact gtggcttctt aatcttttca caaataaa                          878
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<210> 113
<211> 262
<212> PRT
<213> Homo sapiens

<220>
<223> granzyme A

<400> 113
Met Arg Asn Ser Tyr Arg Phe Leu Ala Ser Ser Leu Ser Val Val Val
 1   5   10   15
Ser Leu Leu Leu Ile Pro Glu Asp Val Cys Glu Lys Ile Ile Gly Gly
            20   25   30
Asn Glu Val Thr Pro His Ser Arg Pro Tyr Met Val Leu Leu Ser Leu
        35   40   45
Asp Arg Lys Thr Ile Cys Ala Gly Ala Leu Ile Ala Lys Asp Trp Val
    50   55   60
Leu Thr Ala Ala His Cys Asn Leu Asn Lys Arg Ser Gln Val Ile Leu
65   70   75   80
Gly Ala His Ser Ile Thr Arg Glu Glu Pro Thr Lys Gln Ile Met Leu
                85   90   95
Val Lys Lys Glu Phe Pro Tyr Pro Cys Tyr Asp Pro Ala Thr Arg Glu
            100   105   110
Gly Asp Leu Lys Leu Leu Gln Leu Thr Glu Lys Ala Lys Ile Asn Lys
        115   120   125
Tyr Val Thr Ile Leu His Leu Pro Lys Lys Gly Asp Asp Val Lys Pro
    130   135   140
Gly Thr Met Cys Gln Val Ala Gly Trp Gly Arg Thr His Asn Ser Ala
145   150   155   160
Ser Trp Ser Asp Thr Leu Arg Glu Val Asn Ile Thr Ile Ile Asp Arg
                165   170   175
Lys Val Cys Asn Asp Arg Asn His Tyr Asn Phe Asn Pro Val Ile Gly
            180   185   190
Met Asn Met Val Cys Ala Gly Ser Leu Arg Gly Gly Arg Asp Ser Cys
        195   200   205
Asn Gly Asp Ser Gly Ser Pro Leu Leu Cys Glu Gly Val Phe Arg Gly
    210   215   220
Val Thr Ser Phe Gly Leu Glu Asn Lys Cys Gly Asp Pro Arg Gly Pro
225   230   235   240
Gly Val Tyr Ile Leu Leu Ser Lys Lys His Leu Asn Trp Ile Ile Met

                245   250   255
Thr Ile Lys Gly Ala Val
            260

<210> 114
<211> 947
<212> DNA
<213> Homo sapiens

<220>
<223> granzyme M

<400> 114
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tcttcactgc tggtgctggc cctgggggcc ctgtcagtag gcagctcctt tgggacccag 120
atcatcgggg gccgggaggt gatcccccac tcgcgcccgt acatggcctc actgcagaga 180
aatggctccc acctgtgcgg gggtgtcctg gtgcacccaa agtgggtgct gacggctgcc 240
cactgcctgg cccagcggat ggcccagctg aggctggtgc tggggctcca caccctggac 300
agccccggtc tcaccttcca catcaaggca gccatccagc accctcgcta caagcccgtc 360

cctgccctgg agaacgacct cgcgctgctt cagctggacg ggaaagtgaa gcccagccgg 420
accatccggc cgttggccct gcccagtaag cgccaggtgg tggcagcagg gactcggtgc 480
agcatggccg gctgggggct gacccaccag ggcgggcgcc tgtcccgggt gctgcgggag 540
ctggacctcc aagtgctgga cacccgcatg tgtaacaaca gccgcttctg gaacggcagc 600
ctctccccca gcatggtctg cctggcggcc gactccaagg accaggctcc ctgcaagggt 660
gactcgggcg ggcccctggt gtgtggcaaa ggccgggtgt tggccggagt cctgtccttc 720
agctccaggg tctgcactga catcttcaag cctcccgtgg ccaccgctgt ggcgccttac 780
gtgtcctgga tcaggaaggt caccggccga tcggcctgat gccctggggt gatggggacc 840
ccctcgctgt ctccacagga cccttccct ccaggggtgc agtggggtgg gtgaggacgg 900
gtgggaggga cagggaggga ccaataaatc ataatgaaga aacgctc 947

<210> 115
<211> 257
<212> PRT
<213> Homo sapiens

<220>
<223> granzyme M

<400> 115
Met Glu Ala Cys Val Ser Ser Leu Leu Val Leu Ala Leu Gly Ala Leu
 1   5   10   15
Ser Val Gly Ser Ser Phe Gly Thr Gln Ile Ile Gly Gly Arg Glu Val
            20   25   30
Ile Pro His Ser Arg Pro Tyr Met Ala Ser Leu Gln Arg Asn Gly Ser
        35   40   45
His Leu Cys Gly Gly Val Leu Val His Pro Lys Trp Val Leu Thr Ala
    50   55   60
Ala His Cys Leu Ala Gln Arg Met Ala Gln Leu Arg Leu Val Leu Gly
65   70   75   80
Leu His Thr Leu Asp Ser Pro Gly Leu Thr Phe His Ile Lys Ala Ala
                85   90   95
Ile Gln His Pro Arg Tyr Lys Pro Val Pro Ala Leu Glu Asn Asp Leu
            100   105   110
Ala Leu Leu Gln Leu Asp Gly Lys Val Lys Pro Ser Arg Thr Ile Arg
        115   120   125
Pro Leu Ala Leu Pro Ser Lys Arg Gln Val Val Ala Ala Gly Thr Arg
    130   135   140
Cys Ser Met Ala Gly Trp Gly Leu Thr His Gln Gly Gly Arg Leu Ser
145   150   155   160
Arg Val Leu Arg Glu Leu Asp Leu Gln Val Leu Asp Thr Arg Met Cys
                165   170   175
Asn Asn Ser Arg Phe Trp Asn Gly Ser Leu Ser Pro Ser Met Val Cys
            180   185   190
Leu Ala Ala Asp Ser Lys Asp Gln Ala Pro Cys Lys Gly Asp Ser Gly
        195   200   205
Gly Pro Leu Val Cys Gly Lys Gly Arg Val Leu Ala Gly Val Leu Ser
    210   215   220
Phe Ser Ser Arg Val Cys Thr Asp Ile Phe Lys Pro Pro Val Ala Thr
225   230   235   240
Ala Val Ala Pro Tyr Val Ser Trp Ile Arg Lys Val Thr Gly Arg Ser
                245   250   255
Ala

<210> 116

<211> 784
<212> DNA
<213> Homo sapiens

<220>
<223> chymase (human-type)

<400> 116
agcatttgct caggcagcct ctctgggaag atgctgcttc ttcctctccc cctgctgctc 60
tttctcttgt gctccagagc tgaagctggg gagatcatcg ggggcacaga atgcaagcca 120
cattcccgcc cctacatggc ctacctggaa attgtaactt ccaacggtcc ctcaaaattt 180
tgtggtggtt tccttataag acggaacttt gtgctgacgg ctgctcattg tgcaggaagg 240
tctataacag tcacccttgg agcccataac ataacagagg aagaagacac atggcagaag 300
cttgaggtta taaagcaatt ccgtcatcca aaatataaca cttctactct tcaccacgat 360
atcatgttac taaagttgaa ggagaaagcc agcctgaccc tggctgtggg gacactcccc 420
ttcccatcac aattcaactt tgtcccacct gggagaatgt gccgggtggc tggctgggga 480
agaacaggtg tgttgaagcc gggctcagac actctgcaag aggtgaagct gagactcatg 540
gatccccagg cctgcagcca cttcagagac tttgaccaca atcttcagct gtgtgtgggc 600
aatcccagga agacaaaatc tgcatttaag ggagactctg ggggccctct tctgtgtgct 660
ggggtggccc agggcatcgt atcctatgga cggtcggatg caaagccccc tgctgtcttc 720
acccgaatct cccattaccg gccctggatc aaccagatcc tgcaggcaaa ttaatcctgg 780
atcc 784

<210> 117
<211> 247
<212> PRT
<213> Homo sapiens

<220>
<223> chymase (human-type)

<400> 117
Met Leu Leu Leu Pro Leu Pro Leu Leu Leu Phe Leu Leu Cys Ser Arg
 1   5   10   15
Ala Glu Ala Gly Glu Ile Ile Gly Gly Thr Glu Cys Lys Pro His Ser
            20   25   30
Arg Pro Tyr Met Ala Tyr Leu Glu Ile Val Thr Ser Asn Gly Pro Ser
        35   40   45
Lys Phe Cys Gly Gly Phe Leu Ile Arg Arg Asn Phe Val Leu Thr Ala
    50   55   60
Ala His Cys Ala Gly Arg Ser Ile Thr Val Thr Leu Gly Ala His Asn
65   70   75   80
Ile Thr Glu Glu Glu Asp Thr Trp Gln Lys Leu Glu Val Ile Lys Gln
                85   90   95
Phe Arg His Pro Lys Tyr Asn Thr Ser Thr Leu His His Asp Ile Met
            100   105   110
Leu Leu Lys Leu Lys Glu Lys Ala Ser Leu Thr Leu Ala Val Gly Thr
        115   120   125
Leu Pro Phe Pro Ser Gln Phe Asn Phe Val Pro Pro Gly Arg Met Cys
    130   135   140
Arg Val Ala Gly Trp Gly Arg Thr Gly Val Leu Lys Pro Gly Ser Asp
145   150   155   160
Thr Leu Gln Glu Val Lys Leu Arg Leu Met Asp Pro Gln Ala Cys Ser
                165   170   175
His Phe Arg Asp Phe Asp His Asn Leu Gln Leu Cys Val Gly Asn Pro
            180   185   190
Arg Lys Thr Lys Ser Ala Phe Lys Gly Asp Ser Gly Gly Pro Leu Leu

```
        195                 200                 205
Cys Ala Gly Val Ala Gln Gly Ile Val Ser Tyr Gly Arg Ser Asp Ala
    210                 215                 220
Lys Pro Pro Ala Val Phe Thr Arg Ile Ser His Tyr Arg Pro Trp Ile
225                 230                 235                 240
Asn Gln Ile Leu Gln Ala Asn
                245
```

<210> 118
<211> 1194
<212> DNA
<213> Homo sapiens

<220>
<223> tryptase alpha (1)

<400> 118
ataaatgggg aggggagagc ccactgggta gaaggaacag ggagcggcca ggatgctgaa 60
tctgctgctg ctggcgctgc ccgtcctggc gagccgcgcc tacgcggccc ctgccccagg 120
ccaggccctg cagcgagtgg gcatcgtcgg gggtcaggag gcccccagga gcaagtggcc 180
ctggcaggtg agcctgagag tccacggccc atactggatg cacttctgcg ggggctccct 240
catccacccc cagtgggtgc tgaccgcagc gcactgcgtg ggaccggacg tcaaggatct 300
ggccgccctc agggtgcaac tgcgggagca gcacctctac taccaggacc agctgctgcc 360
ggtcagcagg atcatcgtgc acccacagtt ctacaccgcc cagatcggag cggacatcgc 420
cctgctggag ctggaggagc cggtgaacgt ctccagccac gtccacacgg tcaccctgcc 480
ccctgcctca gagaccttcc ccccggggat gccgtgctgg gtcactggct ggggcgatgt 540
ggacaatgat gagcgcctcc caccgccatt tcctctgaag caggtgaagg tccccataat 600
ggaaaaccac atttgtgacg caaaatacca ccttggcgcc tacacgggag acgacgtccg 660
catcgtccgt gacgacatgc tgtgtgccgg gaacacccgg agggactcat gccagggcga 720
ctccggaggg cccctggtgt gcaaggtgaa tggcacctgg ctgcaggcgg gcgtggtcag 780
ctggggcgag ggctgtgccc agcccaaccg gcctggcatc tacacccgtg tcacctacta 840
cttggactgg atccaccact atgtccccaa aaagccgtga gtcaggcctg ggttggccac 900
ctgggtcact ggaggaccaa cccctgctgt ccaaaacacc actgcttcct acccaggtgg 960
cgactgcccc ccacaccttc cctgccccgt cctgagtgcc ccttcctgtc ctaagccccc 1020
tgctctcttc tgagcccctt cccctgtcct gaggaccctt ccctatcctg agccccccttc 1080
cctgtcctaa gcctgacgcc tgcaccgggc cctccagccc tcccctgccc agatagctgg 1140
tggtgggcgc taatcctcct gagtgctgga cctcattaaa gtgcatggaa atca 1194

<210> 119
<211> 275
<212> PRT
<213> Homo sapiens

<220>
<223> tryptase alpha (1)

<400> 119
```
Met Leu Asn Leu Leu Leu Leu Ala Leu Pro Val Leu Ala Ser Arg Ala
 1               5                  10                  15
Tyr Ala Ala Pro Ala Pro Gly Gln Ala Leu Gln Arg Val Gly Ile Val
            20                  25                  30
Gly Gly Gln Glu Ala Pro Arg Ser Lys Trp Pro Trp Gln Val Ser Leu
        35                  40                  45
Arg Val His Gly Pro Tyr Trp Met His Phe Cys Gly Gly Ser Leu Ile
    50                  55                  60
His Pro Gln Trp Val Leu Thr Ala Ala His Cys Val Gly Pro Asp Val
```

```
65                  70                  75                  80
Lys Asp Leu Ala Ala Leu Arg Val Gln Leu Arg Glu Gln His Leu Tyr
                85                  90                  95
Tyr Gln Asp Gln Leu Leu Pro Val Ser Arg Ile Ile Val His Pro Gln
            100                 105                 110
Phe Tyr Thr Ala Gln Ile Gly Ala Asp Ile Ala Leu Leu Glu Leu Glu
        115                 120                 125
Glu Pro Val Asn Val Ser Ser His Val His Thr Val Thr Leu Pro Pro
    130                 135                 140
Ala Ser Glu Thr Phe Pro Pro Gly Met Pro Cys Trp Val Thr Gly Trp
145                 150                 155                 160
Gly Asp Val Asp Asn Asp Glu Arg Leu Pro Pro Pro Phe Pro Leu Lys
                165                 170                 175
Gln Val Lys Val Pro Ile Met Glu Asn His Ile Cys Asp Ala Lys Tyr
            180                 185                 190

His Leu Gly Ala Tyr Thr Gly Asp Asp Val Arg Ile Val Arg Asp Asp
        195                 200                 205
Met Leu Cys Ala Gly Asn Thr Arg Arg Asp Ser Cys Gln Gly Asp Ser
    210                 215                 220
Gly Gly Pro Leu Val Cys Lys Val Asn Gly Thr Trp Leu Gln Ala Gly
225                 230                 235                 240
Val Val Ser Trp Gly Glu Gly Cys Ala Gln Pro Asn Arg Pro Gly Ile
                245                 250                 255
Tyr Thr Arg Val Thr Tyr Tyr Leu Asp Trp Ile His His Tyr Val Pro
            260                 265                 270
Lys Lys Pro
        275
```

<210> 120
<211> 1074
<212> DNA
<213> Homo sapiens

<220>
<223> granzyme K

<400> 120
gatcaacaca tttcatctgg gcttcttaaa tctaaatctt taaaatgact aagttttctt 60
ccttttctct gtttttccta atagttgggg cttatatgac tcatgtgtgt ttcaatatgg 120
aaattattgg agggaaagaa gtgtcacctc attccaggcc atttatggcc tccatccagt 180
atggcggaca tcacgtttgt ggaggtgttc tgattgatcc acagtgggtg ctgacagcag 240
cccactgcca atatcggttt accaaaggcc agtctcccac tgtggtttta ggcgcacact 300
ctctctcaaa gaatgaggcc tccaaacaaa cactggagat caaaaaattt ataccattct 360
caagagttac atcagatcct caatcaaatg atatcatgct ggttaagctt caaacagccg 420
caaaactcaa taaacatgtc aagatgctcc acataagatc caaaacctct cttagatctg 480
gaaccaaatg caaggttact ggctggggag ccaccgatcc agattcatta agaccttctg 540
acaccctgcg agaagtcact gttactgtcc taagtcgaaa actttgcaac agccaaagtt 600
actacaacgg cgacccttttt atcaccaaag acatggtctg tgcaggagat gccaaaggcc 660
agaaggattc ctgtaagggt gactcagggg gccccttgat ctgtaaaggt gtcttccacg 720
ctatagtctc tggaggtcat gaatgtggtg ttgccacaaa gcctggaatc tacaccctgt 780
taaccaagaa ataccagact tggatcaaaa gcaaccttgt cccgcctcat acaaattaag 840
ttacaaataa ttttattgga tgcacttgct tctttttcc taatatgctc gcaggttaga 900
gttgggtgta agtaaagcag agcacatatg gggtccattt ttgcacttgt aagtcatttt 960
attaaggaat caagttcttt ttcacttgta tcactgatgt atttctacca tgctggtttt 1020
attctaaata aaatttagaa gactcaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 1074

<210> 121
<211> 264
<212> PRT
<213> Homo sapiens

<220>
<223> granzyme K

<400> 121
Met Thr Lys Phe Ser Ser Phe Ser Leu Phe Phe Leu Ile Val Gly Ala
 1   5   10   15
Tyr Met Thr His Val Cys Phe Asn Met Glu Ile Ile Gly Gly Lys Glu
            20   25   30
Val Ser Pro His Ser Arg Pro Phe Met Ala Ser Ile Gln Tyr Gly Gly
        35   40   45
His His Val Cys Gly Gly Val Leu Ile Asp Pro Gln Trp Val Leu Thr
    50   55   60
Ala Ala His Cys Gln Tyr Arg Phe Thr Lys Gly Gln Ser Pro Thr Val
65   70   75   80
Val Leu Gly Ala His Ser Leu Ser Lys Asn Glu Ala Ser Lys Gln Thr
                85   90   95
Leu Glu Ile Lys Lys Phe Ile Pro Phe Ser Arg Val Thr Ser Asp Pro
            100   105   110
Gln Ser Asn Asp Ile Met Leu Val Lys Leu Gln Thr Ala Ala Lys Leu
        115   120   125
Asn Lys His Val Lys Met Leu His Ile Arg Ser Lys Thr Ser Leu Arg
    130   135   140
Ser Gly Thr Lys Cys Lys Val Thr Gly Trp Gly Ala Thr Asp Pro Asp
145   150   155   160
Ser Leu Arg Pro Ser Asp Thr Leu Arg Glu Val Thr Val Thr Val Leu
                165   170   175
Ser Arg Lys Leu Cys Asn Ser Gln Ser Tyr Tyr Asn Gly Asp Pro Phe
            180   185   190
Ile Thr Lys Asp Met Val Cys Ala Gly Asp Ala Lys Gly Gln Lys Asp
        195   200   205
Ser Cys Lys Gly Asp Ser Gly Gly Pro Leu Ile Cys Lys Gly Val Phe
    210   215   220
His Ala Ile Val Ser Gly Gly His Glu Cys Gly Val Ala Thr Lys Pro
225   230   235   240
Gly Ile Tyr Thr Leu Leu Thr Lys Lys Tyr Gln Thr Trp Ile Lys Ser
                245   250   255
Asn Leu Val Pro Pro His Thr Asn
            260

<210> 122
<211> 1047
<212> DNA
<213> Homo sapiens

<220>
<223> granzyme H

<400> 122
ggagtcaaca ccaacagctc tgacctgggc agccttcctg agaaaatgca gccattcctc 60
ctcctgttgg cctttcttct gacccctggg gctgggacag aggagatcat cgggggccat 120

```
gaggccaagc cccactcccg cccctacatg gcctttgttc agtttctgca agagaagagt 180
cggaagaggt gtggcggcat cctagtgaga aaggactttg tgctgacagc tgctcactgc 240
cagggaagct ccataaatgt caccttgggg gcccacaata tcaaggaaca ggagcggacc 300
cagcagttta tccctgtgaa aagacccatc ccccatccag cctataatcc taagaacttc 360
tccaacgaca tcatgctact gcagctggag agaaaggcca agtggaccac agctgtgcgg 420
cctctcaggc tacctagcag caaggcccag gtgaagccag ggcagctgtg cagtgtggct 480
ggctggggtt atgtctcaat gagcacttta gcaaccacac tgcaggaagt gttgctgaca 540
gtgcagaagg actgccagtg tgaacgtctc ttccatggca attacagcag agccactgag 600
atttgtgtgg gggatccaaa gaagacacag accggtttca agggggactc cgggggccc 660
ctcgtgtgta aggacgtagc ccaaggtatt ctctcctatg gaaacaaaaa agggacacct 720
ccaggagtct acatcaaggt ctcacacttc ctgccctgga taaagagaac aatgaagcgc 780
ctctaacagc aggcatgaga ctaaccttcc tctgggcctg accatctctg ggacagaggc 840
aagaatcccc aaggggtggg cagtcagggt tgcaggactg taataaatgg atctctggtg 900
tagaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1020
aaaaaaaaaa aaaaaaaaaa aaaaaaa                                      1047

<210> 123
<211> 246
<212> PRT
<213> Homo sapiens

<220>
<223> granzyme H

<400> 123
Met Gln Pro Phe Leu Leu Leu Ala Phe Leu Leu Thr Pro Gly Ala
 1               5                  10                  15
Gly Thr Glu Glu Ile Ile Gly Gly His Glu Ala Lys Pro His Ser Arg
            20                  25                  30
Pro Tyr Met Ala Phe Val Gln Phe Leu Gln Glu Lys Ser Arg Lys Arg
        35                  40                  45
Cys Gly Gly Ile Leu Val Arg Lys Asp Phe Val Leu Thr Ala Ala His
    50                  55                  60
Cys Gln Gly Ser Ser Ile Asn Val Thr Leu Gly Ala His Asn Ile Lys
65                  70                  75                  80
Glu Gln Glu Arg Thr Gln Gln Phe Ile Pro Val Lys Arg Pro Ile Pro
                85                  90                  95
His Pro Ala Tyr Asn Pro Lys Asn Phe Ser Asn Asp Ile Met Leu Leu
            100                 105                 110
Gln Leu Glu Arg Lys Ala Lys Trp Thr Thr Ala Val Arg Pro Leu Arg
        115                 120                 125
Leu Pro Ser Ser Lys Ala Gln Val Lys Pro Gly Gln Leu Cys Ser Val
    130                 135                 140
Ala Gly Trp Gly Tyr Val Ser Met Ser Thr Leu Ala Thr Thr Leu Gln
145                 150                 155                 160
Glu Val Leu Leu Thr Val Gln Lys Asp Cys Gln Cys Glu Arg Leu Phe
                165                 170                 175
His Gly Asn Tyr Ser Arg Ala Thr Glu Ile Cys Val Gly Asp Pro Lys
            180                 185                 190
Lys Thr Gln Thr Gly Phe Lys Gly Asp Ser Gly Gly Pro Leu Val Cys
        195                 200                 205
Lys Asp Val Ala Gln Gly Ile Leu Ser Tyr Gly Asn Lys Lys Gly Thr
    210                 215                 220
Pro Pro Gly Val Tyr Ile Lys Val Ser His Phe Leu Pro Trp Ile Lys
225                 230                 235                 240
Arg Thr Met Lys Arg Leu
```

245

<210> 124
<211> 865
<212> DNA
<213> Homo sapiens

<220>
<223> chymotrypsin B

<400> 124
ccctgccagc ggcaccatgg ctttcctctg gctcctctcc tgctgggccc tcctgggtac 60
caccttcggc tgcggggtcc ccgccatcca ccctgtgctc agcggcctgt ccaggatcgt 120
gaatggggag gacgccgtcc ccggctcctg gccctggcag gtgtccctgc aggacaaaac 180
cggcttccac ttctgcgggg gctccctcat cagcgaggac tgggtggtca ccgctgccca 240
ctgcggggtc aggacctccg acgtggtcgt ggctggggag tttgaccagg gctctgacga 300
ggagaacatc caggtcctga agatcgccaa ggtcttcaag aaccccaagt tcagcattct 360
gaccgtgaac aatgacatca ccctgctgaa gctggccaca cctgcccgct tctcccagac 420
agtgtccgcc gtgtgcctgc ccagcgccga cgacgacttc cccgcgggga cactgtgtgc 480
caccacaggc tggggcaaga ccaagtacaa cgccaacaag acccctgaca agctgcagca 540
ggcagccctg cccctcctgt ccaatgccga atgcaagaag tcctggggca ggaggatcac 600
cgacgtgatg atctgtgccg gggccagtgg cgtctcctcc tgcatgggcg actctggcgg 660
tcccctggtc tgccaaaagg atggagcctg gaccctggtg ggcattgtgt cctggggcag 720
cgacacctgc tccacctcca gccctggcgt gtacgcccgt gtcaccaagc tcataccttg 780
ggtgcagaag atcctggctg ccaactgagc ccgcggctcc ctccgaccct gctccccaca 840
gagcctcagt aaacccatgg aacac 865

<210> 125
<211> 263
<212> PRT
<213> Homo sapiens

<220>
<223> chymotrypsin B

<400> 125
Met Ala Phe Leu Trp Leu Leu Ser Cys Trp Ala Leu Leu Gly Thr Thr
 1   5   10   15
Phe Gly Cys Gly Val Pro Ala Ile His Pro Val Leu Ser Gly Leu Ser
            20   25   30
Arg Ile Val Asn Gly Glu Asp Ala Val Pro Gly Ser Trp Pro Trp Gln
        35   40   45
Val Ser Leu Gln Asp Lys Thr Gly Phe His Phe Cys Gly Gly Ser Leu
    50   55   60
Ile Ser Glu Asp Trp Val Val Thr Ala Ala His Cys Gly Val Arg Thr
65   70   75   80
Ser Asp Val Val Val Ala Gly Glu Phe Asp Gln Gly Ser Asp Glu Glu
                85   90   95
Asn Ile Gln Val Leu Lys Ile Ala Lys Val Phe Lys Asn Pro Lys Phe
            100   105   110
Ser Ile Leu Thr Val Asn Asn Asp Ile Thr Leu Leu Lys Leu Ala Thr
        115   120   125
Pro Ala Arg Phe Ser Gln Thr Val Ser Ala Val Cys Leu Pro Ser Ala
    130   135   140
Asp Asp Asp Phe Pro Ala Gly Thr Leu Cys Ala Thr Thr Gly Trp Gly

```
145                 150                 155                 160
Lys Thr Lys Tyr Asn Ala Asn Lys Thr Pro Asp Lys Leu Gln Gln Ala
                165                 170                 175
Ala Leu Pro Leu Leu Ser Asn Ala Glu Cys Lys Lys Ser Trp Gly Arg
            180                 185                 190
Arg Ile Thr Asp Val Met Ile Cys Ala Gly Ala Ser Gly Val Ser Ser
        195                 200                 205
Cys Met Gly Asp Ser Gly Gly Pro Leu Val Cys Gln Lys Asp Gly Ala
    210                 215                 220
Trp Thr Leu Val Gly Ile Val Ser Trp Gly Ser Asp Thr Cys Ser Thr
225                 230                 235                 240
Ser Ser Pro Gly Val Tyr Ala Arg Val Thr Lys Leu Ile Pro Trp Val
                245                 250                 255
Gln Lys Ile Leu Ala Ala Asn
            260
```

<210> 126
<211> 952
<212> DNA
<213> Homo sapiens

<220>
<223> pancreatic elastase

<400> 126
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ttggtccaag caagaaggca gtggtctact ccatcggcaa catgctggtc ctttatggac 60
acagcaccca ggaccttccg gaaaccaatg cccgcgtagt cggagggact gaggccggga 120
ggaattcctg gccctctcag atttccctcc agtaccggtc tggaggttcc cggtatcaca 180
cctgtggagg gacccttatc agacagaact gggtgatgac agctgctcac tgcgtggatt 240
accagaagac tttccgcgtg gtggctggag accataacct gagccagaat gatggcactg 300
agcagtacgt gagtgtgcag aagatcgtgg tgcatccata ctggaacagc gataacgtgg 360
ctgccggcta tgacatcgcc ctgctgcgcc tggcccagag cgttaccctc aatagctatg 420
tccagctggg tgttctgccc caggagggag ccatcctggc taacaacagt ccctgctaca 480
tcacaggctg gggcaagacc aagaccaatg ggcagctggc ccagaccctg cagcaggctt 540
acctgccctc tgtggactac gccatctgct ccagctcctc ctactggggc tccactgtga 600
agaacaccat ggtgtgtgct ggtggagatg gagttcgctc tggatgccag ggtgactctg 660
ggggcccccc ccattgcttg gtgaatggca agtattctgt ccatggagtg accagctttg 720
tgtccagccg gggctgtaat gtctccagga agcctacagt cttcacccag gtctctgctt 780
acatctcctg gataaataat gtcatcgcct ccaactgaac attttcctga gtccaacgac 840
cttcccaaaa tggttcttag atctgcaata ggacttgcga tcaaaaagta aaacacattc 900
tgaaagacta ttgagccatt gatagaaaag caaataaaac tagatataca tt         952
```

<210> 127
<211> 258
<212> PRT
<213> Homo sapiens

<220>
<223> pancreatic elastase

<400> 127
```
Met Leu Val Leu Tyr Gly His Ser Thr Gln Asp Leu Pro Glu Thr Asn
 1               5                  10                  15
Ala Arg Val Val Gly Gly Thr Glu Ala Gly Arg Asn Ser Trp Pro Ser
            20                  25                  30
```

```
Gln Ile Ser Leu Gln Tyr Arg Ser Gly Gly Ser Arg Tyr His Thr Cys
        35                  40                  45
Gly Gly Thr Leu Ile Arg Gln Asn Trp Val Met Thr Ala Ala His Cys
    50                  55                  60
Val Asp Tyr Gln Lys Thr Phe Arg Val Val Ala Gly Asp His Asn Leu
65                  70                  75                  80
Ser Gln Asn Asp Gly Thr Glu Gln Tyr Val Ser Val Gln Lys Ile Val
                85                  90                  95
Val His Pro Tyr Trp Asn Ser Asp Asn Val Ala Ala Gly Tyr Asp Ile
            100                 105                 110
Ala Leu Leu Arg Leu Ala Gln Ser Val Thr Leu Asn Ser Tyr Val Gln
        115                 120                 125
Leu Gly Val Leu Pro Gln Glu Gly Ala Ile Leu Ala Asn Asn Ser Pro
    130                 135                 140
Cys Tyr Ile Thr Gly Trp Gly Lys Thr Lys Thr Asn Gly Gln Leu Ala
145                 150                 155                 160
Gln Thr Leu Gln Gln Ala Tyr Leu Pro Ser Val Asp Tyr Ala Ile Cys
                165                 170                 175
Ser Ser Ser Ser Tyr Trp Gly Ser Thr Val Lys Asn Thr Met Val Cys
            180                 185                 190
Ala Gly Gly Asp Gly Val Arg Ser Gly Cys Gln Gly Asp Ser Gly Gly
        195                 200                 205
Pro Leu His Cys Leu Val Asn Gly Lys Tyr Ser Val His Gly Val Thr
    210                 215                 220
Ser Phe Val Ser Ser Arg Gly Cys Asn Val Ser Arg Lys Pro Thr Val
225                 230                 235                 240
Phe Thr Gln Val Ser Ala Tyr Ile Ser Trp Ile Asn Asn Val Ile Ala
                245                 250                 255
Ser Asn
```

<210> 128
<211> 963
<212> DNA
<213> Homo sapiens

<220>
<223> pancreatic endopeptidase E (A)

<400> 128
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tcctatcatc acaaaactca tgatgctccg gctgctcagt tccctcctcc ttgtggccgt 60
tgcctcaggc tatggcccac cttcctctca ctcttccagc cgcgttgtcc atggtgagga 120
tgcggtcccc tacagctggc cctggcaggt ttccctgcag tatgagaaaa gtggaagctt 180
ctaccacacg tgtggcggta gcctcatcgc ccccgattgg gttgtgactg ccggccactg 240
catctcgagg gatctgacct accaggtggt gttgggtgag tacaaccttg ctgtgaagga 300
gggccccgag caggtgatcc ccatcaactc tgaggagctg tttgtgcatc cactctggaa 360
ccgctcgtgt gtggcctgtg gcaatgacat cgccctcatc aagctctcac gcagcgccca 420
gctgggagat gccgtccagc tcgcctcact ccctcccgct ggtgacatcc ttcccaacaa 480
gacaccctgc tacatcaccg gctggggccg tctctatacc aatgggccac tcccagacaa 540
gctgcagcag gcccggctgc ccgtggtgga ctataagcac tgctccaggt ggaactggtg 600
gggttccacc gtgaagaaaa ccatggtgtg tgctggaggg tacatccgct ccggctgcaa 660
cggtgactct ggaggacccc tcaactgccc cacagaggat ggtggctggc aggtccacgg 720
tgtgaccagc tttgtttctg gctttggctg caacttcatc tggaagccca cggtgttcac 780
tcgagtctcc gccttcatcg actggattga ggagaccata gcaagccact agaaccaagg 840
cccagctggc agtgctgatc gatcccacat cctgaataaa gaataaagat ctctcagaaa 900
attccaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960
```

aaa 963

<210> 129
<211> 270
<212> PRT
<213> Homo sapiens

<220>
<223> pancreatic endopeptidase E (A)

<400> 129
Met Met Leu Arg Leu Leu Ser Ser Leu Leu Leu Val Ala Val Ala Ser
1 5 10 15
Gly Tyr Gly Pro Pro Ser Ser His Ser Ser Ser Arg Val Val His Gly
20 25 30
Glu Asp Ala Val Pro Tyr Ser Trp Pro Trp Gln Val Ser Leu Gln Tyr
35 40 45
Glu Lys Ser Gly Ser Phe Tyr His Thr Cys Gly Gly Ser Leu Ile Ala
50 55 60
Pro Asp Trp Val Val Thr Ala Gly His Cys Ile Ser Arg Asp Leu Thr
65 70 75 80
Tyr Gln Val Val Leu Gly Glu Tyr Asn Leu Ala Val Lys Glu Gly Pro
85 90 95
Glu Gln Val Ile Pro Ile Asn Ser Glu Glu Leu Phe Val His Pro Leu
100 105 110
Trp Asn Arg Ser Cys Val Ala Cys Gly Asn Asp Ile Ala Leu Ile Lys
115 120 125
Leu Ser Arg Ser Ala Gln Leu Gly Asp Ala Val Gln Leu Ala Ser Leu
130 135 140
Pro Pro Ala Gly Asp Ile Leu Pro Asn Lys Thr Pro Cys Tyr Ile Thr
145 150 155 160
Gly Trp Gly Arg Leu Tyr Thr Asn Gly Pro Leu Pro Asp Lys Leu Gln
165 170 175
Gln Ala Arg Leu Pro Val Val Asp Tyr Lys His Cys Ser Arg Trp Asn
180 185 190
Trp Trp Gly Ser Thr Val Lys Lys Thr Met Val Cys Ala Gly Gly Tyr
195 200 205
Ile Arg Ser Gly Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Pro
210 215 220
Thr Glu Asp Gly Gly Trp Gln Val His Gly Val Thr Ser Phe Val Ser
225 230 235 240
Gly Phe Gly Cys Asn Phe Ile Trp Lys Pro Thr Val Phe Thr Arg Val
245 250 255
Ser Ala Phe Ile Asp Trp Ile Glu Glu Thr Ile Ala Ser His
260 265 270

<210> 130
<211> 914
<212> DNA
<213> Homo sapiens

<220>
<223> pancreatic elastase II (IIA)

<400> 130
ttttacagaa ctcccacgga cacaccatga taaggacgct gctgctgtcc actttggtgg 60

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ctggagccct cagttgtggg gaccccactt acccacctta tgtgactagg gtggttggcg 120
gtgaagaagc gaggcccaac agctggccct ggcaggtctc cctgcagtac agctccaatg 180
gcaagtggta ccacacctgc ggagggtccc tgatagccaa cagctgggtc ctgacggctg 240
cccactgcat cagctcctcc aggacctacc gcgtggggct gggccggcac aacctctacg 300
ttgcggagtc cggctcgctg gcagtcagtg tctctaagat tgtggtgcac aaggactgga 360
actccaacca aatctccaaa gggaacgaca ttgccctgct caaactggct aaccccgtct 420
ccctcaccga caagatccag ctggcctgcc tccctcctgc cggcaccatt ctacccaaca 480
actacccctg ctacgtcacg ggctggggaa ggctgcagac caacggggct gttcctgatg 540
tcctgcagca gggccggttg ctggttgtgg actatgccac ctgctccagc tctgcctggt 600
ggggcagcag cgtgaaaacc agtatgatct gtgctggggg tgatggcgtg atctccagct 660
gcaacggaga ctctggcggg ccactgaact gtcaggcgtc tgacggccgg tggcaggtgc 720
acggcatcgt cagcttcggg tctcgcctcg gctgcaacta ctaccacaag ccctccgtct 780
tcacgcgggt ctccaattac atcgactgga tcaattcggt gattgcaaat aactaaccaa 840
aagaagtccc tgggactgtt tcagacttgg aaaggtcaca gaaggaaaat aatataataa 900
agtgacaact atgc                                                   914

<210> 131
<211> 269
<212> PRT
<213> Homo sapiens

<220>
<223> pancreatic elastase II (IIA)

<400> 131
Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu Ser
 1               5                  10                  15
Cys Gly Asp Pro Thr Tyr Pro Pro Tyr Val Thr Arg Val Val Gly Gly
            20                  25                  30
Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln Tyr
        35                  40                  45
Ser Ser Asn Gly Lys Trp Tyr His Thr Cys Gly Gly Ser Leu Ile Ala
    50                  55                  60

Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Arg Thr
65                  70                  75                  80
Tyr Arg Val Gly Leu Gly Arg His Asn Leu Tyr Val Ala Glu Ser Gly
                85                  90                  95
Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp Asn
            100                 105                 110
Ser Asn Gln Ile Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu Ala
        115                 120                 125
Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro Pro
    130                 135                 140
Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr Val Thr Gly Trp
145                 150                 155                 160
Gly Arg Leu Gln Thr Asn Gly Ala Val Pro Asp Val Leu Gln Gln Gly
                165                 170                 175
Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser Ser Ala Trp Trp
            180                 185                 190
Gly Ser Ser Val Lys Thr Ser Met Ile Cys Ala Gly Gly Asp Gly Val
        195                 200                 205
Ile Ser Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln Ala
    210                 215                 220
Ser Asp Gly Arg Trp Gln Val His Gly Ile Val Ser Phe Gly Ser Arg
225                 230                 235                 240
Leu Gly Cys Asn Tyr Tyr His Lys Pro Ser Val Phe Thr Arg Val Ser
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245 250 255
Asn Tyr Ile Asp Trp Ile Asn Ser Val Ile Ala Asn Asn
260 265

<210> 132
<211> 3696
<212> DNA
<213> Homo sapiens

<220>
<223> Enteropeptidase

<400> 132
accagacagt tcttaaatta gcaagccttc aaaaccaaaa atggggtcga aaagaggcat 60
atcttctagg catcattctc tcagctccta tgaaatcatg tttgcagctc tctttgccat 120
attggtagtg ctctgtgctg gattaattgc agtatcctgc ctgacaatca aggaatccca 180
acgaggtgca gcacttggac agagtcatga agccagagcg acatttaaaa taacatccgg 240
agttacatat aatcctaatt tgcaagacaa actctcagtg gatttcaaag ttcttgcttt 300
tgaccttcag caaatgatag atgagatctt tctatcaagc aatctgaaga atgaatataa 360
gaactcaaga gttttacaat ttgaaaatgg cagcattata gtcgtatttg acctttttctt 420
tgcccagtgg gtgtcagatc aaaatgtaaa agaagaactg attcaaggcc ttgaagcaaa 480
taaatccagc caactggtca ctttccatat tgatttgaac agcgttgata tcctagacaa 540
gctaacaacc accagtcatc tggcaactcc aggaaatgtc tcaatagagt gcctgcctgg 600
ttcaagtcct tgtactgatg ctctaacgtg tataaaagct gatttatttt gtgatggaga 660
agtaaactgt ccagatggtt ctgacgaaga caataaaatg tgtgccacag tttgtgatgg 720
aagatttttg ttaactggat catctgggtc tttccaggct actcattatc caaaaccttc 780
tgaaacaagt gttgtctgcc agtggatcat acgtgtaaac caaggacttt ccattaaact 840
gagcttcgat gattttaata catattatac agatatatta gatatttatg aaggtgtagg 900
atcaagcaag attttaagag cttctatttg ggaaactaat cctggcacaa taagaatttt 960
ttccaaccaa gttactgcca cctttcttat agaatctgat gaaagtgatt atgttggctt 1020
taatgcaaca tatactgcat ttaacagcag tgagcttaat aattatgaga aaattaattg 1080
taactttgag gatggctttt gtttctgggt ccaggatcta aatgatgata atgaatggga 1140
aaggattcag ggaagcacct tttctccttt tactggaccc aattttgacc acacttttgg 1200
caatgcttca ggattttaca tttctacccc aactggacca ggagggagac aagaacgagt 1260
ggggctttta agcctccctt tggaccccac tttggagcca gcttgcctta gtttctggta 1320
tcatatgtat ggtgaaaatg tccataaatt aagcattaat atcagcaatg accaaaatat 1380
ggagaagaca gttttccaaa aggaaggaaa ttatggagac aattggaatt atggacaagt 1440
aaccctaaat gaaacagtta aatttaaggt tgcttttaat gcttttaaaa acaagatcct 1500
gagtgatatt gcgttggatg acattagcct aacatatggg atttgcaatg ggagtcttta 1560
tccagaacca actttggtgc caactcctcc accagaactt cctacggact gtggaggacc 1620
ttttgagctg tgggagccaa atacaacatt cagttctacg aactttccaa acagctaccc 1680
taatctggct ttctgtgttt ggattttaaa tgcacaaaaa ggaaagaata tacaacttca 1740
ttttcaagaa tttgacttag aaaatattaa cgatgtagtt gaaataagag atggtgaaga 1800
agctgattcc ttgctcttag ctgtgtacac agggcctggc ccagtaaagg atgtgttctc 1860
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ttttcaatgt aaaaatggag agtgtgttcc actggtgaat ctctgtgacg gtcatctgca 2040
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caatggttta gtgcggttca gaatccagag catatggcat acagcttgtg ctgagaactg 2160
gaccacccag atttcaaatg atgtttgtca actgctggga ctagggagtg gaaactcatc 2220
aaagccaatc ttctctaccg atggtggacc atttgtcaaa ttaaacacag cacctgatgg 2280
ccacttaata ctaacaccca gtcaacagtg tttacaggat tccttgattc ggttacagtg 2340
taaccataaa tcttgtggaa aaaaactggc agctcaagac atcaccccaa agattgttgg 2400
aggaagtaat gccaaagaag gggcctggcc ctgggttgtg ggtctgtatt atggcggccg 2460
actgctctgc ggcgcatctc tcgtcagcag tgactggctg gtgtccgccg cacactgcgt 2520
gtatgggaga aacttagagc catccaagtg gacagcaatc ctaggcctgc atatgaaatc 2580

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aaatctgacc tctcctcaaa cagtccctcg attaatagat gaaattgtca taaaccctca 2640
ttacaatagg cgaagaaagg acaacgacat tgccatgatg catctggaat ttaaagtgaa 2700
ttacacagat tacatacaac ctatttgttt accggaagaa aatcaagttt ttcctccagg 2760
aagaaattgt tctattgctg gttgggggac ggttgtatat caaggtacta ctgcaaacat 2820
attgcaagaa gctgatgttc ctcttctatc aaatgagaga tgccaacagc agatgccaga 2880
atataacatt actgaaaata tgatatgtgc aggctatgaa gaaggaggaa tagattcttg 2940
tcaggggat tcaggaggac cattaatgtg ccaagaaaac aacaggtggt tccttgctgg 3000
tgtgacctca tttggataca agtgtgccct gcctaatcgc cccggagtgt atgccagggt 3060
ctcaaggttt accgaatgga tacaaagttt tctacattag cgcatttctt aaactaaaca 3120
ggaaagtcgc attattttcc cattctactc tagaaagcat ggaaattaag tgtttcgtac 3180
aaaaatttta aaaagttacc aaaggttttt attcttacct atgtcaatga aatgctaggg 3240
ggccagggaa acaaaatttt aaaaataata aaattcacca tagcaataca gaataacttt 3300
aaaataccat taaatacatt tgtatttcat tgtgaacagg tatttcttca cagatctcat 3360
ttttaaaatt cttaatgatt atttttatta cttactgttg tttaaaggga tgttatttta 3420
aagcatatac catacactta agaaatttga gcagaattta aaaaagaaag aaaataaatt 3480
gtttttccca aagtatgtca ctgttggaaa taaactgcca taaattttct agttccagtt 3540
tagtttgctg ctattagcag aaactcaatt gtttctctgt cttttctatc aaaattttca 3600
acatatgcat aaccttagta ttttcccaac caatagaaac tatttattgt aagcttatgt 3660
cacaggcctg gactaaattg attttacgtt cctctt                          3696
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<210> 133
<211> 1019
<212> PRT
<213> Homo sapiens

<220>
<223> Enteropeptidase

<400> 133

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Met Gly Ser Lys Arg Gly Ile Ser Ser Arg His His Ser Leu Ser Ser
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Tyr Glu Ile Met Phe Ala Ala Leu Phe Ala Ile Leu Val Val Leu Cys
            20                  25                  30
Ala Gly Leu Ile Ala Val Ser Cys Leu Thr Ile Lys Glu Ser Gln Arg
        35                  40                  45
Gly Ala Ala Leu Gly Gln Ser His Glu Ala Arg Ala Thr Phe Lys Ile
    50                  55                  60
Thr Ser Gly Val Thr Tyr Asn Pro Asn Leu Gln Asp Lys Leu Ser Val
65                  70                  75                  80
Asp Phe Lys Val Leu Ala Phe Asp Leu Gln Gln Met Ile Asp Glu Ile
                85                  90                  95
Phe Leu Ser Ser Asn Leu Lys Asn Glu Tyr Lys Asn Ser Arg Val Leu
            100                 105                 110
Gln Phe Glu Asn Gly Ser Ile Ile Val Val Phe Asp Leu Phe Phe Ala
        115                 120                 125
Gln Trp Val Ser Asp Gln Asn Val Lys Glu Glu Leu Ile Gln Gly Leu
    130                 135                 140
Glu Ala Asn Lys Ser Ser Gln Leu Val Thr Phe His Ile Asp Leu Asn
145                 150                 155                 160
Ser Val Asp Ile Leu Asp Lys Leu Thr Thr Thr Ser His Leu Ala Thr
                165                 170                 175
Pro Gly Asn Val Ser Ile Glu Cys Leu Pro Gly Ser Ser Pro Cys Thr
            180                 185                 190
Asp Ala Leu Thr Cys Ile Lys Ala Asp Leu Phe Cys Asp Gly Glu Val
        195                 200                 205
Asn Cys Pro Asp Gly Ser Asp Glu Asp Asn Lys Met Cys Ala Thr Val
    210                 215                 220
```

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Cys Asp Gly Arg Phe Leu Leu Thr Gly Ser Ser Gly Ser Phe Gln Ala
225                 230                 235                 240
Thr His Tyr Pro Lys Pro Ser Glu Thr Ser Val Val Cys Gln Trp Ile
                245                 250                 255
Ile Arg Val Asn Gln Gly Leu Ser Ile Lys Leu Ser Phe Asp Asp Phe
            260                 265                 270
Asn Thr Tyr Tyr Thr Asp Ile Leu Asp Ile Tyr Glu Gly Val Gly Ser
        275                 280                 285
Ser Lys Ile Leu Arg Ala Ser Ile Trp Glu Thr Asn Pro Gly Thr Ile
    290                 295                 300
Arg Ile Phe Ser Asn Gln Val Thr Ala Thr Phe Leu Ile Glu Ser Asp
305                 310                 315                 320
Glu Ser Asp Tyr Val Gly Phe Asn Ala Thr Tyr Thr Ala Phe Asn Ser
                325                 330                 335
Ser Glu Leu Asn Asn Tyr Glu Lys Ile Asn Cys Asn Phe Glu Asp Gly
            340                 345                 350
Phe Cys Phe Trp Val Gln Asp Leu Asn Asp Asp Asn Glu Trp Glu Arg
        355                 360                 365
Ile Gln Gly Ser Thr Phe Ser Pro Phe Thr Gly Pro Asn Phe Asp His
    370                 375                 380
Thr Phe Gly Asn Ala Ser Gly Phe Tyr Ile Ser Thr Pro Thr Gly Pro
385                 390                 395                 400
Gly Gly Arg Gln Glu Arg Val Gly Leu Leu Ser Leu Pro Leu Asp Pro
                405                 410                 415
Thr Leu Glu Pro Ala Cys Leu Ser Phe Trp Tyr His Met Tyr Gly Glu
            420                 425                 430
Asn Val His Lys Leu Ser Ile Asn Ile Ser Asn Asp Gln Asn Met Glu
        435                 440                 445
Lys Thr Val Phe Gln Lys Glu Gly Asn Tyr Gly Asp Asn Trp Asn Tyr
    450                 455                 460
Gly Gln Val Thr Leu Asn Glu Thr Val Lys Phe Lys Val Ala Phe Asn
465                 470                 475                 480
Ala Phe Lys Asn Lys Ile Leu Ser Asp Ile Ala Leu Asp Asp Ile Ser
                485                 490                 495
Leu Thr Tyr Gly Ile Cys Asn Gly Ser Leu Tyr Pro Glu Pro Thr Leu
            500                 505                 510
Val Pro Thr Pro Pro Pro Glu Leu Pro Thr Asp Cys Gly Gly Pro Phe
        515                 520                 525
Glu Leu Trp Glu Pro Asn Thr Thr Phe Ser Ser Thr Asn Phe Pro Asn
    530                 535                 540
Ser Tyr Pro Asn Leu Ala Phe Cys Val Trp Ile Leu Asn Ala Gln Lys
545                 550                 555                 560
Gly Lys Asn Ile Gln Leu His Phe Gln Glu Phe Asp Leu Glu Asn Ile
                565                 570                 575
Asn Asp Val Val Glu Ile Arg Asp Gly Glu Glu Ala Asp Ser Leu Leu
            580                 585                 590
Leu Ala Val Tyr Thr Gly Pro Gly Pro Val Lys Asp Val Phe Ser Thr
        595                 600                 605
Thr Asn Arg Met Thr Val Leu Leu Ile Thr Asn Asp Val Leu Ala Arg
    610                 615                 620
Gly Gly Phe Lys Ala Asn Phe Thr Thr Gly Tyr His Leu Gly Ile Pro
625                 630                 635                 640
Glu Pro Cys Lys Ala Asp His Phe Gln Cys Lys Asn Gly Glu Cys Val
                645                 650                 655
Pro Leu Val Asn Leu Cys Asp Gly His Leu His Cys Glu Asp Gly Ser
            660                 665                 670
Asp Glu Ala Asp Cys Val Arg Phe Phe Asn Gly Thr Thr Asn Asn Asn
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        675                 680                 685
Gly Leu Val Arg Phe Arg Ile Gln Ser Ile Trp His Thr Ala Cys Ala
    690                 695                 700
Glu Asn Trp Thr Thr Gln Ile Ser Asn Asp Val Cys Gln Leu Leu Gly
705                 710                 715                 720
Leu Gly Ser Gly Asn Ser Ser Lys Pro Ile Phe Ser Thr Asp Gly Gly
                725                 730                 735
Pro Phe Val Lys Leu Asn Thr Ala Pro Asp Gly His Leu Ile Leu Thr
            740                 745                 750
Pro Ser Gln Gln Cys Leu Gln Asp Ser Leu Ile Arg Leu Gln Cys Asn
        755                 760                 765
His Lys Ser Cys Gly Lys Lys Leu Ala Ala Gln Asp Ile Thr Pro Lys
    770                 775                 780
Ile Val Gly Gly Ser Asn Ala Lys Glu Gly Ala Trp Pro Trp Val Val
785                 790                 795                 800
Gly Leu Tyr Tyr Gly Gly Arg Leu Leu Cys Gly Ala Ser Leu Val Ser
                805                 810                 815
Ser Asp Trp Leu Val Ser Ala Ala His Cys Val Tyr Gly Arg Asn Leu
            820                 825                 830
Glu Pro Ser Lys Trp Thr Ala Ile Leu Gly Leu His Met Lys Ser Asn
        835                 840                 845
Leu Thr Ser Pro Gln Thr Val Pro Arg Leu Ile Asp Glu Ile Val Ile
    850                 855                 860
Asn Pro His Tyr Asn Arg Arg Arg Lys Asp Asn Asp Ile Ala Met Met
865                 870                 875                 880
His Leu Glu Phe Lys Val Asn Tyr Thr Asp Tyr Ile Gln Pro Ile Cys
                885                 890                 895
Leu Pro Glu Glu Asn Gln Val Phe Pro Pro Gly Arg Asn Cys Ser Ile
            900                 905                 910
Ala Gly Trp Gly Thr Val Val Tyr Gln Gly Thr Thr Ala Asn Ile Leu
        915                 920                 925
Gln Glu Ala Asp Val Pro Leu Leu Ser Asn Glu Arg Cys Gln Gln Gln
    930                 935                 940
Met Pro Glu Tyr Asn Ile Thr Glu Asn Met Ile Cys Ala Gly Tyr Glu
945                 950                 955                 960
Glu Gly Gly Ile Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Met
                965                 970                 975
Cys Gln Glu Asn Asn Arg Trp Phe Leu Ala Gly Val Thr Ser Phe Gly
            980                 985                 990
Tyr Lys Cys Ala Leu Pro Asn Arg Pro Gly Val Tyr Ala Arg Val Ser
        995                 1000                1005
Arg Phe Thr Glu Trp Ile Gln Ser Phe Leu His
    1010                1015
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<210> 134
<211> 917
<212> DNA
<213> Homo sapiens

<220>
<223> chymotrypsin C

<400> 134
cagccagtcc tgagcaccta accatgttgg gcatcactgt cctcgctgcg ctcttggcct 60
gtgcctccag ctgtggggtg cccagcttcc cgcccaacct atccgcccga gtggtgggag 120
gagaggatgc ccggccccac agctggccct ggcagatctc cctccagtac ctcaagaacg 180

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acacgtggag gcatacgtgt ggcgggactt tgattgctag caacttcgtc ctcactgccg 240
cccactgcat cagcaacacc cggacctacc gtgtggccgt gggaaagaac aacctggagg 300
tggaagacga agaaggatcc ctgtttgtgg gtgtggacac catccacgtc cacaagagat 360
ggaatgccct cctgttgcgc aatgatattg ccctcatcaa gcttgcagag catgtggagc 420
tgagtgacac catccaggtg gcctgcctgc cagagaagga ctccctgctc cccaaggact 480
acccctgcta tgtcaccggc tggggccgcc tctggaccaa cggccccatt gctgataagc 540
tgcagcaggg cctgcagccc gtggtggatc acgccacgtg ctccaggatt gactggtggg 600
gcttcagggt gaagaaaacc atggtgtgcg ctgggggcga tggcgtcatc tcagcctgca 660
atggggactc cggtggccca ctgaactgcc agttggagaa cggttcctgg gaggtgtttg 720
gcatcgtcag ctttggctcc cggcggggct gcaacacccg caagaagccg gtagtctaca 780
cccgggtgtc cgcctacatc gactggatca acgagaaaat gcagctgtga tttgttgctg 840
ggagcggcgg cagcgagtcc ctgcaacagc aataaacttc cttctcctcg ggccacctga 900
aaaaaaaaaa aaaaaaa                                                 917

<210> 135
<211> 268
<212> PRT
<213> Homo sapiens

<220>
<223> chymotrypsin C

<400> 135
Met Leu Gly Ile Thr Val Leu Ala Ala Leu Leu Ala Cys Ala Ser Ser
 1               5                  10                  15
Cys Gly Val Pro Ser Phe Pro Pro Asn Leu Ser Ala Arg Val Val Gly
            20                  25                  30
Gly Glu Asp Ala Arg Pro His Ser Trp Pro Trp Gln Ile Ser Leu Gln
        35                  40                  45
Tyr Leu Lys Asn Asp Thr Trp Arg His Thr Cys Gly Gly Thr Leu Ile
    50                  55                  60
Ala Ser Asn Phe Val Leu Thr Ala Ala His Cys Ile Ser Asn Thr Arg
65                  70                  75                  80
Thr Tyr Arg Val Ala Val Gly Lys Asn Asn Leu Glu Val Glu Asp Glu
                85                  90                  95
Glu Gly Ser Leu Phe Val Gly Val Asp Thr Ile His Val His Lys Arg
            100                 105                 110
Trp Asn Ala Leu Leu Leu Arg Asn Asp Ile Ala Leu Ile Lys Leu Ala
        115                 120                 125
Glu His Val Glu Leu Ser Asp Thr Ile Gln Val Ala Cys Leu Pro Glu
    130                 135                 140
Lys Asp Ser Leu Leu Pro Lys Asp Tyr Pro Cys Tyr Val Thr Gly Trp
145                 150                 155                 160
Gly Arg Leu Trp Thr Asn Gly Pro Ile Ala Asp Lys Leu Gln Gln Gly
                165                 170                 175
Leu Gln Pro Val Val Asp His Ala Thr Cys Ser Arg Ile Asp Trp Trp
            180                 185                 190
Gly Phe Arg Val Lys Lys Thr Met Val Cys Ala Gly Gly Asp Gly Val
        195                 200                 205
Ile Ser Ala Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln Leu
    210                 215                 220
Glu Asn Gly Ser Trp Glu Val Phe Gly Ile Val Ser Phe Gly Ser Arg
225                 230                 235                 240
Arg Gly Cys Asn Thr Arg Lys Lys Pro Val Val Tyr Thr Arg Val Ser
                245                 250                 255
Ala Tyr Ile Asp Trp Ile Asn Glu Lys Met Gln Leu
            260                 265
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<210> 136
<211> 1938
<212> DNA
<213> Homo sapoens

<220>
<223> Prostasin

<400> 136
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cgtccacact gctcgcttcg gatactccag gcgtctcccg ttgcggccgc tccctgcctt 180
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agcaccacaa ggaagcctat gaggtcaagc tgggggccca ccagctagac tcctactccg 660
aggacgccaa ggtcagcacc ctgaaggaca tcatccccca ccccagctac ctccaggagg 720
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ttactgcctg tagcaatggc cagagcctct ggcccctcac ccaccatgga ccagcccatt 1620
ggccgagctc ctggggagct cctgggaccc ttggctatga aaatgagccc tggctcccac 1680
ctgtttctgg aagactgctc ccggcccgcc tgcccagact gatgagcaca tctctctgcc 1740
ctctccctgt gttctgggct ggggccacct ttgtgcagct tcgaggacag gaaaggcccc 1800
aatcttgccc actggccgct gagcgccccc gagccctgac tcctggactc cggaggactg 1860
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attaaaatgt ttgagcac 1938

<210> 137
<211> 343
<212> PRT
<213> Homo sapiens

<220>
<223> Prostasin

<400> 137
Met Ala Gln Lys Gly Val Leu Gly Pro Gly Gln Leu Gly Ala Val Ala
 1   5   10   15
Ile Leu Leu Tyr Leu Gly Leu Leu Arg Ser Gly Thr Gly Ala Glu Gly

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            20                  25                  30
Ala Glu Ala Pro Cys Gly Val Ala Pro Gln Ala Arg Ile Thr Gly Gly
        35                  40                  45
Ser Ser Ala Val Ala Gly Gln Trp Pro Trp Gln Val Ser Ile Thr Tyr
    50                  55                  60
Glu Gly Val His Val Cys Gly Gly Ser Leu Val Ser Glu Gln Trp Val
65                  70                  75                  80
Leu Ser Ala Ala His Cys Phe Pro Ser Glu His His Lys Glu Ala Tyr
                85                  90                  95
Glu Val Lys Leu Gly Ala His Gln Leu Asp Ser Tyr Ser Glu Asp Ala
            100                 105                 110
Lys Val Ser Thr Leu Lys Asp Ile Ile Pro His Pro Ser Tyr Leu Gln
        115                 120                 125
Glu Gly Ser Gln Gly Asp Ile Ala Leu Leu Gln Leu Ser Arg Pro Ile
    130                 135                 140
Thr Phe Ser Arg Tyr Ile Arg Pro Ile Cys Leu Pro Ala Ala Asn Ala
145                 150                 155                 160
Ser Phe Pro Asn Gly Leu His Cys Thr Val Thr Gly Trp Gly His Val
                165                 170                 175
Ala Pro Ser Val Ser Leu Leu Thr Pro Lys Pro Leu Gln Gln Leu Glu
            180                 185                 190
Val Pro Leu Ile Ser Arg Glu Thr Cys Asn Cys Leu Tyr Asn Ile Asp
        195                 200                 205
Ala Lys Pro Glu Glu Pro His Phe Val Gln Glu Asp Met Val Cys Ala
    210                 215                 220
Gly Tyr Val Glu Gly Gly Lys Asp Ala Cys Gln Gly Asp Ser Gly Gly
225                 230                 235                 240
Pro Leu Ser Cys Pro Val Glu Gly Leu Trp Tyr Leu Thr Gly Ile Val

                245                 250                 255
Ser Trp Gly Asp Ala Cys Gly Ala Arg Asn Arg Pro Gly Val Tyr Thr
            260                 265                 270
Leu Ala Ser Ser Tyr Ala Ser Trp Ile Gln Ser Lys Val Thr Glu Leu
        275                 280                 285
Gln Pro Arg Val Val Pro Gln Thr Gln Glu Ser Gln Pro Asp Ser Asn
    290                 295                 300
Leu Cys Gly Ser His Leu Ala Phe Ser Ser Ala Pro Ala Gln Gly Leu
305                 310                 315                 320
Leu Arg Pro Ile Leu Phe Leu Pro Leu Gly Leu Ala Leu Gly Leu Leu
                325                 330                 335
Ser Pro Trp Leu Ser Glu His
            340
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<210> 138
<211> 874
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 1

<400> 138
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ggctgggagt gtgagcagca ttcccagccc tggcaggcgg ctctgtacca tttcagcact 180
ttccagtgtg ggggcatcct ggtgcaccgc cagtgggtgc tcacagctgc tcattgcatc 240

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cagtttgttc atgtcagtga gagcttccca caccctggct tcaacatgag cctcctggag 360
aaccacaccc gccaagcaga cgaggactac agccacgacc tcatgctgct ccgcctgaca 420
gagcctgctg ataccatcac agatgctgtg aaggtcgtgg agttgcccac cgaggaaccc 480
gaagtgggga gcacctgttt ggcttccggc tggggcagca tcgaaccaga gaatttctca 540
tttccagatg atctccagtg tgtggacctc aaaatcctgc ctaatgatga gtgcaaaaaa 600
gcccacgtcc agaaggtgac agacttcatg ctgtgtgtcg gacacctgga aggtggcaaa 660
gacacctgtg tgggtgattc aggggggccg ctgatgtgtg atggtgtgct ccaaggtgtc 720
acatcatggg gctacgtccc ttgtggcacc cccaataagc cttctgtcgc cgtcagagtg 780
ctgtcttatg tgaagtggat cgaggacacc atagcggaga actcctgaac gcccagccct 840
gtcccctacc cccagtaaaa tcaaatgtgc atcc                              874
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<210> 139
<211> 262
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 1

<400> 139

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Ala Ala Pro Pro Ile Gln Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20                  25                  30
Gln His Ser Gln Pro Trp Gln Ala Ala Leu Tyr His Phe Ser Thr Phe
        35                  40                  45
Gln Cys Gly Gly Ile Leu Val His Arg Gln Trp Val Leu Thr Ala Ala
    50                  55                  60
His Cys Ile Ser Asp Asn Tyr Gln Leu Trp Leu Gly Arg His Asn Leu
65                  70                  75                  80
Phe Asp Asp Glu Asn Thr Ala Gln Phe Val His Val Ser Glu Ser Phe
                85                  90                  95
Pro His Pro Gly Phe Asn Met Ser Leu Leu Glu Asn His Thr Arg Gln
            100                 105                 110
Ala Asp Glu Asp Tyr Ser His Asp Leu Met Leu Leu Arg Leu Thr Glu
        115                 120                 125
Pro Ala Asp Thr Ile Thr Asp Ala Val Lys Val Val Glu Leu Pro Thr
    130                 135                 140
Glu Glu Pro Glu Val Gly Ser Thr Cys Leu Ala Ser Gly Trp Gly Ser
145                 150                 155                 160
Ile Glu Pro Glu Asn Phe Ser Phe Pro Asp Asp Leu Gln Cys Val Asp
                165                 170                 175
Leu Lys Ile Leu Pro Asn Asp Glu Cys Lys Lys Ala His Val Gln Lys
            180                 185                 190
Val Thr Asp Phe Met Leu Cys Val Gly His Leu Glu Gly Gly Lys Asp
        195                 200                 205
Thr Cys Val Gly Asp Ser Gly Gly Pro Leu Met Cys Asp Gly Val Leu
    210                 215                 220
Gln Gly Val Thr Ser Trp Gly Tyr Val Pro Cys Gly Thr Pro Asn Lys
225                 230                 235                 240
Pro Ser Val Ala Val Arg Val Leu Ser Tyr Val Lys Trp Ile Glu Asp
                245                 250                 255
Thr Ile Ala Glu Asn Ser
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<210> 140
<211> 2855
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK2 transcript variant 1

<400> 140
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gaggctggga gtgtgagaag cattcccaac cctggcaggt ggctgtgtac agtcatggat 180
gggcacactg tgggggtgtc ctggtgcacc cccagtgggt gctcacagct gcccattgcc 240
taaagaagaa tagccaggtc tggctgggtc ggcacaacct gtttgagcct gaagacacag 300
gccagagggt ccctgtcagc cacagcttcc cacacccgct ctacaatatg agccttctga 360
agcatcaaag ccttagacca gatgaagact ccagccatga cctcatgctg ctccgcctgt 420
cagagcctgc caagatcaca gatgttgtga aggtcctggg cctgcccacc caggagccag 480
cactggggac cacctgctac gcctcaggct ggggcagcat cgaaccagag gagttcttgc 540
gccccaggag tcttcagtgt gtgagcctcc atctcctgtc caatgacatg tgtgctagag 600
cttactctga gaaggtgaca gagttcatgt tgtgtgctgg gctctggaca ggtggtaaag 660
acacttgtgg gggtgattct gggggtccac ttgtctgtaa tggtgtgctt caaggtatca 720
catcatgggg ccctgagcca tgtgccctgc ctgaaaagcc tgctgtgtac accaaggtgg 780
tgcattaccg gaagtggatc aaggacacca tcgcagccaa cccctgagtg cccctgtccc 840
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cctagataag gccgtgagca gaaagaaggg gaggatcctc ctatgttgtt gaaggaggga 1380
ctaggggggag aaactgaaag ctgattaatt acaggaggtt tgttcaggtc ccccaaacca 1440
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caaagaagaa tccagaaata ggggcacatt gaggaatgat actgagccca aagagcattc 2340
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acccagctga tagaggaagt agccaggtgg gagcctttcc cagtgggtgt gggacatatc 2760
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tgttttcaga ccttaaaaaa aaaaaaaaaa aaaaa 2855

<210> 141
<211> 261
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK2 isoform 1

<400> 141
Met Trp Asp Leu Val Leu Ser Ile Ala Leu Ser Val Gly Cys Thr Gly
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Ala Val Pro Leu Ile Gln Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20   25   30
Lys His Ser Gln Pro Trp Gln Val Ala Val Tyr Ser His Gly Trp Ala
        35   40   45
His Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50   55   60
His Cys Leu Lys Lys Asn Ser Gln Val Trp Leu Gly Arg His Asn Leu
65   70   75   80
Phe Glu Pro Glu Asp Thr Gly Gln Arg Val Pro Val Ser His Ser Phe
                85   90   95
Pro His Pro Leu Tyr Asn Met Ser Leu Leu Lys His Gln Ser Leu Arg
            100   105   110
Pro Asp Glu Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
        115   120   125
Pro Ala Lys Ile Thr Asp Val Val Lys Val Leu Gly Leu Pro Thr Gln
    130   135   140
Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
145   150   155   160
Glu Pro Glu Glu Phe Leu Arg Pro Arg Ser Leu Gln Cys Val Ser Leu
                165   170   175
His Leu Leu Ser Asn Asp Met Cys Ala Arg Ala Tyr Ser Glu Lys Val
            180   185   190
Thr Glu Phe Met Leu Cys Ala Gly Leu Trp Thr Gly Gly Lys Asp Thr
        195   200   205
Cys Gly Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln
    210   215   220
Gly Ile Thr Ser Trp Gly Pro Glu Pro Cys Ala Leu Pro Glu Lys Pro
225   230   235   240
Ala Val Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr
                245   250   255
Ile Ala Ala Asn Pro
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<210> 142
<211> 2892
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK2 transcript variant 2

<400> 142
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gaggctggga gtgtgagaag cattcccaac cctggcaggt ggctgtgtac agtcatggat 180
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taaagaagaa tagccaggtc tggctgggtc ggcacaacct gtttgagcct gaagacacag 300
gccagagggt ccctgtcagc cacagcttcc cacacccgct ctacaatatg agccttctga 360
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cagagcctgc caagatcaca gatgttgtga aggtcctggg cctgcccacc caggagccag 480
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gccccaggag tcttcagtgt gtgagcctcc atctcctgtc caatgacatg tgtgctagag 600
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ggtccacttg tctgtaatgg tgtgcttcaa ggtatcacat catggggccc tgagccatgt 780
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aaaaaaaaaa aa 2892

<210> 143
<211> 223
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK2 isoform 2

<400> 143

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            20                  25                  30
Lys His Ser Gln Pro Trp Gln Val Ala Val Tyr Ser His Gly Trp Ala
        35                  40                  45
His Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50                  55                  60
His Cys Leu Lys Lys Asn Ser Gln Val Trp Leu Gly Arg His Asn Leu
65                  70                  75                  80
Phe Glu Pro Glu Asp Thr Gly Gln Arg Val Pro Val Ser His Ser Phe
                85                  90                  95
Pro His Pro Leu Tyr Asn Met Ser Leu Leu Lys His Gln Ser Leu Arg
            100                 105                 110
Pro Asp Glu Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
        115                 120                 125
Pro Ala Lys Ile Thr Asp Val Val Lys Val Leu Gly Leu Pro Thr Gln
    130                 135                 140
Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
145                 150                 155                 160
Glu Pro Glu Glu Phe Leu Arg Pro Arg Ser Leu Gln Cys Val Ser Leu
                165                 170                 175
His Leu Leu Ser Asn Asp Met Cys Ala Arg Ala Tyr Ser Glu Lys Val
            180                 185                 190
Thr Glu Phe Met Leu Cys Ala Gly Leu Trp Thr Gly Gly Lys Asp Thr
        195                 200                 205
Cys Gly Val Ser His Pro Tyr Ser Gln His Leu Glu Gly Lys Gly
    210                 215                 220
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<210> 144
<211> 2879
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK2 transcript variant 3

<400> 144
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caccctggaa gagtggacag tgacacaagg tggacactct ctacagatca ctgaggataa 1260
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tgatactgag cccaaagagc attcaatcat tgttttattt gccttctttt cacaccattg 2400
gtgagggagg gattaccacc ctggggttat gaagatggtt gaacacccca cacatagcac 2460
cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga gcaggaggac 2520
gctgcacacc atgcaggatg acatgggggа tgcgctcggg attggtgtga agaagcaagg 2580
actgttagag gcaggcttta tagtaacaag acggtggggc aaactctgat ttccgtgggg 2640
gaatgtcatg gtcttgcttt actaagtttt gagactggca ggtagtgaaa ctcattaggc 2700
tgagaacctt gtggaatgca gctgacccag ctgatagagg aagtagccag gtgggagcct 2760
ttcccagtgg gtgtgggaca tatctggcaa gattttgtgg cactcctggt tacagatact 2820
ggggcagcaa ataaaactga atcttgtttt cagaccttaa aaaaaaaaaa aaaaaaaaa  2879
```

<210> 145
<211> 164
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK2 isoform 3

<400> 145

```
Met Trp Asp Leu Val Leu Ser Ile Ala Leu Ser Val Gly Cys Thr Gly
 1               5                  10                  15
Ala Val Pro Leu Ile Gln Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20                  25                  30
Lys His Ser Gln Pro Trp Gln Val Ala Val Tyr Ser His Gly Trp Ala
        35                  40                  45
His Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50                  55                  60
His Cys Leu Lys Lys Asn Ser Gln Val Trp Leu Gly Arg His Asn Leu
65                  70                  75                  80
Phe Glu Pro Glu Asp Thr Gly Gln Arg Val Pro Val Ser His Ser Phe
                85                  90                  95
Pro His Pro Leu Tyr Asn Met Ser Leu Leu Lys His Gln Ser Leu Arg
            100                 105                 110
Pro Asp Glu Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
        115                 120                 125
```

```
Pro Ala Lys Ile Thr Asp Val Val Lys Val Leu Gly Leu Pro Thr Gln
    130                 135                 140
Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
145                 150                 155                 160
Glu Pro Glu Glu
```

<210> 146
<211> 1464
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 3 transcript variant 1

<400> 146
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agccccaagc ttaccacctg cacccggaga gctgtgtcac catgtgggtc ccggttgtct 60
tcctcaccct gtccgtgacg tggattggtg ctgcacccct catcctgtct cggattgtgg 120
gaggctggga gtgcgagaag cattcccaac cctggcaggt gcttgtggcc tctcgtggca 180
gggcagtctg cggcggtgtt ctggtgcacc cccagtgggt cctcacagct gcccactgca 240
tcaggaacaa aagcgtgatc ttgctgggtc ggcacagcct gtttcatcct gaagacacag 300
gccaggtatt tcaggtcagc cacagcttcc cacacccgct ctacgatatg agcctcctga 360
agaatcgatt cctcaggcca ggtgatgact ccagccacga cctcatgctg ctccgcctgt 420
cagagcctgc cgagctcacg gatgctgtga aggtcatgga cctgcccacc caggagccag 480
cactggggac cacctgctac gcctcaggct ggggcagcat tgaaccagag gagttcttga 540
ccccaaagaa acttcagtgt gtggacctcc atgttatttc caatgacgtg tgtgcgcaag 600
ttcaccctca gaaggtgacc aagttcatgc tgtgtgctgg acgctggaca gggggcaaaa 660
gcacctgctc gggtgattct gggggcccac ttgtctgtaa tggtgtgctt caaggtatca 720
cgtcatgggg cagtgaacca tgtgccctgc ccgaaaggcc ttccctgtac accaaggtgg 780
tgcattaccg gaagtggatc aaggacacca tcgtggccaa cccctgagca cccctatcaa 840
ccccctattg tagtaaactt ggaaccttgg aaatgaccag gccaagactc aagcctcccc 900
agttctactg acctttgtcc ttaggtgtga ggtccagggt tgctaggaaa agaaatcagc 960
agacacaggt gtagaccaga gtgtttctta aatggtgtaa ttttgtcctc tctgtgtcct 1020
ggggaatact ggccatgcct ggagacatat cactcaattt ctctgaggac acagatagga 1080
tggggtgtct gtgttatttg tggggtacag agatgaaaga ggggtgggat ccacactgag 1140
agagtggaga gtgacatgtg ctggacactg tccatgaagc actgagcaga agctggaggc 1200
acaacgcacc agacactcac agcaaggatg gagctgaaaa cataacccac tctgtcctgg 1260
aggcactggg aagcctagag aaggctgtga gccaaggagg gagggtcttc ctttggcatg 1320
ggatggggat gaagtaagga gagggactgg acccccctgga agctgattca ctatgggggg 1380
aggtgtattg aagtcctcca gacaaccctc agatttgatg atttcctagt agaactcaca 1440
gaaataaaga gctgttatac tgtg                                        1464
```

<210> 147
<211> 261
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 3 isoform 1

<400> 147
```
Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
 1               5                  10                  15
Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20                  25                  30
Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
```

```
        35                  40                  45
Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50                  55                  60
His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
65                  70                  75                  80
Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
                85                  90                  95
Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
            100                 105                 110
Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
        115                 120                 125
Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
    130                 135                 140
Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
145                 150                 155                 160
Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
                165                 170                 175
His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
            180                 185                 190
Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
        195                 200                 205
Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln
    210                 215                 220
Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro
225                 230                 235                 240
Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr
                245                 250                 255
Ile Val Ala Asn Pro
            260
```

<210> 148
<211> 1906
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 3 transcript variant 3

<400> 148
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agccccaagc ttaccacctg cacccggaga gctgtgtcac catgtgggtc ccggttgtct 60
tcctcaccct gtccgtgacg tggattggtg ctgcaccccc catcctgtct cggattgtgg 120
gaggctggga gtgcgagaag cattcccaac cctggcaggt gcttgtggcc tctcgtggca 180
gggcagtctg cggcggtgtt ctggtgcacc cccagtgggt cctcacagct gcccactgca 240
tcaggaacaa aagcgtgatc ttgctgggtc ggcacagcct gtttcatcct gaagacacag 300
gccaggtatt tcaggtcagc cacagcttcc cacacccgct ctacgatatg agcctcctga 360
agaatcgatt cctcaggcca ggtgatgact ccagccacga cctcatgctg ctccgcctgt 420
cagagcctgc cgagctcacg gatgctgtga aggtcatgga cctgcccacc caggagccag 480
cactggggac cacctgctac gcctcaggct ggggcagcat tgaaccagag gagttcttga 540
ccccaaagaa acttcagtgt gtggacctcc atgttatttc caatgacgtg tgtgcgcaag 600
ttcaccctca gaaggtgacc aagttcatgc tgtgtgctgg acgctggaca gggggcaaaa 660
gcacctgctc gtgggtcatt ctgatcaccg aactgaccat gccagccctg ccgatggtcc 720
tccatggctc cctagtgccc tggagaggag gtgtctagtc agagagtagt cctggaaggt 780
ggcctctgtg aggagccacg gggacagcat cctgcagatg gtcctggccc ttgtcccacc 840
gacctgtcta caaggactgt cctcgtggac cctcccctct gcacaggagc tggaccctga 900
agtcccttcc ccaccggcca ggactggagc ccctacccct ctgttggaat ccctgcccac 960
cttcttctgg aagtcggctc tggagacatt tctctcttct tccaaagctg ggaactgcta 1020
```

```
tctgttatct gcctgtccag gtctgaaaga taggattgcc caggcagaaa ctgggactga 1080
cctatctcac tctctccctg cttttaccct tagggtgatt ctgggggccc acttgtctgt 1140
aatggtgtgc ttcaaggtat cacgtcatgg ggcagtgaac catgtgccct gcccgaaagg 1200
ccttccctgt acaccaaggt ggtgcattac cggaagtgga tcaaggacac catcgtggcc 1260
aacccctgag cacccctatc aacccccctat tgtagtaaac ttggaacctt ggaaatgacc 1320
aggccaagac tcaagcctcc ccagttctac tgacctttgt ccttaggtgt gaggtccagg 1380
gttgctagga aaagaaatca gcagacacag gtgtagacca gagtgtttct taaatggtgt 1440
aattttgtcc tctctgtgtc ctggggaata ctggccatgc ctggagacat atcactcaat 1500
ttctctgagg acacagatag gatggggtgt ctgtgttatt tgtggggtac agagatgaaa 1560
gaggggtggg atccacactg agagagtgga gagtgacatg tgctggacac tgtccatgaa 1620
gcactgagca gaagctggag gcacaacgca ccagacactc acagcaagga tggagctgaa 1680
aacataaccc actctgtcct ggaggcactg ggaagcctag agaaggctgt gagccaagga 1740
gggagggtct tcctttggca tgggatgggg atgaagtaag gagagggact ggacccccctg 1800
gaagctgatt cactatgggg ggaggtgtat tgaagtcctc cagacaaccc tcagatttga 1860
tgatttccta gtagaactca cagaaataaa gagctgttat actgtg                 1906

<210> 149
<211> 238
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 3 isoform 3

<400> 149
Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
 1               5                  10                  15
Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20                  25                  30
Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
        35                  40                  45
Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50                  55                  60
His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
65                  70                  75                  80
Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
                85                  90                  95
Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
            100                 105                 110
Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu
        115                 120                 125
Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln
    130                 135                 140
Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile
145                 150                 155                 160
Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu
                165                 170                 175
His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val
            180                 185                 190
Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr
        195                 200                 205
Cys Ser Trp Val Ile Leu Ile Thr Glu Leu Thr Met Pro Ala Leu Pro
    210                 215                 220
Met Val Leu His Gly Ser Leu Val Pro Trp Arg Gly Gly Val
225                 230                 235
```

<210> 150
<211> 1335
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 3 transcript variant 4

<400> 150
agccccaagc ttaccacctg cacccggaga gctgtgtcac catgtgggtc ccggttgtct 60
tcctcaccct gtccgtgacg tggattggtg ctgcaccct catcctgtct cggattgtgg 120
gaggctggga gtgcgagaag cattcccaac cctggcaggt gcttgtggcc tctcgtggca 180
gggcagtctg cggcggtgtt ctggtgcacc cccagtgggt cctcacagct gcccactgca 240
tcaggaagcc aggtgatgac tccagccacg acctcatgct gctccgcctg tcagagcctg 300
ccgagctcac ggatgctgtg aaggtcatgg acctgcccac ccaggagcca gcactgggga 360
ccacctgcta cgcctcaggc tggggcagca ttgaaccaga ggagttcttg accccaaaga 420
aacttcagtg tgtggacctc catgttattt ccaatgacgt gtgtgcgcaa gttcaccctc 480
agaaggtgac caagttcatg ctgtgtgctg gacgctggac agggggcaaa agcacctgct 540
cgggtgattc tgggggccca cttgtctgta atggtgtgct tcaaggtatc acgtcatggg 600
gcagtgaacc atgtgccctg cccgaaaggc cttccctgta caccaaggtg gtgcattacc 660
ggaagtggat caaggacacc atcgtggcca acccctgagc acccctatca acccccctatt 720
gtagtaaact tggaaccttg gaaatgacca ggccaagact caagcctccc cagttctact 780
gacctttgtc cttaggtgtg aggtccaggg ttgctaggaa aagaaatcag cagacacagg 840
tgtagaccag agtgtttctt aaatggtgta attttgtcct ctctgtgtcc tggggaatac 900
tggccatgcc tggagacata tcactcaatt tctctgagga cacagatagg atggggtgtc 960
tgtgttattt gtggggtaca gagatgaaag aggggtggga tccacactga gagagtggag 1020
agtgacatgt gctggacact gtccatgaag cactgagcag aagctggagg cacaacgcac 1080
cagacactca cagcaaggat ggagctgaaa acataaccca ctctgtcctg gaggcactgg 1140
gaagcctaga gaaggctgtg agccaaggag ggagggtctt cctttggcat gggatgggga 1200
tgaagtaagg agagggactg gacccccctgg aagctgattc actatggggg gaggtgtatt 1260
gaagtcctcc agacaaccct cagatttgat gatttcctag tagaactcac agaaataaag 1320
agctgttata ctgtg 1335

<210> 151
<211> 218
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 3 isoform 4

<400> 151
Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
 1   5   10   15
Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20   25   30
Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
        35   40   45
Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50   55   60
His Cys Ile Arg Lys Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu
65   70   75   80
Leu Arg Leu Ser Glu Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met
                85   90   95
Asp Leu Pro Thr Gln Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser
            100   105   110
Gly Trp Gly Ser Ile Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu

```
        115                 120                 125
Gln Cys Val Asp Leu His Val Ile Ser Asn Asp Val Cys Ala Gln Val
    130                 135                 140
His Pro Gln Lys Val Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr
145                 150                 155                 160
Gly Gly Lys Ser Thr Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys
                165                 170                 175
Asn Gly Val Leu Gln Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala
            180                 185                 190
Leu Pro Glu Arg Pro Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys
        195                 200                 205
Trp Ile Lys Asp Thr Ile Val Ala Asn Pro
    210                 215
```

<210> 152
<211> 1341
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 3 transcript variant 5

<400> 152
agccccaagc ttaccacctg cacccggaga gctgtgtcac catgtgggtc ccggttgtct 60
tcctcaccct gtccgtgacg tggattggtg ctgcacccct catcctgtct cggattgtgg 120
gaggctggga gtgcgagaag cattcccaac cctggcaggt gcttgtggcc tctcgtggca 180
gggcagtctg cggcggtgtt ctggtgcacc cccagtgggt cctcacagct gcccactgca 240
tcaggaacaa aagcgtgatc ttgctgggtc ggcacagcct gtttcatcct gaagacacag 300
gccaggtatt tcaggtcagc cacagcttcc cacacccgct ctacgatatg agcctcctga 360
agaatcgatt cctcaggcca ggtgatgact ccagcattga accagaggag ttcttgaccc 420
caaagaaact tcagtgtgtg gacctccatg ttatttccaa tgacgtgtgt gcgcaagttc 480
accctcagaa ggtgaccaag ttcatgctgt gtgctggacg ctggacaggg ggcaaaagca 540
cctgctcggg tgattctggg ggcccacttg tctgtaatgg tgtgcttcaa ggtatcacgt 600
catggggcag tgaaccatgt gccctgcccg aaaggccttc cctgtacacc aaggtggtgc 660
attaccggaa gtggatcaag gacaccatcg tggccaaccc ctgagcaccc ctatcaaccc 720
cctattgtag taaacttgga accttggaaa tgaccaggcc aagactcaag cctccccagt 780
tctactgacc tttgtcctta ggtgtgaggt ccagggttgc taggaaaaga aatcagcaga 840
cacaggtgta gaccagagtg tttcttaaat ggtgtaattt tgtcctctct gtgtcctggg 900
gaatactggc catgcctgga gacatatcac tcaatttctc tgaggacaca gataggatgg 960
ggtgtctgtg ttatttgtgg ggtacagaga tgaaagaggg gtgggatcca cactgagaga 1020
gtggagagtg acatgtgctg gacactgtcc atgaagcact gagcagaagc tggaggcaca 1080
acgcaccaga cactcacagc aaggatggag ctgaaaacat aacccactct gtcctggagg 1140
cactgggaag cctagagaag gctgtgagcc aaggagggag ggtcttcctt tggcatggga 1200
tggggatgaa gtaaggagag ggactggacc ccctggaagc tgattcacta tgggggggagg 1260
tgtattgaag tcctccagac aaccctcaga tttgatgatt tcctagtaga actcacagaa 1320
ataaagagct gttatactgt g   1341

<210> 153
<211> 220
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 3 isoform 5

<400> 153

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Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
 1               5                  10                  15
Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20                  25                  30
Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
        35                  40                  45
Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50                  55                  60
His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu
65                  70                  75                  80
Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe
                85                  90                  95
Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg
            100                 105                 110
Pro Gly Asp Asp Ser Ser Ile Glu Pro Glu Glu Phe Leu Thr Pro Lys
        115                 120                 125
Lys Leu Gln Cys Val Asp Leu His Val Ile Ser Asn Asp Val Cys Ala
    130                 135                 140
Gln Val His Pro Gln Lys Val Thr Lys Phe Met Leu Cys Ala Gly Arg
145                 150                 155                 160
Trp Thr Gly Gly Lys Ser Thr Cys Ser Gly Asp Ser Gly Gly Pro Leu
                165                 170                 175
Val Cys Asn Gly Val Leu Gln Gly Ile Thr Ser Trp Gly Ser Glu Pro
            180                 185                 190
Cys Ala Leu Pro Glu Arg Pro Ser Leu Tyr Thr Lys Val Val His Tyr
        195                 200                 205
Arg Lys Trp Ile Lys Asp Thr Ile Val Ala Asn Pro
    210                 215                 220
```

<210> 154
<211> 555
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 3 transcript variant 6

<400> 154
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agccccaagc ttaccacctg cacccggaga gctgtgtcac catgtgggtc ccggttgtct 60
tcctcaccct gtccgtgacg tggattggtg ctgcaccccc catcctgtct cggattgtgg 120
gaggctggga gtgcgagaag cattcccaac cctggcaggt gcttgtggcc tctcgtggca 180
gggcagtctg cggcggtgtt ctggtgcacc cccagtgggt cctcacagct gcccactgca 240
tcaggaagtg agtaggggcc tggggtctgg ggagcaggtg tctgtgtccc agaggaataa 300
cagctgggca ttttccccag gataacctct aaggccagcc ttgggactgg gggagagagg 360
gaaagttctg gttcaggtca catggggagg cagggttggg gctggaccac cctccccatg 420
gctgcctggg tctccatctg tgttcctcta tgtctctttg tgtcgctttc attatgtctc 480
ttggtaactg gcttcggttg tgtctctccg tgtgactatt ttgttctctc tctccctctc 540
ttctctgtct tcagt                                                  555
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<210> 155
<211> 69
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 3 isoform 6

<400> 155
Met Trp Val Pro Val Val Phe Leu Thr Leu Ser Val Thr Trp Ile Gly
 1   5   10   15
Ala Ala Pro Leu Ile Leu Ser Arg Ile Val Gly Gly Trp Glu Cys Glu
            20   25   30
Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala
        35   40   45
Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala
    50   55   60
His Cys Ile Arg Lys
65

<210> 156
<211> 807
<212> DNA
<213> Homo sapiens

<220>
<223> Mesotrypsin

<400> 156
acactctacc accatgaatc cattcctgat ccttgccttt gtgggagctg ctgttgctgt 60
ccccttttgac gatgatgaca agattgttgg gggctacacc tgtgaggaga attctctccc 120
ctaccaggtg tccctgaatt ctggctccca cttctgcggt ggctccctca tcagcgaaca 180
gtgggtggta tcagcagctc actgctacaa gacccgcatc caggtgagac tgggagagca 240
caacatcaaa gtcctggagg ggaatgagca gttcatcaat gcggccaaga tcatccgcca 300
ccctaaatac aacagggaca ctctggacaa tgacatcatg ctgatcaaac tctcctcacc 360
tgccgtcatc aatgcccgcg tgtccaccat ctctctgccc accgcccctc cagctgctgg 420
cactgagtgc ctcatctccg gctggggcaa cactctgagc tttggtgctg actacccaga 480
cgagctgaag tgcctggatg ctccggtgct gacccaggct gagtgtaaag cctcctaccc 540
tggaaagatt accaacagca tgttctgtgt gggcttcctt gagggaggca aggattcctg 600
ccagcgtgac tctggtggcc ctgtggtctg caacggacag ctccaaggag ttgtctcctg 660
gggccatggc tgtgcctgga agaacaggcc tggagtctac accaaggtct acaactatgt 720
ggactggatt aaggacacca tcgctgccaa cagctaaagc ccccggtccc tctgcagtct 780
ctataccaat aaagtggccc tgctctc   807

<210> 157
<211> 247
<212> PRT
<213> Homo sapiens

<220>
<223> Mesotrypsin

<400> 157
Met Asn Pro Phe Leu Ile Leu Ala Phe Val Gly Ala Ala Val Ala Val
 1   5   10   15
Pro Phe Asp Asp Asp Asp Lys Ile Val Gly Gly Tyr Thr Cys Glu Glu
            20   25   30
Asn Ser Leu Pro Tyr Gln Val Ser Leu Asn Ser Gly Ser His Phe Cys
        35   40   45
Gly Gly Ser Leu Ile Ser Glu Gln Trp Val Val Ser Ala Ala His Cys
    50   55   60
Tyr Lys Thr Arg Ile Gln Val Arg Leu Gly Glu His Asn Ile Lys Val

```
65                  70                  75                  80
Leu Glu Gly Asn Glu Gln Phe Ile Asn Ala Ala Lys Ile Ile Arg His
                85                  90                  95
Pro Lys Tyr Asn Arg Asp Thr Leu Asp Asn Asp Ile Met Leu Ile Lys
            100                 105                 110
Leu Ser Ser Pro Ala Val Ile Asn Ala Arg Val Ser Thr Ile Ser Leu
        115                 120                 125
Pro Thr Ala Pro Pro Ala Ala Gly Thr Glu Cys Leu Ile Ser Gly Trp
    130                 135                 140
Gly Asn Thr Leu Ser Phe Gly Ala Asp Tyr Pro Asp Glu Leu Lys Cys
145                 150                 155                 160
Leu Asp Ala Pro Val Leu Thr Gln Ala Glu Cys Lys Ala Ser Tyr Pro
                165                 170                 175
Gly Lys Ile Thr Asn Ser Met Phe Cys Val Gly Phe Leu Glu Gly Gly
            180                 185                 190
Lys Asp Ser Cys Gln Arg Asp Ser Gly Gly Pro Val Val Cys Asn Gly
        195                 200                 205
Gln Leu Gln Gly Val Val Ser Trp Gly His Gly Cys Ala Trp Lys Asn
    210                 215                 220
Arg Pro Gly Val Tyr Thr Lys Val Tyr Asn Tyr Val Asp Trp Ile Lys
225                 230                 235                 240
Asp Thr Ile Ala Ala Asn Ser
                245
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<210> 158
<211> 1055
<212> DNA
<213> Homo sapiens

<220>
<223> pancreatic endopeptidase E form B (B)

<400> 158
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acctgcattt ccaccacctg ttctgggagt ggggcccagt cagccccctt tgcttacctt 60
ctgccctata ttagagcccc aggttctgtg ccctttttcct atcatcgcaa aactcatgat 120
gctccggctg ctcagttccc tcctccttgt ggccgttgcc tcaggctatg gcccaccttc 180
ctctcgccct tccagccgcg ttgtcaatgg tgaggatgcg gtcccctaca gctggccctg 240
gcaggtttcc ctgcagtatg agaaaagcgg aagcttctac cacacctgtg gcggtagcct 300
catcgccccc gactgggttg tgactgccgg ccactgcatc tcgagctccc ggacctacca 360
ggtggtgttg ggcgagtacg accgtgctgt gaaggagggc cccgagcagg tgatccccat 420
caactctggg gacctctttg tgcatccact ctggaaccgc tcgtgtgtgg cctgtggcaa 480
tgacatcgcc ctcatcaagc tctcacgcag cgcccagctg ggagacgccg tccagctcgc 540
ctcactccct ccggctggtg acatccttcc caacgagaca ccctgctaca tcaccggctg 600
gggccgtctc tataccaacg ggccactccc agacaagctg caggaggccc tgctgccggt 660
ggtggactat gaacactgct ccaggtggaa ctggtggggt tcctccgtga agaagaccat 720
ggtgtgtgct ggaggggaca tccgctccgg ctgcaatggt gactctggag gacccctcaa 780
ctgccccaca gaggatggtg gctggcaggt ccatggcgtg accagctttg tttctgcctt 840
tggctgcaac acccgcagga agcccacggt gttcactcga gtctccgcct tcattgactg 900
gattgaggag accatagcaa gccactagaa ccaaggccca gctggcagtg ctgatcgatc 960
ccacatcctg aataaagaat aaagatctct cagaaaattc caaaaaaaaa aaaaaaaaaa 1020
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa                           1055
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<210> 159
<211> 270
<212> PRT
<213> Homo sapiens

<220>
<223> pancreatic endopeptidase E form B (B)

<400> 159
Met Met Leu Arg Leu Leu Ser Ser Leu Leu Leu Val Ala Val Ala Ser
 1   5   10   15
Gly Tyr Gly Pro Pro Ser Ser Arg Pro Ser Ser Arg Val Val Asn Gly
            20   25   30
Glu Asp Ala Val Pro Tyr Ser Trp Pro Trp Gln Val Ser Leu Gln Tyr
        35   40   45
Glu Lys Ser Gly Ser Phe Tyr His Thr Cys Gly Gly Ser Leu Ile Ala
    50   55   60
Pro Asp Trp Val Val Thr Ala Gly His Cys Ile Ser Ser Ser Arg Thr
65   70   75   80
Tyr Gln Val Val Leu Gly Glu Tyr Asp Arg Ala Val Lys Glu Gly Pro
                85   90   95
Glu Gln Val Ile Pro Ile Asn Ser Gly Asp Leu Phe Val His Pro Leu
            100   105   110
Trp Asn Arg Ser Cys Val Ala Cys Gly Asn Asp Ile Ala Leu Ile Lys
        115   120   125
Leu Ser Arg Ser Ala Gln Leu Gly Asp Ala Val Gln Leu Ala Ser Leu
    130   135   140
Pro Pro Ala Gly Asp Ile Leu Pro Asn Glu Thr Pro Cys Tyr Ile Thr
145   150   155   160
Gly Trp Gly Arg Leu Tyr Thr Asn Gly Pro Leu Pro Asp Lys Leu Gln
                165   170   175
Glu Ala Leu Leu Pro Val Val Asp Tyr Glu His Cys Ser Arg Trp Asn
            180   185   190
Trp Trp Gly Ser Ser Val Lys Lys Thr Met Val Cys Ala Gly Gly Asp
        195   200   205
Ile Arg Ser Gly Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Pro
    210   215   220
Thr Glu Asp Gly Gly Trp Gln Val His Gly Val Thr Ser Phe Val Ser
225   230   235   240
Ala Phe Gly Cys Asn Thr Arg Arg Lys Pro Thr Val Phe Thr Arg Val
                245   250   255
Ser Ala Phe Ile Asp Trp Ile Glu Glu Thr Ile Ala Ser His
            260   265   270

<210> 160
<211> 941
<212> DNA
<213> Homo sapiens

<220>
<223> pancreatic elastase II form B (Homos sapiens) (IIB)

<400> 160
cttacagaac tcccacggac acaccatgat taggaccctg ctgctgtcca ctttggtggc 60
tggagccctc agttgtgggg tctccactta cgcgcctgat atgtctagga tgcttggagg 120
tgaagaagcg aggcccaaca gctggccctg gcaggtctcc ctgcagtaca gctccaatgg 180
ccagtggtac cacacctgcg gagggtccct gatagccaac agctgggtcc tgacggctgc 240
ccactgcatc agctcctccg ggatctaccg cgtgatgctg ggccagcata acctctacgt 300
tgcagagtcc ggctcgctgg ccgtcagtgt ctctaagatt gtggtgcaca aggactggaa 360
ctccgaccag gtctccaaag ggaacgacat tgccctgctc aaactggcta accccgtctc 420

cctcaccgac aagatccagc tggcctgcct ccctcctgcc ggcaccattc tacccaacaa 480
ctacccctgc tacgtcacgg gctggggaag gctgcagacc aacggggctc tccctgatga 540
cctgaagcag ggccggttgc tggttgtgga ctatgccacc tgctccagct ctggctggtg 600
gggcagcacc gtgaagacga atatgatctg tgctgggggt gatggcgtga tatgcacctg 660
caacggagac tccggtgggc cgctgaactg tcaggcatct gacggccggt gggaggtgca 720
tggcatcggc agcctcacgt cggtccttgg ttgcaactac tactacaagc cctccatctt 780
cacgcgggtc tccaactaca acgactggat caattcggtg attgcaaata actaaccaaa 840
agaagtccct gggactgttt cagacttgga aaggtcacag aaggaaaata atattatata 900
aagtgacaac tatgcaaatc acaaaaaaaa aaaaaaaaaa a 941

<210> 161
<211> 269
<212> PRT
<213> Homo sapiens

<220>
<223> pancreatic elastase II form B (Homos sapiens) (IIB)

<400> 161
Met Ile Arg Thr Leu Leu Leu Ser Thr Leu Val Ala Gly Ala Leu Ser
1 5 10 15
Cys Gly Val Ser Thr Tyr Ala Pro Asp Met Ser Arg Met Leu Gly Gly
20 25 30
Glu Glu Ala Arg Pro Asn Ser Trp Pro Trp Gln Val Ser Leu Gln Tyr
35 40 45
Ser Ser Asn Gly Gln Trp Tyr His Thr Cys Gly Gly Ser Leu Ile Ala
50 55 60
Asn Ser Trp Val Leu Thr Ala Ala His Cys Ile Ser Ser Ser Gly Ile
65 70 75 80
Tyr Arg Val Met Leu Gly Gln His Asn Leu Tyr Val Ala Glu Ser Gly
85 90 95
Ser Leu Ala Val Ser Val Ser Lys Ile Val Val His Lys Asp Trp Asn
100 105 110
Ser Asp Gln Val Ser Lys Gly Asn Asp Ile Ala Leu Leu Lys Leu Ala
115 120 125
Asn Pro Val Ser Leu Thr Asp Lys Ile Gln Leu Ala Cys Leu Pro Pro
130 135 140
Ala Gly Thr Ile Leu Pro Asn Asn Tyr Pro Cys Tyr Val Thr Gly Trp
145 150 155 160
Gly Arg Leu Gln Thr Asn Gly Ala Leu Pro Asp Asp Leu Lys Gln Gly
165 170 175
Arg Leu Leu Val Val Asp Tyr Ala Thr Cys Ser Ser Ser Gly Trp Trp
180 185 190
Gly Ser Thr Val Lys Thr Asn Met Ile Cys Ala Gly Gly Asp Gly Val
195 200 205
Ile Cys Thr Cys Asn Gly Asp Ser Gly Gly Pro Leu Asn Cys Gln Ala
210 215 220
Ser Asp Gly Arg Trp Glu Val His Gly Ile Gly Ser Leu Thr Ser Val
225 230 235 240
Leu Gly Cys Asn Tyr Tyr Tyr Lys Pro Ser Ile Phe Thr Arg Val Ser
245 250 255
Asn Tyr Asn Asp Trp Ile Asn Ser Val Ile Ala Asn Asn
260 265

<210> 162
<211> 2048

<212> DNA
<213> Homo sapiens

<220>
<223> coagulation factor XIIa

<400> 162
ctattgatct ggactcctgg ataggcagct ggaccaacgg acggacgcca tgagggctct 60
gctgctcctg gggttcctgc tggtgagctt ggagtcaaca ctttcgattc caccttggga 120
agcccccaag gagcataagt acaaagctga agagcacaca gtcgttctca ctgtcaccgg 180
ggagccctgc cacttccct tccagtacca ccggcagctg taccacaaat gtacccacaa 240
gggccggcca ggccctcagc cctggtgtgc taccaccccc aactttgatc aggaccagcg 300
atggggatac tgtttggagc ccaagaaagt gaaagaccac tgcagcaaac acagcccctg 360
ccagaaagga gggacctgtg tgaacatgcc aagcggcccc cactgtctct gtccacaaca 420
cctcactgga aaccactgcc agaaagagaa gtgctttgag cctcagcttc tccggttttt 480
ccacaagaat gagatatggt atagaactga gcaagcagct gtggccagat gccagtgcaa 540
gggtcctgat gcccactgcc agcggctggc cagccaggcc tgccgcacca acccgtgcct 600
ccatgggggt cgctgcctag aggtggaggg ccaccgcctg tgccactgcc cggtgggcta 660
caccggaccc ttctgcgacg tggacaccaa ggcaagctgc tatgatggcc gcgggctcag 720
ctaccgcggc ctggccagga ccacgctctc gggtgcgccc tgtcagccgt gggcctcgga 780
ggccacctac cggaacgtga ctgccgagca agcgcggaac tggggactgg gcggccacgc 840
cttctgccgg aacccggaca acgacatccg cccgtggtgc ttcgtgctga accgcgaccg 900
gctgagctgg gagtactgcg acctggcaca gtgccagacc ccaacccagg cggcgcctcc 960
gaccccggtg tcccctaggc ttcatgtccc actcatgccc gcgcagccgg caccgccgaa 1020
gcctcagccc acgacccgga ccccgcctca gtcccagacc ccgggagcct tgccggcgaa 1080
gcgggagcag ccgccttccc tgaccaggaa cggcccactg agctgcgggc agcggctccg 1140
caagagtctg tcttcgatga cccgcgtcgt tggcgggctg gtggcgctac gcggggcgca 1200
cccctacatc gccgcgctgt actggggcca cagtttctgc gccggcagcc tcatcgcccc 1260
ctgctgggtg ctgacggccg ctcactgcct gcaggaccgg cccgcacccg aggatctgac 1320
ggtggtgctc ggccaggaac gccgtaacca cagctgtgag ccgtgccaga cgttggccgt 1380
gcgctcctac cgcttgcacg aggccttctc gcccgtcagc taccagcacg acctggctct 1440
gttgcgcctt caggaggatg cggacggcag ctgcgcgctc ctgtcgcctt acgttcagcc 1500
ggtgtgcctg ccaagcggcg ccgcgcgacc ctccgagacc acgctctgcc aggtggccgg 1560
ctggggccac cagttcgagg gggcggagga atatgccagc ttcctgcagg aggcgcaggt 1620
accgttcctc tccctggagc gctgctcagc cccggacgtg cacggatcct ccatcctccc 1680
cggcatgctc tgcgcagggt tcctcgaggg cggcaccgat gcgtgccagg gtgattccgg 1740
aggcccgctg gtgtgtgagg accaagctgc agagcgccgg ctcaccctgc aaggcatcat 1800
cagctgggga tcgggctgtg gtgaccgcaa caagccaggc gtctacaccg atgtggccta 1860
ctacctggcc tggatccggg agcacaccgt ttcctgattg ctcagggact catctttccc 1920
tccttggtga ttccgcagtg agagagtggc tggggcatgg aaggcaagat tgtgtcccat 1980
tcccccagtg cggccagctc cgcgccagga tggcgaggaa ctcaataaag tgctttgaaa 2040
atgctgag 2048

<210> 163
<211> 615
<212> PRT
<213> Homo sapiens

<220>
<223> coagulation factor XIIa

<400> 163
Met Arg Ala Leu Leu Leu Leu Gly Phe Leu Leu Val Ser Leu Glu Ser
 1   5   10   15
Thr Leu Ser Ile Pro Pro Trp Glu Ala Pro Lys Glu His Lys Tyr Lys
            20   25   30

```
Ala Glu Glu His Thr Val Val Leu Thr Val Thr Gly Glu Pro Cys His
          35                  40                  45
Phe Pro Phe Gln Tyr His Arg Gln Leu Tyr His Lys Cys Thr His Lys
      50                  55                  60
Gly Arg Pro Gly Pro Gln Pro Trp Cys Ala Thr Thr Pro Asn Phe Asp
65                  70                  75                  80
Gln Asp Gln Arg Trp Gly Tyr Cys Leu Glu Pro Lys Lys Val Lys Asp
                85                  90                  95
His Cys Ser Lys His Ser Pro Cys Gln Lys Gly Gly Thr Cys Val Asn
            100                 105                 110
Met Pro Ser Gly Pro His Cys Leu Cys Pro Gln His Leu Thr Gly Asn
          115                 120                 125
His Cys Gln Lys Glu Lys Cys Phe Glu Pro Gln Leu Leu Arg Phe Phe
      130                 135                 140
His Lys Asn Glu Ile Trp Tyr Arg Thr Glu Gln Ala Ala Val Ala Arg
145                 150                 155                 160
Cys Gln Cys Lys Gly Pro Asp Ala His Cys Gln Arg Leu Ala Ser Gln
                165                 170                 175
Ala Cys Arg Thr Asn Pro Cys Leu His Gly Gly Arg Cys Leu Glu Val
            180                 185                 190
Glu Gly His Arg Leu Cys His Cys Pro Val Gly Tyr Thr Gly Pro Phe
          195                 200                 205
Cys Asp Val Asp Thr Lys Ala Ser Cys Tyr Asp Gly Arg Gly Leu Ser
      210                 215                 220
Tyr Arg Gly Leu Ala Arg Thr Thr Leu Ser Gly Ala Pro Cys Gln Pro
225                 230                 235                 240
Trp Ala Ser Glu Ala Thr Tyr Arg Asn Val Thr Ala Glu Gln Ala Arg
                245                 250                 255
Asn Trp Gly Leu Gly Gly His Ala Phe Cys Arg Asn Pro Asp Asn Asp
            260                 265                 270
Ile Arg Pro Trp Cys Phe Val Leu Asn Arg Asp Arg Leu Ser Trp Glu
          275                 280                 285
Tyr Cys Asp Leu Ala Gln Cys Gln Thr Pro Thr Gln Ala Ala Pro Pro
      290                 295                 300
Thr Pro Val Ser Pro Arg Leu His Val Pro Leu Met Pro Ala Gln Pro
305                 310                 315                 320
Ala Pro Pro Lys Pro Gln Pro Thr Thr Arg Thr Pro Pro Gln Ser Gln
                325                 330                 335
Thr Pro Gly Ala Leu Pro Ala Lys Arg Glu Gln Pro Pro Ser Leu Thr
            340                 345                 350
Arg Asn Gly Pro Leu Ser Cys Gly Gln Arg Leu Arg Lys Ser Leu Ser
          355                 360                 365
Ser Met Thr Arg Val Val Gly Gly Leu Val Ala Leu Arg Gly Ala His
      370                 375                 380
Pro Tyr Ile Ala Ala Leu Tyr Trp Gly His Ser Phe Cys Ala Gly Ser
385                 390                 395                 400
Leu Ile Ala Pro Cys Trp Val Leu Thr Ala Ala His Cys Leu Gln Asp
                405                 410                 415
Arg Pro Ala Pro Glu Asp Leu Thr Val Val Leu Gly Gln Glu Arg Arg
            420                 425                 430
Asn His Ser Cys Glu Pro Cys Gln Thr Leu Ala Val Arg Ser Tyr Arg
          435                 440                 445
Leu His Glu Ala Phe Ser Pro Val Ser Tyr Gln His Asp Leu Ala Leu
      450                 455                 460
Leu Arg Leu Gln Glu Asp Ala Asp Gly Ser Cys Ala Leu Leu Ser Pro
465                 470                 475                 480
Tyr Val Gln Pro Val Cys Leu Pro Ser Gly Ala Ala Arg Pro Ser Glu
```

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                485                 490                 495
Thr Thr Leu Cys Gln Val Ala Gly Trp Gly His Gln Phe Glu Gly Ala
            500                 505                 510
Glu Glu Tyr Ala Ser Phe Leu Gln Glu Ala Gln Val Pro Phe Leu Ser
        515                 520                 525
Leu Glu Arg Cys Ser Ala Pro Asp Val His Gly Ser Ser Ile Leu Pro
    530                 535                 540
Gly Met Leu Cys Ala Gly Phe Leu Glu Gly Gly Thr Asp Ala Cys Gln
545                 550                 555                 560
Gly Asp Ser Gly Gly Pro Leu Val Cys Glu Asp Gln Ala Ala Glu Arg
                565                 570                 575
Arg Leu Thr Leu Gln Gly Ile Ile Ser Trp Gly Ser Gly Cys Gly Asp
            580                 585                 590
Arg Asn Lys Pro Gly Val Tyr Thr Asp Val Ala Tyr Tyr Leu Ala Trp
        595                 600                 605
Ile Arg Glu His Thr Val Ser
    610                 615
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<210> 164
<211> 2245
<212> DNA
<213> Homo sapiens

<220>
<223> plasma kallikrein

<400> 164

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agaacagctt gaagaccgtt catttttaag tgacaagaga ctcacctcca agaagcaatt 60
gtgttttcag aatgatttta ttcaagcaag caacttattt catttccttg tttgctacag 120
tttcctgtgg atgtctgact caactctatg aaaacgcctt cttcagaggt ggggatgtag 180
cttccatgta caccccaaat gcccaatact gccagatgag gtgcacattc cacccaaggt 240
gtttgctatt cagttttctt ccagcaagtt caatcaatga catggagaaa aggtttggtt 300
gcttcttgaa agatagtgtt acaggaaccc tgccaaaagt acatcgaaca ggtgcagttt 360
ctggacattc cttgaagcaa tgtggtcatc aaataagtgc ttgccatcga gacatttata 420
aaggagttga tatgagagga gtcaatttta atgtgtctaa ggttagcagt gttgaagaat 480
gccaaaaaag gtgcaccaat aacattcgct gccagttttt ttcatatgcc acgcaaacat 540
ttcacaaggc agagtaccgg aacaattgcc tattaaagta cagtcccgga ggaacaccta 600
ccgctataaa ggtgctgagt aacgtggaat ctggattctc actgaagccc tgtgcccttt 660
cagaaattgg ttgccacatg aacatcttcc agcatcttgc gttctcagat gtggatgttg 720
ccagggttct cactccagat gcttttgtgt gtcggaccat ctgcacctat caccccaact 780
gcctcttctt tacattctat acaaatgtat ggaaaatcga gtcacaaaga aatgtttgtc 840
ttcttaaaac atctgaaagt ggcacaccaa gttcctctac tcctcaagaa aacaccatat 900
ctggatatag ccttttaacc tgcaaaagaa ctttacctga accctgccat tctaaaattt 960
acccgggagt tgactttgga ggagaagaat tgaatgtgac ttttgttaaa ggagtgaatg 1020
tttgccaaga gacttgcaca aagatgattc gctgtcagtt tttcacttat tctttactcc 1080
cagaagactg taaggaagag aagtgtaagt gtttcttaag attatctatg gatggttctc 1140
caactaggat tgcgtatggg acacaaggga gctctggtta ctctttgaga ttgtgtaaca 1200
ctggggacaa ctctgtctgc acaacaaaaa caagcacacg cattgttgga ggaacaaact 1260
cttcttgggg agagtggccc tggcaggtga gcctgcaggt gaagctgaca gctcagaggc 1320
acctgtgtgg agggtcactc ataggacacc agtgggtcct cactgctgcc cactgctttg 1380
atgggcttcc cctgcaggat gtttggcgca tctatagtgg cattttaaat ctgtcagaca 1440
ttacaaaaga tacacctttc tcacaaataa aagagattat tattcaccaa aactataaag 1500
tctcagaagg gaatcatgat atcgccttga taaaactcca ggctcctttg aattacactg 1560
aattccaaaa accaatatgc ctaccttcca aaggtgacac aagcacaatt tataccaact 1620
gttgggtaac cggatggggc ttctcgaagg agaaaggtga aatccaaaat attctacaaa 1680
aggtaaatat tcctttggta acaaatgaag aatgccagaa aagatatcaa gattataaaa 1740
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taacccaacg gatggtctgt gctggctata aagaaggggg aaaagatgct tgtaagggag 1800
attcaggtgg tcccttagtt tgcaaacaca acggaatgtg gcgtttggtg ggcatcacaa 1860
gctggggtga aggctgtgcc cgcagggagc aacctggtgt ctacaccaaa gtcgctgagt 1920
acatggactg gattttagag aaaacacaga gcagtgatgg aaaagctcag atgcagtcac 1980
cagcatgaga agcagtccag agtctaggca atttttacaa cctgagttca agtcaaattc 2040
tgagcctggg gggtcctcat ctgcaaagca tggagagtgg catcttcttt gcatcctaag 2100
gacgaaagac acagtgcact cagagctgct gaggacaatg tctgctgaag cccgctttca 2160
gcacgccgta accaggggct gacaatgcga ggtcgcaact gagatctcca tgactgtgtg 2220
ttgtgaaata aaatggtgaa agatc                                       2245
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<210> 165
<211> 638
<212> PRT
<213> Homo sapiens

<220>
<223> plasma kallikrein

<400> 165

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Met Ile Leu Phe Lys Gln Ala Thr Tyr Phe Ile Ser Leu Phe Ala Thr
 1               5                  10                  15
Val Ser Cys Gly Cys Leu Thr Gln Leu Tyr Glu Asn Ala Phe Phe Arg
            20                  25                  30
Gly Gly Asp Val Ala Ser Met Tyr Thr Pro Asn Ala Gln Tyr Cys Gln
        35                  40                  45
Met Arg Cys Thr Phe His Pro Arg Cys Leu Leu Phe Ser Phe Leu Pro
    50                  55                  60
Ala Ser Ser Ile Asn Asp Met Glu Lys Arg Phe Gly Cys Phe Leu Lys
65                  70                  75                  80
Asp Ser Val Thr Gly Thr Leu Pro Lys Val His Arg Thr Gly Ala Val
                85                  90                  95
Ser Gly His Ser Leu Lys Gln Cys Gly His Gln Ile Ser Ala Cys His
            100                 105                 110
Arg Asp Ile Tyr Lys Gly Val Asp Met Arg Gly Val Asn Phe Asn Val
        115                 120                 125
Ser Lys Val Ser Ser Val Glu Glu Cys Gln Lys Arg Cys Thr Asn Asn
    130                 135                 140
Ile Arg Cys Gln Phe Phe Ser Tyr Ala Thr Gln Thr Phe His Lys Ala
145                 150                 155                 160
Glu Tyr Arg Asn Asn Cys Leu Leu Lys Tyr Ser Pro Gly Gly Thr Pro
                165                 170                 175
Thr Ala Ile Lys Val Leu Ser Asn Val Glu Ser Gly Phe Ser Leu Lys
            180                 185                 190
Pro Cys Ala Leu Ser Glu Ile Gly Cys His Met Asn Ile Phe Gln His
        195                 200                 205
Leu Ala Phe Ser Asp Val Asp Val Ala Arg Val Leu Thr Pro Asp Ala
    210                 215                 220
Phe Val Cys Arg Thr Ile Cys Thr Tyr His Pro Asn Cys Leu Phe Phe
225                 230                 235                 240
Thr Phe Tyr Thr Asn Val Trp Lys Ile Glu Ser Gln Arg Asn Val Cys
                245                 250                 255
Leu Leu Lys Thr Ser Glu Ser Gly Thr Pro Ser Ser Ser Thr Pro Gln
            260                 265                 270
Glu Asn Thr Ile Ser Gly Tyr Ser Leu Leu Thr Cys Lys Arg Thr Leu
        275                 280                 285
Pro Glu Pro Cys His Ser Lys Ile Tyr Pro Gly Val Asp Phe Gly Gly
    290                 295                 300
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Glu Glu Leu Asn Val Thr Phe Val Lys Gly Val Asn Val Cys Gln Glu
305                 310                 315                 320
Thr Cys Thr Lys Met Ile Arg Cys Gln Phe Phe Thr Tyr Ser Leu Leu
                325                 330                 335
Pro Glu Asp Cys Lys Glu Glu Lys Cys Lys Cys Phe Leu Arg Leu Ser
            340                 345                 350
Met Asp Gly Ser Pro Thr Arg Ile Ala Tyr Gly Thr Gln Gly Ser Ser
        355                 360                 365
Gly Tyr Ser Leu Arg Leu Cys Asn Thr Gly Asp Asn Ser Val Cys Thr
    370                 375                 380
Thr Lys Thr Ser Thr Arg Ile Val Gly Gly Thr Asn Ser Ser Trp Gly
385                 390                 395                 400
Glu Trp Pro Trp Gln Val Ser Leu Gln Val Lys Leu Thr Ala Gln Arg
                405                 410                 415
His Leu Cys Gly Gly Ser Leu Ile Gly His Gln Trp Val Leu Thr Ala
            420                 425                 430
Ala His Cys Phe Asp Gly Leu Pro Leu Gln Asp Val Trp Arg Ile Tyr
        435                 440                 445
Ser Gly Ile Leu Asn Leu Ser Asp Ile Thr Lys Asp Thr Pro Phe Ser
    450                 455                 460
Gln Ile Lys Glu Ile Ile Ile His Gln Asn Tyr Lys Val Ser Glu Gly
465                 470                 475                 480
Asn His Asp Ile Ala Leu Ile Lys Leu Gln Ala Pro Leu Asn Tyr Thr
                485                 490                 495
Glu Phe Gln Lys Pro Ile Cys Leu Pro Ser Lys Gly Asp Thr Ser Thr
            500                 505                 510
Ile Tyr Thr Asn Cys Trp Val Thr Gly Trp Gly Phe Ser Lys Glu Lys
        515                 520                 525
Gly Glu Ile Gln Asn Ile Leu Gln Lys Val Asn Ile Pro Leu Val Thr
    530                 535                 540
Asn Glu Glu Cys Gln Lys Arg Tyr Gln Asp Tyr Lys Ile Thr Gln Arg
545                 550                 555                 560
Met Val Cys Ala Gly Tyr Lys Glu Gly Gly Lys Asp Ala Cys Lys Gly
                565                 570                 575
Asp Ser Gly Gly Pro Leu Val Cys Lys His Asn Gly Met Trp Arg Leu
            580                 585                 590
Val Gly Ile Thr Ser Trp Gly Glu Gly Cys Ala Arg Arg Glu Gln Pro
        595                 600                 605
Gly Val Tyr Thr Lys Val Ala Glu Tyr Met Asp Trp Ile Leu Glu Lys
    610                 615                 620
Thr Gln Ser Ser Asp Gly Lys Ala Gln Met Gln Ser Pro Ala
625                 630                 635
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<210> 166
<211> 2217
<212> DNA
<213> Homo sapiens

<220>
<223> coagulation factor XIa transcript variant 1

<400> 166
tgctgtactg agagagaatg ttacataaca ttgagaacta gtacaagtaa atattaaagt 60
gaagtgacca tttcctacac aagctcattc agaggaggat gaagaccatt ttggaggaag 120
aaaagcaccc ttattaagaa ttgcagcaag taagccaaca aggtcttttc aggatgattt 180
tcttatatca agtggtacat ttcattttat ttacttcagt ttctggtgaa tgtgtgactc 240

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agttgttgaa ggacacctgc tttgaaggag gggacattac tacggtcttc acaccaagcg 300
ccaagtactg ccaggtagtc tgcacttacc acccaagatg tttactcttc actttcacgg 360
cggaatcacc atctgaggat cccacccgat ggtttacttg tgtcctgaaa gacagtgtta 420
cagaaacact gccaagagtg aataggacag cagcgatttc tgggtattct ttcaagcaat 480
gctcacacca aataagcgct tgcaacaaag acatttatgt ggacctagac atgaagggca 540
taaactataa cagctcagtt gccaagagtg ctcaagaatg ccaagaaaga tgcacggatg 600
acgtccactg ccacttttтc acgtacgcca caaggcagtt tcccagcctg gagcatcgta 660
acatttgtct actgaagcac acccaaacag ggacaccaac cagaataacg aagctcgata 720
aagtggtgtc tggattttca ctgaaatcct gtgcactttc taatctggct tgtattaggg 780
acattttccc taatacggtg tttgcagaca gcaacatcga cagtgtcatg gctcccgatg 840
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gagaagaact ggatattgtt gctgcaaaaa gtcacgaggc ctgccagaaa ctgtgcacca 1140
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agggcaagtg ttacttaaag ctttcttcaa acggatctcc aactaaaata cttcacggga 1260
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tgaccctgca cacaacctca cccactcaga gacacctgtg tggaggctcc atcattggaa 1440
accagtggat attaacagcc gctcactgtt tctatggggt agagtcacct aagattttgc 1500
gtgtctacag tggcatttta aatcaatctg aaataaaaga ggacacatct ttctttgggg 1560
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aagagtgcca gaagagatac agaggacata aaataaccca taagatgatc tgtgccggct 1860
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agcggccagg tgtttacacc aacgtggtcg agtacgtgga ctggattctg gagaaaactc 2040
aagcagtgtg aatgggttcc caggggccat tggagtccct gaaggaccca ggatttgctg 2100
ggagagggtg ttgagttcac tgtgccagca tgcttcctcc acagtaacac gctgaagggg 2160
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<210> 167
<211> 625
<212> PRT
<213> Homo sapiens

<220>
<223> coagulation factor XIa isoform 1

<400> 167

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Met Ile Phe Leu Tyr Gln Val Val His Phe Ile Leu Phe Thr Ser Val
 1               5                  10                  15
Ser Gly Glu Cys Val Thr Gln Leu Leu Lys Asp Thr Cys Phe Glu Gly
            20                  25                  30
Gly Asp Ile Thr Thr Val Phe Thr Pro Ser Ala Lys Tyr Cys Gln Val
        35                  40                  45
Val Cys Thr Tyr His Pro Arg Cys Leu Leu Phe Thr Phe Thr Ala Glu
    50                  55                  60
Ser Pro Ser Glu Asp Pro Thr Arg Trp Phe Thr Cys Val Leu Lys Asp
65                  70                  75                  80
Ser Val Thr Glu Thr Leu Pro Arg Val Asn Arg Thr Ala Ala Ile Ser
                85                  90                  95
Gly Tyr Ser Phe Lys Gln Cys Ser His Gln Ile Ser Ala Cys Asn Lys
            100                 105                 110
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Asp Ile Tyr Val Asp Leu Asp Met Lys Gly Ile Asn Tyr Asn Ser Ser
        115                 120                 125
Val Ala Lys Ser Ala Gln Glu Cys Gln Glu Arg Cys Thr Asp Asp Val
    130                 135                 140
His Cys His Phe Phe Thr Tyr Ala Thr Arg Gln Phe Pro Ser Leu Glu
145                 150                 155                 160
His Arg Asn Ile Cys Leu Leu Lys His Thr Gln Thr Gly Thr Pro Thr
                165                 170                 175
Arg Ile Thr Lys Leu Asp Lys Val Val Ser Gly Phe Ser Leu Lys Ser
            180                 185                 190
Cys Ala Leu Ser Asn Leu Ala Cys Ile Arg Asp Ile Phe Pro Asn Thr
        195                 200                 205
Val Phe Ala Asp Ser Asn Ile Asp Ser Val Met Ala Pro Asp Ala Phe
    210                 215                 220
Val Cys Gly Arg Ile Cys Thr His His Pro Gly Cys Leu Phe Phe Thr
225                 230                 235                 240
Phe Phe Ser Gln Glu Trp Pro Lys Glu Ser Gln Arg Asn Leu Cys Leu
                245                 250                 255
Leu Lys Thr Ser Glu Ser Gly Leu Pro Ser Thr Arg Ile Lys Lys Ser
            260                 265                 270
Lys Ala Leu Ser Gly Phe Ser Leu Gln Ser Cys Arg His Ser Ile Pro
        275                 280                 285
Val Phe Cys His Ser Ser Phe Tyr His Asp Thr Asp Phe Leu Gly Glu
    290                 295                 300
Glu Leu Asp Ile Val Ala Ala Lys Ser His Glu Ala Cys Gln Lys Leu
305                 310                 315                 320
Cys Thr Asn Ala Val Arg Cys Gln Phe Phe Thr Tyr Thr Pro Ala Gln
                325                 330                 335
Ala Ser Cys Asn Glu Gly Lys Gly Lys Cys Tyr Leu Lys Leu Ser Ser
            340                 345                 350
Asn Gly Ser Pro Thr Lys Ile Leu His Gly Arg Gly Gly Ile Ser Gly
        355                 360                 365
Tyr Thr Leu Arg Leu Cys Lys Met Asp Asn Glu Cys Thr Thr Lys Ile
    370                 375                 380
Lys Pro Arg Ile Val Gly Gly Thr Ala Ser Val Arg Gly Glu Trp Pro
385                 390                 395                 400
Trp Gln Val Thr Leu His Thr Thr Ser Pro Thr Gln Arg His Leu Cys
                405                 410                 415
Gly Gly Ser Ile Ile Gly Asn Gln Trp Ile Leu Thr Ala Ala His Cys
            420                 425                 430
Phe Tyr Gly Val Glu Ser Pro Lys Ile Leu Arg Val Tyr Ser Gly Ile
        435                 440                 445
Leu Asn Gln Ser Glu Ile Lys Glu Asp Thr Ser Phe Phe Gly Val Gln
    450                 455                 460
Glu Ile Ile Ile His Asp Gln Tyr Lys Met Ala Glu Ser Gly Tyr Asp
465                 470                 475                 480
Ile Ala Leu Leu Lys Leu Glu Thr Thr Val Asn Tyr Thr Asp Ser Gln
                485                 490                 495
Arg Pro Ile Cys Leu Pro Ser Lys Gly Asp Arg Asn Val Ile Tyr Thr
            500                 505                 510
Asp Cys Trp Val Thr Gly Trp Gly Tyr Arg Lys Leu Arg Asp Lys Ile
        515                 520                 525
Gln Asn Thr Leu Gln Lys Ala Lys Ile Pro Leu Val Thr Asn Glu Glu
    530                 535                 540
Cys Gln Lys Arg Tyr Arg Gly His Lys Ile Thr His Lys Met Ile Cys
545                 550                 555                 560
Ala Gly Tyr Arg Glu Gly Gly Lys Asp Ala Cys Lys Gly Asp Ser Gly
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                565                 570                 575
Gly Pro Leu Ser Cys Lys His Asn Glu Val Trp His Leu Val Gly Ile
            580                 585                 590
Thr Ser Trp Gly Glu Gly Cys Ala Gln Arg Glu Arg Pro Gly Val Tyr
        595                 600                 605
Thr Asn Val Val Glu Tyr Val Asp Trp Ile Leu Glu Lys Thr Gln Ala
    610                 615                 620
Val
625
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<210> 168
<211> 2055
<212> DNA
<213> Homo sapiens

<220>
<223> coagulation factor XIa transcript variant 2

<400> 168

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aaaagcaccc ttattaagaa ttgcagcaag taagccaaca aggtcttttc aggatgattt 180
tcttatatca agtggtacat ttcattttat ttacttcagt ttctggtgaa tgtgtgactc 240
agttgttgaa ggacacctgc tttgaaggag gggacattac tacggtcttc acaccaagcg 300
ccaagtactg ccaggtagtc tgcacttacc acccaagatg tttactcttc actttcacgg 360
cggaatcacc atctgaggat cccacccgat ggtttacttg tgtcctgaaa gacagtgtta 420
cagaaacact gccaagagtg aataggacag cagcgatttc tgggtattct ttcaagcaat 480
gctcacacca aataagtaac atttgtctac tgaagcacac ccaaacaggg acaccaacca 540
gaataacgaa gctcgataaa gtggtgtctg gattttcact gaaatcctgt gcactttcta 600
atctggcttg tattagggac attttcccta atacggtgtt tgcagacagc aacatcgaca 660
gtgtcatggc tcccgatgct tttgtctgtg gccgaatctg cactcatcat cccggttgct 720
tgtttttac cttcttttcc caggaatggc ccaaagaatc tcaaagaaat ctttgtctcc 780
ttaaaacatc tgagagtgga ttgcccagta cacgcattaa aaagagcaaa gctctttctg 840
gtttcagtct acaaagctgc aggcacagca tcccagtgtt ctgccattct tcattttacc 900
atgacactga tttcttggga gaagaactgg atattgttgc tgcaaaaagt cacgaggcct 960
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ctaaaatact tcacgggaga ggaggcatct ctggatacac attaaggttg tgtaaaatgg 1140
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gtgagtggcc gtggcaggtg accctgcaca caacctcacc cactcagaga cacctgtgtg 1260
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acacatcttt ctttggggtt caagaaataa taatccatga tcagtataaa atggcagaaa 1440
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gacccatatg cctgccttcc aaaggagata gaaatgtaat atacactgat tgctgggtga 1560
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tacccttagt gaccaacgaa gagtgccaga agagatacag aggacataaa ataacccata 1680
agatgatctg tgccggctac agggaaggag ggaaggacgc ttgcaaggga gattcgggag 1740
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aaggctgtgc tcaaagggag cggccaggtg tttacaccaa cgtggtcgag tacgtggact 1860
ggattctgga gaaaactcaa gcagtgtgaa tgggttccca ggggccattg gagtccctga 1920
aggacccagg atttgctggg agagggtgtt gagttcactg tgccagcatg cttcctccac 1980
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caagttgtta tgtcc                                                  2055
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<210> 169

<211> 571
<212> PRT
<213> Homo sapiens

<220>
<223> coagulation factor XIa isoform 2

<400> 169
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            20   25   30
Gly Asp Ile Thr Thr Val Phe Thr Pro Ser Ala Lys Tyr Cys Gln Val
        35   40   45
Val Cys Thr Tyr His Pro Arg Cys Leu Leu Phe Thr Phe Thr Ala Glu
    50   55   60
Ser Pro Ser Glu Asp Pro Thr Arg Trp Phe Thr Cys Val Leu Lys Asp
65   70   75   80
Ser Val Thr Glu Thr Leu Pro Arg Val Asn Arg Thr Ala Ala Ile Ser
                85   90   95
Gly Tyr Ser Phe Lys Gln Cys Ser His Gln Ile Ser Asn Ile Cys Leu
            100   105   110
Leu Lys His Thr Gln Thr Gly Thr Pro Thr Arg Ile Thr Lys Leu Asp
        115   120   125
Lys Val Val Ser Gly Phe Ser Leu Lys Ser Cys Ala Leu Ser Asn Leu
    130   135   140
Ala Cys Ile Arg Asp Ile Phe Pro Asn Thr Val Phe Ala Asp Ser Asn
145   150   155   160
Ile Asp Ser Val Met Ala Pro Asp Ala Phe Val Cys Gly Arg Ile Cys
                165   170   175
Thr His His Pro Gly Cys Leu Phe Phe Thr Phe Phe Ser Gln Glu Trp
            180   185   190
Pro Lys Glu Ser Gln Arg Asn Leu Cys Leu Leu Lys Thr Ser Glu Ser
        195   200   205
Gly Leu Pro Ser Thr Arg Ile Lys Lys Ser Lys Ala Leu Ser Gly Phe
    210   215   220
Ser Leu Gln Ser Cys Arg His Ser Ile Pro Val Phe Cys His Ser Ser
225   230   235   240
Phe Tyr His Asp Thr Asp Phe Leu Gly Glu Glu Leu Asp Ile Val Ala
                245   250   255
Ala Lys Ser His Glu Ala Cys Gln Lys Leu Cys Thr Asn Ala Val Arg
            260   265   270
Cys Gln Phe Phe Thr Tyr Thr Pro Ala Gln Ala Ser Cys Asn Glu Gly
        275   280   285
Lys Gly Lys Cys Tyr Leu Lys Leu Ser Ser Asn Gly Ser Pro Thr Lys
    290   295   300
Ile Leu His Gly Arg Gly Gly Ile Ser Gly Tyr Thr Leu Arg Leu Cys
305   310   315   320
Lys Met Asp Asn Glu Cys Thr Thr Lys Ile Lys Pro Arg Ile Val Gly
                325   330   335
Gly Thr Ala Ser Val Arg Gly Glu Trp Pro Trp Gln Val Thr Leu His
            340   345   350
Thr Thr Ser Pro Thr Gln Arg His Leu Cys Gly Gly Ser Ile Ile Gly
        355   360   365
Asn Gln Trp Ile Leu Thr Ala Ala His Cys Phe Tyr Gly Val Glu Ser
    370   375   380
Pro Lys Ile Leu Arg Val Tyr Ser Gly Ile Leu Asn Gln Ser Glu Ile

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385                 390                 395                 400
Lys Glu Asp Thr Ser Phe Phe Gly Val Gln Glu Ile Ile Ile His Asp
                405                 410                 415
Gln Tyr Lys Met Ala Glu Ser Gly Tyr Asp Ile Ala Leu Leu Lys Leu
            420                 425                 430
Glu Thr Thr Val Asn Tyr Thr Asp Ser Gln Arg Pro Ile Cys Leu Pro
        435                 440                 445
Ser Lys Gly Asp Arg Asn Val Ile Tyr Thr Asp Cys Trp Val Thr Gly
    450                 455                 460
Trp Gly Tyr Arg Lys Leu Arg Asp Lys Ile Gln Asn Thr Leu Gln Lys
465                 470                 475                 480
Ala Lys Ile Pro Leu Val Thr Asn Glu Glu Cys Gln Lys Arg Tyr Arg
                485                 490                 495
Gly His Lys Ile Thr His Lys Met Ile Cys Ala Gly Tyr Arg Glu Gly
            500                 505                 510
Gly Lys Asp Ala Cys Lys Gly Asp Ser Gly Gly Pro Leu Ser Cys Lys
        515                 520                 525
His Asn Glu Val Trp His Leu Val Gly Ile Thr Ser Trp Gly Glu Gly
    530                 535                 540
Cys Ala Gln Arg Glu Arg Pro Gly Val Tyr Thr Asn Val Val Glu Tyr
545                 550                 555                 560
Val Asp Trp Ile Leu Glu Lys Thr Gln Ala Val
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<210> 170
<211> 2804
<212> DNA
<213> Homo sapiens

<220>
<223> coagulation factor IXa

<400> 170

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ttcttgatca tgaaaacgcc aacaaaattc tgaatcggcc aaagaggtat aattcaggta 180
aattggaaga gtttgttcaa gggaaccttg agagagaatg tatggaagaa aagtgtagtt 240
ttgaagaagc acgagaagtt tttgaaaaca ctgaaagaac aactgaattt tggaagcagt 300
atgttgatgg agatcagtgt gagtccaatc catgtttaaa tggcggcagt tgcaaggatg 360
acattaattc ctatgaatgt tggtgtccct ttggatttga aggaaagaac tgtgaattag 420
atgtaacatg taacattaag aatggcagat gcgagcagtt ttgtaaaaat agtgctgata 480
acaaggtggt ttgctcctgt actgagggat atcgacttgc agaaaaccag aagtcctgtg 540
aaccagcagt gccatttcca tgtggaagag tttctgtttc acaaacttct aagctcaccc 600
gtgctgagac tgtttttcct gatgtggact atgtaaattc tactgaagct gaaaccattt 660
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agatttgaat atatacattc tatgatcatt gctttttctc tttacagggg agaatttcat 1560
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tgaagaaaga acacaggagt agctgagagg ctaaaactca tcaaaaacac tactcctttt 1920
cctctaccct attcctcaat cttttacctt ttccaaatcc caatccccaa atcagttttt 1980
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attttgatta tagttaatcc ttctatcttg aatcttctag agagttgctg accaactgac 2760
gtatgtttcc ctttgtgaat taataaactg gtgttctggt tcat                  2804
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<210> 171
<211> 461
<212> PRT
<213> Homo sapiens

<220>
<223> coagulation factor IXa

<400> 171

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
 1               5                  10                  15
Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu

            20                  25                  30
Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45
Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60
Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80
Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95
Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110
Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125
Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140
Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160
Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175
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Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr Arg Ala
            180                 185                 190
Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205
Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220
Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240
Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255
Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270
Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285
His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300
Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320
Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335
Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350
Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365
Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Arg
    370                 375                 380
Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400
Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415
Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430
Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
        435                 440                 445
Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
    450                 455                 460
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<210> 172
<211> 2478
<212> DNA
<213> Homo sapiens

<220>
<223> coagulation factor VIIa transcript variant 1

<400> 172
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cagctccagt cctatatctg cttctgcctc cctgccttcg agggccggaa ctgtgagacg 480
cacaaggatg accagctgat ctgtgtgaac gagaacggcg gctgtgagca gtactgcagt 540
gaccacacgg gcaccaagcg ctcctgtcgg tgccacgagg ggtactctct gctggcagac 600
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atcgagtggc tgcaaaagct catgcgctca gagccacgcc caggagtcct cctgcgagcc 1440
ccatttccct agcccagcag ccctggcctg tggagagaaa gccaaggctg cgtcgaactg 1500
tcctggcacc aaatcccata tattcttctg cagttaatgg ggtagaggag ggcatgggag 1560
ggagggagag gtggggaggg agacagagac agaaacagag agagacagag acagagagag 1620
actgagggag agactctgag gacatggaga gagactcaaa gagactccaa gattcaaaga 1680
gactaataga gacacagaga tggaatagaa aagatgagag gcagaggcag acaggcgctg 1740
gacagagggg caggggagtg ccaaggttgt cctggaggca gacagcccag ctgagcctcc 1800
ttacctccct tcagccaagc cccacctgca cgtgatctgc tggccctcag gctgctgctc 1860
tgccttcatt gctggagaca gtagaggcat gaacacacat ggatgcacac acacacacgc 1920
caatgcacac acacagagat atgcacacac acggatgcac acacagatgg tcacacagag 1980
atacgcaaac acaccgatgc acacgcacat agagatatgc acacacagat gcacacacag 2040
atatacacat ggatgcacgc acatgccaat gcacgcacac atcagtgcac acggatgcac 2100
agagatatgc acacaccgat gtgcgcacac acagatatgc acacacatgg atgagcacac 2160
acacaccaag tgcgcacaca caccgatgta cacacacaga tgcacacaca gatgcacaca 2220
caccgatgct gactccatgt gtgctgtcct ctgaaggcgg ttgtttagct ctcacttttc 2280
tggttcttat ccattatcat cttcacttca gacaattcag aagcatcacc atgcatggtg 2340
gcgaatgccc ccaaactctc ccccaaatgt atttctccct tcgctgggtg ccgggctgca 2400
cagactattc cccacctgct tcccagcttc acaataaacg gctgcgtctc ctccgcacac 2460
ctgtggtgcc tgccaccc                                              2478

<210> 173
<211> 466
<212> PRT
<213> Homo sapiens

<220>
<223> coagulation factor VIIa isoform 1

<400> 173
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
 1               5                  10                  15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
            20                  25                  30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
        35                  40                  45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
    50                  55                  60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65                  70                  75                  80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
                85                  90                  95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
            100                 105                 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
```

```
        115                 120                 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
    130                 135                 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145                 150                 155                 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
                165                 170                 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
            180                 185                 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
        195                 200                 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
    210                 215                 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225                 230                 235                 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
                245                 250                 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
            260                 265                 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
        275                 280                 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
    290                 295                 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305                 310                 315                 320
Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
                325                 330                 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
            340                 345                 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
        355                 360                 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
    370                 375                 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385                 390                 395                 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
                405                 410                 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
            420                 425                 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
        435                 440                 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
    450                 455                 460
Phe Pro
465
```

<210> 174
<211> 2412
<212> DNA
<213> Homo sapiens

<220>
<223> coagulation factor VIIa transcript variant 2

<400> 174
agtcccatgg ggaatgtcaa caggcagggg cagcactgca gagatttcat catggtctcc 60

```
caggccctca ggctcctctg ccttctgctt gggcttcagg gctgcctggc tgcagtcttc 120
gtaacccagg aggaagccca cggcgtcctg caccggcgcc ggcgcgccaa cgcgttcctg 180
gaggagctgc ggccgggctc cctggagagg gagtgcaagg aggagcagtg ctccttcgag 240
gaggcccggg agatcttcaa ggacgcggag aggacgaagc tgttctggat ttcttacagt 300
gatggggacc agtgtgcctc aagtccatgc cagaatgggg gctcctgcaa ggaccagctc 360
cagtcctata tctgcttctg cctccctgcc ttcgagggcc ggaactgtga gacgcacaag 420
gatgaccagc tgatctgtgt gaacgagaac ggcggctgtg agcagtactg cagtgaccac 480
acgggcacca agcgctcctg tcggtgccac gaggggtact ctctgctggc agacggggtg 540
tcctgcacac ccacagttga atatccatgt ggaaaaatac ctattctaga aaaaagaaat 600
gccagcaaac cccaaggccg aattgtgggg ggcaaggtgt gccccaaagg ggagtgtcca 660
tggcaggtcc tgttgttggt gaatggagct cagttgtgtg gggggaccct gatcaacacc 720
atctgggtgg tctccgcggc ccactgtttc gacaaaatca agaactggag gaacctgatc 780
gcggtgctgg gcgagcacga cctcagcgag cacgacgggg atgagcagag ccggcgggtg 840
gcgcaggtca tcatccccag cacgtacgtc ccgggcacca ccaaccacga catcgcgctg 900
ctccgcctgc accagcccgt ggtcctcact gaccatgtgg tgcccctctg cctgcccgaa 960
cggacgttct ctgagaggac gctggccttc gtgcgcttct cattggtcag cggctggggc 1020
cagctgctgg accgtggcgc cacggccctg gagctcatgg tgctcaacgt gccccggctg 1080
atgacccagg actgcctgca gcagtcacgg aaggtgggag actccccaaa tatcacggag 1140
tacatgttct gtgccggcta ctcggatggc agcaaggact cctgcaaggg ggacagtgga 1200
ggcccacatg ccacccacta ccggggcacg tggtacctga cgggcatcgt cagctggggc 1260
cagggctgcg caaccgtggg ccactttggg gtgtacacca gggtctccca gtacatcgag 1320
tggctgcaaa agctcatgcg ctcagagcca cgcccaggag tcctcctgcg agccccattt 1380
ccctagccca gcagccctgg cctgtggaga gaaagccaag gctgcgtcga actgtcctgg 1440
caccaaatcc catatattct tctgcagtta atggggtaga ggagggcatg ggagggaggg 1500
agaggtgggg agggagacag agacagaaac agagagagac agagacagag agagactgag 1560
ggagagactc tgaggacatg gagagagact caaagagact ccaagattca aagagactaa 1620
tagagacaca gagatggaat agaaaagatg agaggcagag gcagacaggc gctggacaga 1680
ggggcagggg agtgccaagg ttgtcctgga ggcagacagc ccagctgagc ctccttacct 1740
cccttcagcc aagccccacc tgcacgtgat ctgctggccc tcaggctgct gctctgcctt 1800
cattgctgga gacagtagag gcatgaacac acatggatgc acacacacac acgccaatgc 1860
acacacacag agatatgcac acacacggat gcacacacag atggtcacac agagatacgc 1920
aaacacaccg atgcacacgc acatagagat atgcacacac agatgcacac acagatatac 1980
acatggatgc acgcacatgc caatgcacgc acacatcagt gcacacggat gcacagagat 2040
atgcacacac cgatgtgcgc acacacagat atgcacacac atggatgagc acacacacac 2100
caagtgcgca cacacaccga tgtacacaca cagatgcaca cacagatgca cacacaccga 2160
tgctgactcc atgtgtgctg tcctctgaag gcggttgttt agctctcact tttctggttc 2220
ttatccatta tcatcttcac ttcagacaat tcagaagcat caccatgcat ggtggcgaat 2280
gcccccaaac tctcccccaa atgtatttct cccttcgctg ggtgccgggc tgcacagact 2340
attccccacc tgcttcccag cttcacaata aacggctgcg tctcctccgc acacctgtgg 2400
tgcctgccac cc                                                    2412
```

<210> 175
<211> 444
<212> PRT
<213> Homo sapiens

<220>
<223> coagulation factor VIIa isoform 2

<400> 175

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Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
 1               5                  10                  15
Gly Cys Leu Ala Ala Val Phe Val Thr Gln Glu Glu Ala His Gly Val
            20                  25                  30
Leu His Arg Arg Arg Arg Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro
        35                  40                  45
Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu
```

```
    50                  55                  60
Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile
65                  70                  75                  80
Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly
                85                  90                  95
Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro
            100                 105                 110
Ala Phe Glu Gly Arg Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile
        115                 120                 125
Cys Val Asn Glu Asn Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr
    130                 135                 140
Gly Thr Lys Arg Ser Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala
145                 150                 155                 160
Asp Gly Val Ser Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile
                165                 170                 175
Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val
            180                 185                 190
Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu
        195                 200                 205
Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile
    210                 215                 220
Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg
225                 230                 235                 240
Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly
                245                 250                 255
Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr
            260                 265                 270
Val Pro Gly Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln
        275                 280                 285
Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg
    290                 295                 300
Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser
305                 310                 315                 320
Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met
                325                 330                 335
Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser
            340                 345                 350
Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala
        355                 360                 365
Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly
    370                 375                 380
Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val
385                 390                 395                 400
Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr
                405                 410                 415
Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu
            420                 425                 430
Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
        435                 440
```

<210> 176
<211> 1502
<212> DNA
<213> Homo sapiens

<220>

<223> coagulation factor Xa

<400> 176
cagggacaca gtactcggcc acaccatggg gcgcccactg cacctcgtcc tgctcagtgc 60
ctccctggct ggcctcctgc tgctcgggga aagtctgttc atccgcaggg agcaggccaa 120
caacatcctg gcgagggtca cgagggccaa ttcctttctt gaagagatga agaaaggaca 180
cctcgaaaga gagtgcatgg aagagacctg ctcatacgaa gaggcccgcg aggtctttga 240
ggacagcgac aagacgaatg aattctggaa taaatacaaa gatggcgacc agtgtgagac 300
cagtccttgc cagaaccagg gcaaatgtaa agacggcctc ggggaataca cctgcacctg 360
tttagaagga ttcgaaggca aaaactgtga attattcaca cggaagctct gcagcctgga 420
caacggggac tgtgaccagt tctgccacga ggaacagaac tctgtggtgt gctcctgcgc 480
ccgcgggtac accctggctg acaacggcaa ggcctgcatt cccacagggc cctacccctg 540
tgggaaacag accctggaac gcaggaagag gtcagtggcc caggccacca gcagcagcgg 600
ggaggccccc gacagcatca catggaagcc atatgatgca gccgacctgg accccaccga 660
gaaccccttc gacctgcttg acttcaacca gacgcagcct gagaggggcg acaacaacct 720
caccaggatc gtgggaggcc aggaatgcaa ggacggggag tgtccctggc aggccctgct 780
catcaatgag gaaaacgagg gtttctgtgg tggaaccatt ctgagcgagt tctacatcct 840
aacggcagcc cactgtctct accaagccaa gagattcaag gtgagggtag gggaccggaa 900
cacggagcag gaggagggcg gtgaggcggt gcacgaggtg gaggtggtca tcaagcacaa 960
ccggttcaca aaggagacct atgacttcga catcgccgtg ctccggctca agaccccccat 1020
caccttccgc atgaacgtgg cgcctgcctg cctccccgag cgtgactggg ccgagtccac 1080
gctgatgacg cagaagacgg ggattgtgag cggcttcggg cgcacccacg agaagggccg 1140
gcagtccacc aggctcaaga tgctggaggt gccctacgtg gaccgcaaca gctgcaagct 1200
gtccagcagc ttcatcatca cccagaacat gttctgtgcc ggctacgaca ccaagcagga 1260
ggatgcctgc caggggggaca gcgggggccc gcacgtcacc cgcttcaagg acacctactt 1320
cgtgacaggc atcgtcagct ggggagaggg ctgtgcccgt aaggggaagt acgggatcta 1380
caccaaggtc accgccttcc tcaagtggat cgacaggtcc atgaaaacca ggggcttgcc 1440
caaggccaag agccatgccc cggaggtcat aacgtcctct ccattaaagt gagatcccac 1500
tc 1502

<210> 177
<211> 488
<212> PRT
<213> Homo sapiens

<220>
<223> coagulation factor Xa

<400> 177
Met Gly Arg Pro Leu His Leu Val Leu Leu Ser Ala Ser Leu Ala Gly
 1   5   10   15
Leu Leu Leu Leu Gly Glu Ser Leu Phe Ile Arg Arg Glu Gln Ala Asn
            20   25   30
Asn Ile Leu Ala Arg Val Thr Arg Ala Asn Ser Phe Leu Glu Glu Met
        35   40   45
Lys Lys Gly His Leu Glu Arg Glu Cys Met Glu Glu Thr Cys Ser Tyr
    50   55   60
Glu Glu Ala Arg Glu Val Phe Glu Asp Ser Asp Lys Thr Asn Glu Phe
65   70   75   80
Trp Asn Lys Tyr Lys Asp Gly Asp Gln Cys Glu Thr Ser Pro Cys Gln
                85   90   95
Asn Gln Gly Lys Cys Lys Asp Gly Leu Gly Glu Tyr Thr Cys Thr Cys
            100   105   110
Leu Glu Gly Phe Glu Gly Lys Asn Cys Glu Leu Phe Thr Arg Lys Leu
        115   120   125
Cys Ser Leu Asp Asn Gly Asp Cys Asp Gln Phe Cys His Glu Glu Gln
    130   135   140

```
Asn Ser Val Val Cys Ser Cys Ala Arg Gly Tyr Thr Leu Ala Asp Asn
145                 150                 155                 160
Gly Lys Ala Cys Ile Pro Thr Gly Pro Tyr Pro Cys Gly Lys Gln Thr
                165                 170                 175
Leu Glu Arg Arg Lys Arg Ser Val Ala Gln Ala Thr Ser Ser Ser Gly
            180                 185                 190
Glu Ala Pro Asp Ser Ile Thr Trp Lys Pro Tyr Asp Ala Ala Asp Leu
        195                 200                 205

Asp Pro Thr Glu Asn Pro Phe Asp Leu Leu Asp Phe Asn Gln Thr Gln
    210                 215                 220
Pro Glu Arg Gly Asp Asn Asn Leu Thr Arg Ile Val Gly Gly Gln Glu
225                 230                 235                 240
Cys Lys Asp Gly Glu Cys Pro Trp Gln Ala Leu Leu Ile Asn Glu Glu
                245                 250                 255
Asn Glu Gly Phe Cys Gly Gly Thr Ile Leu Ser Glu Phe Tyr Ile Leu
            260                 265                 270
Thr Ala Ala His Cys Leu Tyr Gln Ala Lys Arg Phe Lys Val Arg Val
        275                 280                 285
Gly Asp Arg Asn Thr Glu Gln Glu Glu Gly Gly Glu Ala Val His Glu
    290                 295                 300
Val Glu Val Val Ile Lys His Asn Arg Phe Thr Lys Glu Thr Tyr Asp
305                 310                 315                 320
Phe Asp Ile Ala Val Leu Arg Leu Lys Thr Pro Ile Thr Phe Arg Met
                325                 330                 335
Asn Val Ala Pro Ala Cys Leu Pro Glu Arg Asp Trp Ala Glu Ser Thr
            340                 345                 350
Leu Met Thr Gln Lys Thr Gly Ile Val Ser Gly Phe Gly Arg Thr His
        355                 360                 365
Glu Lys Gly Arg Gln Ser Thr Arg Leu Lys Met Leu Glu Val Pro Tyr
    370                 375                 380
Val Asp Arg Asn Ser Cys Lys Leu Ser Ser Ser Phe Ile Ile Thr Gln
385                 390                 395                 400
Asn Met Phe Cys Ala Gly Tyr Asp Thr Lys Gln Glu Asp Ala Cys Gln
                405                 410                 415
Gly Asp Ser Gly Gly Pro His Val Thr Arg Phe Lys Asp Thr Tyr Phe
            420                 425                 430
Val Thr Gly Ile Val Ser Trp Gly Glu Gly Cys Ala Arg Lys Gly Lys
        435                 440                 445
Tyr Gly Ile Tyr Thr Lys Val Thr Ala Phe Leu Lys Trp Ile Asp Arg
    450                 455                 460
Ser Met Lys Thr Arg Gly Leu Pro Lys Ala Lys Ser His Ala Pro Glu
465                 470                 475                 480
Val Ile Thr Ser Ser Pro Leu Lys
                485
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<210> 178
<211> 1997
<212> DNA
<213> Homo sapiens

<220>
<223> Thrombin

<400> 178
aattcctcag tgacccagga gctgacacac tatggcgcac gtccgaggct tgcagctgcc 60

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tggctgcctg gccctggctg ccctgtgtag ccttgtgcac agccagcatg tgttcctggc 120
tcctcagcaa gcacggtcgc tgctccagcg ggtccggcga gccaacacct tcttggagga 180
ggtgcgcaag ggcaacctag agcgagagtg cgtggaggag acgtgcagct acgaggaggc 240
cttcgaggct ctggagtcct ccacggctac ggatgtgttc tgggccaagt acacagcttg 300
tgagacagcg aggacgcctc gagataagct tgctgcatgt ctggaaggta actgtgctga 360
gggtctgggt acgaactacc gagggcatgt gaacatcacc cggtcaggca ttgagtgcca 420
gctatggagg agtcgctacc cacataagcc tgaaatcaac tccactaccc atcctggggc 480
cgacctacag gagaatttct gccgcaaccc cgacagcagc accacgggac cctggtgcta 540
cactacagac cccaccgtga ggaggcagga atgcagcatc cctgtctgtg gccaggatca 600
agtcactgta gcgatgactc cacgctccga aggctccagt gtgaatctgt cacctccatt 660
ggagcagtgt gtccctgatc gggggcagca gtaccagggg cgcctggcgg tgaccacaca 720
tgggctcccc tgcctggcct gggccagcgc acaggccaag gccctgagca agcaccagga 780
cttcaactca gctgtgcagc tggtggagaa cttctgccgc aacccagacg gggatgagga 840
gggcgtgtgg tgctatgtgg ccgggaagcc tggcgacttt gggtactgcg acctcaacta 900
ttgtgaggag gccgtggagg aggagacagg agatgggctg gatgaggact cagacagggc 960
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ctcgggagag gcagactgtg ggctgcgacc tctgttcgag aagaagtcgc tggaggacaa 1080
aaccgaaaga gagctcctgg aatcctacat cgacgggcgc attgtggagg gctcggatgc 1140
agagatcggc atgtcacctt ggcaggtgat gcttttccgg aagagtcccc aggagctgct 1200
gtgtggggcc agcctcatca gtgaccgctg ggtcctcacc gccgcccact gcctcctgta 1260
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ccgcacaagg tacgagcgaa acattgaaaa gatatccatg ttggaaaaga tctacatcca 1380
ccccaggtac aactggcggg agaacctgga ccgggacatt gccctgatga agctgaagaa 1440
gcctgttgcc ttcagtgact acattcaccc tgtgtgtctg cccgacaggg agacggcagc 1500
cagcttgctc caggctggat acaaggggcg ggtgacaggc tggggcaacc tgaaggagac 1560
gtggacagcc aacgttggta aggggcagcc cagtgtcctg caggtggtga acctgcccat 1620
tgtggagcgg ccggtctgca aggactccac ccggatccgc atcactgaca acatgttctg 1680
tgctggttac aagcctgatg aagggaaacg aggggatgcc tgtgaaggtg acagtggggg 1740
acccttttgtc atgaagagcc cctttaacaa ccgctggtat caaatgggca tcgtctcatg 1800
gggtgaaggc tgtgaccggg atgggaaata tggcttctac acacatgtgt tccgcctgaa 1860
gaagtggata cagaaggtca ttgatcagtt tggagagtag gggccactca tattctgggc 1920
tcctggaacc aatcccgtga aagaattatt tttgtgtttc taaaactatg gttcccaata 1980
aaagtgactc tcagcgg                                                1997
```

<210> 179
<211> 622
<212> PRT
<213> Homo sapiens

<220>
<223> Thrombin

<400> 179

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Met Ala His Val Arg Gly Leu Gln Leu Pro Gly Cys Leu Ala Leu Ala
 1               5                  10                  15
Ala Leu Cys Ser Leu Val His Ser Gln His Val Phe Leu Ala Pro Gln
            20                  25                  30
Gln Ala Arg Ser Leu Leu Gln Arg Val Arg Arg Ala Asn Thr Phe Leu
        35                  40                  45
Glu Glu Val Arg Lys Gly Asn Leu Glu Arg Glu Cys Val Glu Glu Thr
    50                  55                  60
Cys Ser Tyr Glu Glu Ala Phe Glu Ala Leu Glu Ser Ser Thr Ala Thr
65                  70                  75                  80
Asp Val Phe Trp Ala Lys Tyr Thr Ala Cys Glu Thr Ala Arg Thr Pro
                85                  90                  95
Arg Asp Lys Leu Ala Ala Cys Leu Glu Gly Asn Cys Ala Glu Gly Leu
            100                 105                 110
```

```
Gly Thr Asn Tyr Arg Gly His Val Asn Ile Thr Arg Ser Gly Ile Glu
        115                 120                 125
Cys Gln Leu Trp Arg Ser Arg Tyr Pro His Lys Pro Glu Ile Asn Ser
    130                 135                 140
Thr Thr His Pro Gly Ala Asp Leu Gln Glu Asn Phe Cys Arg Asn Pro
145                 150                 155                 160
Asp Ser Ser Thr Thr Gly Pro Trp Cys Tyr Thr Thr Asp Pro Thr Val
                165                 170                 175
Arg Arg Gln Glu Cys Ser Ile Pro Val Cys Gly Gln Asp Gln Val Thr
            180                 185                 190
Val Ala Met Thr Pro Arg Ser Glu Gly Ser Ser Val Asn Leu Ser Pro
        195                 200                 205
Pro Leu Glu Gln Cys Val Pro Asp Arg Gly Gln Gln Tyr Gln Gly Arg
    210                 215                 220
Leu Ala Val Thr Thr His Gly Leu Pro Cys Leu Ala Trp Ala Ser Ala
225                 230                 235                 240
Gln Ala Lys Ala Leu Ser Lys His Gln Asp Phe Asn Ser Ala Val Gln
                245                 250                 255
Leu Val Glu Asn Phe Cys Arg Asn Pro Asp Gly Asp Glu Glu Gly Val
            260                 265                 270
Trp Cys Tyr Val Ala Gly Lys Pro Gly Asp Phe Gly Tyr Cys Asp Leu
        275                 280                 285
Asn Tyr Cys Glu Glu Ala Val Glu Glu Glu Thr Gly Asp Gly Leu Asp
    290                 295                 300
Glu Asp Ser Asp Arg Ala Ile Glu Gly Arg Thr Ala Thr Ser Glu Tyr
305                 310                 315                 320
Gln Thr Phe Phe Asn Pro Arg Thr Phe Gly Ser Gly Glu Ala Asp Cys
                325                 330                 335
Gly Leu Arg Pro Leu Phe Glu Lys Lys Ser Leu Glu Asp Lys Thr Glu
            340                 345                 350
Arg Glu Leu Leu Glu Ser Tyr Ile Asp Gly Arg Ile Val Glu Gly Ser
        355                 360                 365
Asp Ala Glu Ile Gly Met Ser Pro Trp Gln Val Met Leu Phe Arg Lys
    370                 375                 380
Ser Pro Gln Glu Leu Leu Cys Gly Ala Ser Leu Ile Ser Asp Arg Trp
385                 390                 395                 400
Val Leu Thr Ala Ala His Cys Leu Leu Tyr Pro Pro Trp Asp Lys Asn
                405                 410                 415
Phe Thr Glu Asn Asp Leu Leu Val Arg Ile Gly Lys His Ser Arg Thr
            420                 425                 430
Arg Tyr Glu Arg Asn Ile Glu Lys Ile Ser Met Leu Glu Lys Ile Tyr
        435                 440                 445
Ile His Pro Arg Tyr Asn Trp Arg Glu Asn Leu Asp Arg Asp Ile Ala
    450                 455                 460
Leu Met Lys Leu Lys Lys Pro Val Ala Phe Ser Asp Tyr Ile His Pro
465                 470                 475                 480
Val Cys Leu Pro Asp Arg Glu Thr Ala Ala Ser Leu Leu Gln Ala Gly
                485                 490                 495
Tyr Lys Gly Arg Val Thr Gly Trp Gly Asn Leu Lys Glu Thr Trp Thr
            500                 505                 510
Ala Asn Val Gly Lys Gly Gln Pro Ser Val Leu Gln Val Val Asn Leu
        515                 520                 525
Pro Ile Val Glu Arg Pro Val Cys Lys Asp Ser Thr Arg Ile Arg Ile
    530                 535                 540
Thr Asp Asn Met Phe Cys Ala Gly Tyr Lys Pro Asp Glu Gly Lys Arg
545                 550                 555                 560
Gly Asp Ala Cys Glu Gly Asp Ser Gly Gly Pro Phe Val Met Lys Ser
```

```
                565                 570                 575
Pro Phe Asn Asn Arg Trp Tyr Gln Met Gly Ile Val Ser Trp Gly Glu
            580                 585                 590
Gly Cys Asp Arg Asp Gly Lys Tyr Gly Phe Tyr Thr His Val Phe Arg
        595                 600                 605
Leu Lys Lys Trp Ile Gln Lys Val Ile Asp Gln Phe Gly Glu
    610                 615                 620
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<210> 180
<211> 1843
<212> DNA
<213> Homo sapiens

<220>
<223> protein C (activated)

<400> 180
ctgcaggggg ggggggggg gggggctgtc atggcggcag gacggcgaac ttgcagtatc 60
tccacgaccc gcccctacag gtgccagtgc ctccagaatg tggcagctca caagcctcct 120
gctgttcgtg gccacctggg gaatttccgg cacaccagct cctcttgact cagtgttctc 180
cagcagcgag cgtgcccacc aggtgctgcg gatccgcaaa cgtgccaact ccttcctgga 240
ggagctccgt cacagcagcc tggagcggga gtgcatagag gagatctgtg acttcgagga 300
ggccaaggaa attttccaaa atgtggatga cacactggcc ttctggtcca agcacgtcga 360
cggtgaccag tgcttggtct tgcccttgga gcacccgtgc gccagcctgt gctgcgggca 420
cggcacgtgc atcgacggca tcggcagctt cagctgcgac tgccgcagcg gctgggaggg 480
ccgcttctgc cagcgcgagg tgagcttcct caattgctcg ctggacaacg gcggctgcac 540
gcattactgc ctagaggagg tgggctggcg gcgctgtagc tgtgcgcctg gctacaagct 600
gggggacgac ctcctgcagt gtcaccccgc agtgaagttc ccttgtggga ggccctggaa 660
gcggatggag aagaagcgca gtcacctgaa acgagacaca gaagaccaag aagaccaagt 720
agatccgcgg ctcattgatg ggaagatgac caggcgggga gacagccccc ggcaggtggt 780
cctgctggac tcaaagaaga agctggcctg cggggcagtg ctcatccacc cctcctgggt 840
gctgacagcg gcccactgca tggatgagtc caagaagctc cttgtcaggc ttggagagta 900
tgacctgcgg cgctgggaga agtgggagct ggacctggac atcaaggagg tcttcgtcca 960
ccccaactac agcaagagca ccaccgacaa tgacatcgca ctgctgcacc tggcccagcc 1020
cgccaccctc tcgcagacca tagtgcccat ctgcctcccg gacagcggcc ttgcagagcg 1080
cgagctcaat caggccggcc aggagaccct cgtgacgggc tggggctacc acagcagccg 1140
agagaaggag gccaagagaa accgcacctt cgtcctcaac ttcatcaaga ttcccgtggt 1200
cccgcacaat gagtgcagcg aggtcatgag caacatggtg tctgagaaca tgctgtgtgc 1260
gggcatcctc ggggaccggc aggatgcctg cgagggcgac agtggggggc ccatggtcgc 1320
ctccttccac ggcacctggt tcctggtggg cctggtgagc tggggtgagg gctgtgggct 1380
ccttcacaac tacggcgttt acaccaaagt cagccgctac ctcgactgga tccatgggca 1440
catcagagac aaggaagccc cccagaagag ctgggcacct tagcgaccct ccctgcaggg 1500
ctgggctttt gcatggcaat ggatgggaca ttaaagggac atgtaacaag cacaccggcc 1560
tgctgttctg tccttccatc cctcttttgg gctcttctgg agggaagtaa catttactga 1620
gcacctgttg tatgtcacat gccttatgaa tagaatctta actcctagag caactctgtg 1680
gggtggggag gagcagatcc aagttttgcg gggtctaaag ctgtgtgtgt tgaggggat 1740
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aaaaaaaaaa aaaaaaaccc ccccccgccc ccccccccctg cag 1843

<210> 181
<211> 461
<212> PRT
<213> Homo sapiens

<220>
<223> protein C (activated)

<400> 181
Met Trp Gln Leu Thr Ser Leu Leu Leu Phe Val Ala Thr Trp Gly Ile
 1   5   10   15
Ser Gly Thr Pro Ala Pro Leu Asp Ser Val Phe Ser Ser Ser Glu Arg
            20   25   30
Ala His Gln Val Leu Arg Ile Arg Lys Arg Ala Asn Ser Phe Leu Glu
        35   40   45
Glu Leu Arg His Ser Ser Leu Glu Arg Glu Cys Ile Glu Glu Ile Cys
    50   55   60
Asp Phe Glu Glu Ala Lys Glu Ile Phe Gln Asn Val Asp Asp Thr Leu
65   70   75   80
Ala Phe Trp Ser Lys His Val Asp Gly Asp Gln Cys Leu Val Leu Pro
                85   90   95
Leu Glu His Pro Cys Ala Ser Leu Cys Cys Gly His Gly Thr Cys Ile
            100   105   110
Asp Gly Ile Gly Ser Phe Ser Cys Asp Cys Arg Ser Gly Trp Glu Gly
        115   120   125
Arg Phe Cys Gln Arg Glu Val Ser Phe Leu Asn Cys Ser Leu Asp Asn
    130   135   140
Gly Gly Cys Thr His Tyr Cys Leu Glu Glu Val Gly Trp Arg Arg Cys
145   150   155   160
Ser Cys Ala Pro Gly Tyr Lys Leu Gly Asp Asp Leu Leu Gln Cys His
                165   170   175
Pro Ala Val Lys Phe Pro Cys Gly Arg Pro Trp Lys Arg Met Glu Lys
            180   185   190
Lys Arg Ser His Leu Lys Arg Asp Thr Glu Asp Gln Glu Asp Gln Val
        195   200   205
Asp Pro Arg Leu Ile Asp Gly Lys Met Thr Arg Arg Gly Asp Ser Pro
    210   215   220
Trp Gln Val Val Leu Leu Asp Ser Lys Lys Lys Leu Ala Cys Gly Ala
225   230   235   240
Val Leu Ile His Pro Ser Trp Val Leu Thr Ala Ala His Cys Met Asp
                245   250   255
Glu Ser Lys Lys Leu Leu Val Arg Leu Gly Glu Tyr Asp Leu Arg Arg
            260   265   270
Trp Glu Lys Trp Glu Leu Asp Leu Asp Ile Lys Glu Val Phe Val His
        275   280   285
Pro Asn Tyr Ser Lys Ser Thr Thr Asp Asn Asp Ile Ala Leu Leu His
    290   295   300
Leu Ala Gln Pro Ala Thr Leu Ser Gln Thr Ile Val Pro Ile Cys Leu
305   310   315   320
Pro Asp Ser Gly Leu Ala Glu Arg Glu Leu Asn Gln Ala Gly Gln Glu
                325   330   335
Thr Leu Val Thr Gly Trp Gly Tyr His Ser Ser Arg Glu Lys Glu Ala
            340   345   350
Lys Arg Asn Arg Thr Phe Val Leu Asn Phe Ile Lys Ile Pro Val Val
        355   360   365
Pro His Asn Glu Cys Ser Glu Val Met Ser Asn Met Val Ser Glu Asn
    370   375   380
Met Leu Cys Ala Gly Ile Leu Gly Asp Arg Gln Asp Ala Cys Glu Gly
385   390   395   400
Asp Ser Gly Gly Pro Met Val Ala Ser Phe His Gly Thr Trp Phe Leu
                405   410   415
Val Gly Leu Val Ser Trp Gly Glu Gly Cys Gly Leu Leu His Asn Tyr
            420   425   430

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Gly Val Tyr Thr Lys Val Ser Arg Tyr Leu Asp Trp Ile His Gly His
        435                 440                 445
Ile Arg Asp Lys Glu Ala Pro Gln Lys Ser Trp Ala Pro
    450                 455                 460


<210> 182
<211> 1388
<212> DNA
<213> Homo sapiens

<220>
<223> Acrosin

<400> 182
caggcagtgc aggagtatgg ttgagatgct accaactgcc attctgctgg tcttggcagt 60
gtccgtggtt gctaaagata acgccacgtg tgatggcccc tgtgggttac ggttcaggca 120
aaacccacag ggtggtgtcc gcatcgtcgg cgggaaggct gcacagcatg gggcctggcc 180
ctggatggtc agcctccaga tcttcacgta caacagccac aggtaccaca catgtggagg 240
cagcttgctg aattcacgat gggtgctcac tgctgctcac tgcttcgtcg gcaaaaataa 300
tgtgcatgac tggagactgg ttttcggagc aaaggaaatt acatatggga acaataaacc 360
agtaaaggcg cctgtgcaag agagatatgt ggagaaaatc atcattcatg aaaaatacaa 420
ctctgcgaca gagggaaatg acattgccct cgtggagatc acccctccca tttcgtgtgg 480
gcgcttcatt gggccgggct gcctgcccca cttgaaggca ggcctcccca gaggctccca 540
gagctgctgg gtggccggct ggggatatat agaagagaaa gcccccaggc catcatctat 600
actgatggag gcacgtgtgg atctcatcga cctggacttg tgtaactcga cccagtggta 660
caatgggcgc gttcagccaa ccaatgtgtg cgcggggtat cctgtaggca agatcgacac 720
ctgccaggga gacagcggcg ggcctctcat gtgcaaagac agcaaggaaa gcgcctatgt 780
ggtcgtggga atcacaagct gggggggtagg ctgtgcccgt gccaagcgcc ccggaatcta 840
cacggccacc tggccttatc tgaactggat cgcctccaag attggttcta acgctttgcg 900
tatgattcaa tcggccaccc ctccaccgcc caccactcga ccgcccccga ttcgaccccc 960
cttctcccac cctatctctg ctcaccttcc ttggtatttc caaccgcccc ctcgaccact 1020
tccaccccga ccaccggcag cccagccccg acccccacct tcaccccccgc ccccaccccc 1080
acctccagcc tcacctttac ccccaccccc acccccaccc ccacctacac cctcatctac 1140
cacaaaactt ccccaaggac tttcttttgc caagcgccta cagcagctca tagaggtctt 1200
gaaggggaag acctattccg acggaaagaa ccattatgac atggagacca cagagctccc 1260
agaactgacc tcgacctcct gatctgacct ggttctcaac agacccagtg agcccttcac 1320
tcctgagaaa aaggaaagat gaaataaata aataaacata tatatataga tataaaaaaa 1380
aaaaaaaa                                                        1388

<210> 183
<211> 421
<212> PRT
<213> Homo sapiens

<220>
<223> Acrosin

<400> 183
Met Val Glu Met Leu Pro Thr Ala Ile Leu Leu Val Leu Ala Val Ser
 1               5                  10                  15
Val Val Ala Lys Asp Asn Ala Thr Cys Asp Gly Pro Cys Gly Leu Arg
            20                  25                  30
Phe Arg Gln Asn Pro Gln Gly Gly Val Arg Ile Val Gly Gly Lys Ala
        35                  40                  45
Ala Gln His Gly Ala Trp Pro Trp Met Val Ser Leu Gln Ile Phe Thr
    50                  55                  60
```

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Tyr Asn Ser His Arg Tyr His Thr Cys Gly Gly Ser Leu Leu Asn Ser
65                  70                  75                  80
Arg Trp Val Leu Thr Ala Ala His Cys Phe Val Gly Lys Asn Asn Val
                85                  90                  95
His Asp Trp Arg Leu Val Phe Gly Ala Lys Glu Ile Thr Tyr Gly Asn
            100                 105                 110
Asn Lys Pro Val Lys Ala Pro Val Gln Glu Arg Tyr Val Glu Lys Ile
        115                 120                 125
Ile Ile His Glu Lys Tyr Asn Ser Ala Thr Glu Gly Asn Asp Ile Ala
    130                 135                 140
Leu Val Glu Ile Thr Pro Pro Ile Ser Cys Gly Arg Phe Ile Gly Pro
145                 150                 155                 160
Gly Cys Leu Pro His Leu Lys Ala Gly Leu Pro Arg Gly Ser Gln Ser
                165                 170                 175
Cys Trp Val Ala Gly Trp Gly Tyr Ile Glu Glu Lys Ala Pro Arg Pro
            180                 185                 190
Ser Ser Ile Leu Met Glu Ala Arg Val Asp Leu Ile Asp Leu Asp Leu
        195                 200                 205
Cys Asn Ser Thr Gln Trp Tyr Asn Gly Arg Val Gln Pro Thr Asn Val
    210                 215                 220
Cys Ala Gly Tyr Pro Val Gly Lys Ile Asp Thr Cys Gln Gly Asp Ser
225                 230                 235                 240
Gly Gly Pro Leu Met Cys Lys Asp Ser Lys Glu Ser Ala Tyr Val Val
                245                 250                 255
Val Gly Ile Thr Ser Trp Gly Val Gly Cys Ala Arg Ala Lys Arg Pro
            260                 265                 270
Gly Ile Tyr Thr Ala Thr Trp Pro Tyr Leu Asn Trp Ile Ala Ser Lys
        275                 280                 285
Ile Gly Ser Asn Ala Leu Arg Met Ile Gln Ser Ala Thr Pro Pro Pro
    290                 295                 300
Pro Thr Thr Arg Pro Pro Pro Ile Arg Pro Pro Phe Ser His Pro Ile
305                 310                 315                 320
Ser Ala His Leu Pro Trp Tyr Phe Gln Pro Pro Pro Arg Pro Leu Pro
                325                 330                 335
Pro Arg Pro Pro Ala Ala Gln Pro Arg Pro Pro Pro Ser Pro Pro Pro
            340                 345                 350

Pro Pro Pro Pro Pro Ala Ser Pro Leu Pro Pro Pro Pro Pro Pro Pro
        355                 360                 365
Pro Pro Thr Pro Ser Ser Thr Thr Lys Leu Pro Gln Gly Leu Ser Phe
    370                 375                 380
Ala Lys Arg Leu Gln Gln Leu Ile Glu Val Leu Lys Gly Lys Thr Tyr
385                 390                 395                 400
Ser Asp Gly Lys Asn His Tyr Asp Met Glu Thr Thr Glu Leu Pro Glu
                405                 410                 415
Leu Thr Ser Thr Ser
            420
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<210> 184
<211> 2363
<212> DNA
<213> Homo sapiens

<220>
<223> Hepsin transcript variant 1

<400> 184
tcgagcccgc tttccaggga ccctacctga gggcccacag gtgaggcagc ctggcctagc 60
aggccccacg ccaccgcctc tgcctccagg ccgcccgctg ctgcggggcc accatgctcc 120
tgcccaggcc tggagactga cccgaccccg gcactacctc gaggctccgc ccccacctgc 180
tggaccccag ggtaaggaca agggcccccа gactcacagt tccagccctg aggacagggg 240
ttccctcatc cccccaccca gcctaatgcc cacctcctaa tagaggggtt cctggggacc 300
tgaagagggg gcactatgac gtctccccaa gcacctaggt gttctgtcct gctcttcctt 360
cagactcagc cgttggaccc cagtcctttc ctccccagac ccaggagttc cagccctcag 420
gcccctcctc cctcatacta gggagtcctg gcccccaaat tcctcctttc ccaagactta 480
tgatttcagg tcctcagctg tctcctccct caaaccggga tcctcagtcc cctgctccac 540
caggctcagg catgggggtc cccatccctg caaatccagg cgtccccccg ctgctggtca 600
gacactgacc ccatccttga acccagccca atctgcgtcc gtgatcacgg cgtgctctgg 660
ccaaggccca gtccctacag cctgcctgga tggacgcctg ggactggggg cgccaggact 720
gggctgggct gggctccccc aggccctgcc tccccgtcca tctcctcaca ggtcccaccc 780
tggcccagga ggtcagccag ggaatcatta acaagaggca gtgacatggc gcagaaggag 840
ggtggccgga ctgtgccatg ctgctccaga cccaaggtgg cagctctcac tgcggggacc 900
ctgctacttc tgacagccat cggggcggca tcctgggcca ttgtggctgt tctcctcagg 960
agtgaccagg agccgctgta cccagtgcag gtcagctctg cggacgctcg gctcatggtc 1020
tttgacaaga cggaagggac gtggcggctg ctgtgctcct cgcgctccaa cgccagggta 1080
gccggactca gctgcgagga gatgggcttc ctcagggcac tgacccactc cgagctggac 1140
gtgcgaacgg cgggcgccaa tggcacgtcg ggcttcttct gtgtggacga ggggaggctg 1200
ccccacaccc agaggctgct ggaggtcatc tccgtgtgtg attgccccag aggccgtttc 1260
ttggccgcca tctgccaaga ctgtggccgc aggaagctgc ccgtggaccg catcgtggga 1320
ggccgggaca ccagcttggg ccggtggccg tggcaagtca gccttcgcta tgatggagca 1380
cacctctgtg ggggatccct gctctccggg gactgggtgc tgacagccgc ccactgcttc 1440
ccggagcgga accgggtcct gtcccgatgg cgagtgtttg ccggtgccgt ggcccaggcc 1500
tctccccacg gtctgcagct gggggtgcag gctgtggtct accacggggg ctatcttccc 1560
tttcgggacc ccaacagcga ggagaacagc aacgatattg ccctggtcca cctctccagt 1620
cccctgcccc tcacagaata catccagcct gtgtgcctcc cagctgccgg ccaggccctg 1680
gtggatggca agatctgtac cgtgacgggc tggggcaaca cgcagtacta tggccaacag 1740
gccggggtac tccaggaggc tcgagtcccc ataatcagca atgatgtctg caatggcgct 1800
gacttctatg gaaaccagat caagcccaag atgttctgtg ctggctaccc cgagggtggc 1860
attgatgcct gccagggcga cagcggtggt ccctttgtgt gtgaggacag catctctcgg 1920
acgccacgtt ggcggctgtg tggcattgtg agttggggca ctggctgtgc cctggcccag 1980
aagccaggcg tctacaccaa agtcagtgac ttccgggagt ggatcttcca ggccataaag 2040
actcactccg aagccagcgg catggtgacc cagctctgac cggtggcttc tcgctgcgca 2100
gcctccaggg cccgaggtga tcccggtggt gggatccacg ctgggccgag gatgggacgt 2160
ttttcttctt gggcccggtc cacaggtcca aggacaccct ccctccaggg tcctctcttc 2220
cacagtggcg ggcccactca gccccgagac cacccaacct caccctcctg acccccatgt 2280
aaatattgtt ctgctgtctg ggactcctgt ctaggtgccc ctgatgatgg gatgctcttt 2340
aaataataaa gatggttttg att 2363

<210> 185
<211> 417
<212> PRT
<213> Homo sapiens

<220>
<223> Hepsin

<400> 185
Met Ala Gln Lys Glu Gly Gly Arg Thr Val Pro Cys Cys Ser Arg Pro
 1   5   10   15
Lys Val Ala Ala Leu Thr Ala Gly Thr Leu Leu Leu Leu Thr Ala Ile
            20   25   30
Gly Ala Ala Ser Trp Ala Ile Val Ala Val Leu Leu Arg Ser Asp Gln
        35   40   45

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Glu Pro Leu Tyr Pro Val Gln Val Ser Ser Ala Asp Ala Arg Leu Met
    50                  55                  60
Val Phe Asp Lys Thr Glu Gly Thr Trp Arg Leu Leu Cys Ser Ser Arg
65                  70                  75                  80
Ser Asn Ala Arg Val Ala Gly Leu Ser Cys Glu Glu Met Gly Phe Leu
                85                  90                  95
Arg Ala Leu Thr His Ser Glu Leu Asp Val Arg Thr Ala Gly Ala Asn
            100                 105                 110
Gly Thr Ser Gly Phe Phe Cys Val Asp Glu Gly Arg Leu Pro His Thr
        115                 120                 125
Gln Arg Leu Leu Glu Val Ile Ser Val Cys Asp Cys Pro Arg Gly Arg
    130                 135                 140
Phe Leu Ala Ala Ile Cys Gln Asp Cys Gly Arg Arg Lys Leu Pro Val
145                 150                 155                 160
Asp Arg Ile Val Gly Gly Arg Asp Thr Ser Leu Gly Arg Trp Pro Trp
                165                 170                 175
Gln Val Ser Leu Arg Tyr Asp Gly Ala His Leu Cys Gly Gly Ser Leu
            180                 185                 190
Leu Ser Gly Asp Trp Val Leu Thr Ala Ala His Cys Phe Pro Glu Arg
        195                 200                 205
Asn Arg Val Leu Ser Arg Trp Arg Val Phe Ala Gly Ala Val Ala Gln
    210                 215                 220
Ala Ser Pro His Gly Leu Gln Leu Gly Val Gln Ala Val Val Tyr His
225                 230                 235                 240
Gly Gly Tyr Leu Pro Phe Arg Asp Pro Asn Ser Glu Glu Asn Ser Asn
                245                 250                 255
Asp Ile Ala Leu Val His Leu Ser Ser Pro Leu Pro Leu Thr Glu Tyr
            260                 265                 270
Ile Gln Pro Val Cys Leu Pro Ala Ala Gly Gln Ala Leu Val Asp Gly
        275                 280                 285
Lys Ile Cys Thr Val Thr Gly Trp Gly Asn Thr Gln Tyr Tyr Gly Gln
    290                 295                 300
Gln Ala Gly Val Leu Gln Glu Ala Arg Val Pro Ile Ile Ser Asn Asp
305                 310                 315                 320
Val Cys Asn Gly Ala Asp Phe Tyr Gly Asn Gln Ile Lys Pro Lys Met
                325                 330                 335
Phe Cys Ala Gly Tyr Pro Glu Gly Gly Ile Asp Ala Cys Gln Gly Asp
            340                 345                 350
Ser Gly Gly Pro Phe Val Cys Glu Asp Ser Ile Ser Arg Thr Pro Arg
        355                 360                 365
Trp Arg Leu Cys Gly Ile Val Ser Trp Gly Thr Gly Cys Ala Leu Ala
    370                 375                 380
Gln Lys Pro Gly Val Tyr Thr Lys Val Ser Asp Phe Arg Glu Trp Ile
385                 390                 395                 400
Phe Gln Ala Ile Lys Thr His Ser Glu Ala Ser Gly Met Val Thr Gln
                405                 410                 415
Leu
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<210> 186
<211> 1783
<212> DNA
<213> Homo sapiens

<220>
<223> Hepsin transcript variant 2

<400> 186

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aggccccacg ccaccgcctc tgcctccagg ccgcccgctg ctgcggggcc accatgctcc 120
tgcccaggcc tggagactga cccgaccccg gcactacctc gaggctccgc ccccacctgc 180
tggaccccag ggtcccaccc tggcccagga ggtcagccag ggaatcatta acaagaggca 240
gtgacatggc gcagaaggag ggtggccgga ctgtgccatg ctgctccaga cccaaggtgg 300
cagctctcac tgcggggacc ctgctacttc tgacagccat cggggcggca tcctgggcca 360
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cggacgctcg gctcatggtc tttgacaaga cggaagggac gtggcggctg ctgtgctcct 480
cgcgctccaa cgccagggta gccggactca gctgcgagga gatgggcttc ctcagggcac 540
tgacccactc cgagctggac gtgcgaacgg cgggcgccaa tggcacgtcg ggcttcttct 600
gtgtggacga ggggaggctg ccccacaccc agaggctgct ggaggtcatc tccgtgtgtg 660
attgccccag aggccgtttc ttggccgcca tctgccaaga ctgtggccgc aggaagctgc 720
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gccttcgcta tgatggagca cacctctgtg ggggatccct gctctccggg gactgggtgc 840
tgacagccgc ccactgcttc ccggagcgga accgggtcct gtcccgatgg cgagtgtttg 900
ccggtgccgt ggcccaggcc tctccccacg gtctgcagct gggggtgcag gctgtggtct 960
accacggggg ctatcttccc tttcgggacc ccaacagcga ggagaacagc aacgatattg 1020
ccctggtcca cctctccagt cccctgcccc tcacagaata catccagcct gtgtgcctcc 1080
cagctgccgg ccaggccctg gtggatggca agatctgtac cgtgacgggc tggggcaaca 1140
cgcagtacta tggccaacag gccggggtac tccaggaggc tcgagtcccc ataatcagca 1200
atgatgtctg caatggcgct gacttctatg gaaaccagat caagcccaag atgttctgtg 1260
ctggctaccc cgagggtggc attgatgcct gccagggcga cagcggtggt ccctttgtgt 1320
gtgaggacag catctctcgg acgccacgtt ggcggctgtg tggcattgtg agttggggca 1380
ctggctgtgc cctggcccag aagccaggcg tctacaccaa agtcagtgac ttccgggagt 1440
ggatcttcca ggccataaag actcactccg aagccagcgg catggtgacc cagctctgac 1500
cggtggcttc tcgctgcgca gcctccaggg cccgaggtga tcccggtggt gggatccacg 1560
ctgggccgag gatgggacgt ttttcttctt gggcccggtc cacaggtcca aggacaccct 1620
ccctccaggg tcctctcttc cacagtggcg ggcccactca gccccgagac cacccaacct 1680
caccctcctg acccccatgt aaatattgtt ctgctgtctg ggactcctgt ctaggtgccc 1740
ctgatgatgg gatgctcttt aaataataaa gatggttttg att 1783

<210> 187
<211> 417
<212> PRT
<213> Homo sapiens

<220>
<223> Hepsin

<400> 187
Met Ala Gln Lys Glu Gly Gly Arg Thr Val Pro Cys Cys Ser Arg Pro
 1   5   10   15
Lys Val Ala Ala Leu Thr Ala Gly Thr Leu Leu Leu Leu Thr Ala Ile
            20   25   30
Gly Ala Ala Ser Trp Ala Ile Val Ala Val Leu Leu Arg Ser Asp Gln
        35   40   45
Glu Pro Leu Tyr Pro Val Gln Val Ser Ser Ala Asp Ala Arg Leu Met
    50   55   60
Val Phe Asp Lys Thr Glu Gly Thr Trp Arg Leu Leu Cys Ser Ser Arg
65   70   75   80
Ser Asn Ala Arg Val Ala Gly Leu Ser Cys Glu Glu Met Gly Phe Leu
                85   90   95
Arg Ala Leu Thr His Ser Glu Leu Asp Val Arg Thr Ala Gly Ala Asn
            100   105   110

```
Gly Thr Ser Gly Phe Phe Cys Val Asp Glu Gly Arg Leu Pro His Thr
        115                 120                 125
Gln Arg Leu Leu Glu Val Ile Ser Val Cys Asp Cys Pro Arg Gly Arg
    130                 135                 140
Phe Leu Ala Ala Ile Cys Gln Asp Cys Gly Arg Arg Lys Leu Pro Val
145                 150                 155                 160
Asp Arg Ile Val Gly Gly Arg Asp Thr Ser Leu Gly Arg Trp Pro Trp
                165                 170                 175
Gln Val Ser Leu Arg Tyr Asp Gly Ala His Leu Cys Gly Gly Ser Leu
            180                 185                 190
Leu Ser Gly Asp Trp Val Leu Thr Ala Ala His Cys Phe Pro Glu Arg
        195                 200                 205
Asn Arg Val Leu Ser Arg Trp Arg Val Phe Ala Gly Ala Val Ala Gln
    210                 215                 220
Ala Ser Pro His Gly Leu Gln Leu Gly Val Gln Ala Val Val Tyr His
225                 230                 235                 240
Gly Gly Tyr Leu Pro Phe Arg Asp Pro Asn Ser Glu Glu Asn Ser Asn
                245                 250                 255
Asp Ile Ala Leu Val His Leu Ser Ser Pro Leu Pro Leu Thr Glu Tyr
            260                 265                 270
Ile Gln Pro Val Cys Leu Pro Ala Ala Gly Gln Ala Leu Val Asp Gly
        275                 280                 285
Lys Ile Cys Thr Val Thr Gly Trp Gly Asn Thr Gln Tyr Tyr Gly Gln
    290                 295                 300
Gln Ala Gly Val Leu Gln Glu Ala Arg Val Pro Ile Ile Ser Asn Asp
305                 310                 315                 320
Val Cys Asn Gly Ala Asp Phe Tyr Gly Asn Gln Ile Lys Pro Lys Met
                325                 330                 335
Phe Cys Ala Gly Tyr Pro Glu Gly Gly Ile Asp Ala Cys Gln Gly Asp
            340                 345                 350
Ser Gly Gly Pro Phe Val Cys Glu Asp Ser Ile Ser Arg Thr Pro Arg
        355                 360                 365
Trp Arg Leu Cys Gly Ile Val Ser Trp Gly Thr Gly Cys Ala Leu Ala
    370                 375                 380
Gln Lys Pro Gly Val Tyr Thr Lys Val Ser Asp Phe Arg Glu Trp Ile
385                 390                 395                 400
Phe Gln Ala Ile Lys Thr His Ser Glu Ala Ser Gly Met Val Thr Gln
                405                 410                 415
Leu
```

<210> 188
<211> 2038
<212> DNA
<213> Homo sapiens

<220>
<223> hepatocyte growth factor activator

<400> 188
gccatggggc gctgggcctg ggtccccagc ccctggcccc caccggggct gggccccttc 60
ctcctcctcc tcctgctgct gctgctgctg ccacgggggt tccagcccca gcctggcggg 120
aaccgtacgg agtccccaga acctaatgcc acagcgaccc ctgcgatccc cactatcctg 180
gtgacctctg tgacctctga gaccccagca acaagtgctc cagaggcaga gggaccccaa 240
agtgggggggc tcccgccccc gcccagggca gttcccctcga gcagtagccc ccaggcccaa 300
gcactcaccg aggacgggag gccctgcagg ttccccttcc gctacggggg ccgcatgctg 360

catgcctgca cttcggaggg cagtgcacac aggaagtggt gtgccacaac tcacaactac 420
gaccgggaca gggcctgggg ctactgtgtg gaggccaccc cgcctccagg gggcccagct 480
gccctggatc cctgtgcctc cggcccctgc ctcaatggag gctcctgctc caatacccag 540
gacccccagt cctatcactg cagctgcccc cgggccttca ccggcaagga ctgcggcaca 600
gagaaatgct ttgatgagac ccgctacgag tacctggagg ggggcgaccg ctgggcccgc 660
gtgcgccagg gccacgtgga acagtgcgag tgcttcgggg gccggacctg gtgcgaaggc 720
acccgacata cagcttgtct gagcagccct tgcctgaacg ggggcacctg ccacctgatc 780
gtggccaccg ggaccaccgt gtgtgcctgc ccaccaggct tcgctggacg gctctgcaac 840
atcgagcctg atgagcgctg cttcttgggg aacggcactg ggtaccgtgg cgtggccagc 900
acctcagcct cgggcctcag ctgcctggcc tggaactccg atctgctcta ccaggagctg 960
cacgtggact ccgtgggcgc cgcggccctg ctgggcctgg gcccccatgc ctactgccgg 1020
aatccggaca atgacgagag gccctggtgc tacgtggtga aggacagcgc gctctcctgg 1080
gagtactgcc gcctggaggc ctgcgaatcc ctcaccagag tccaactgtc accggatctc 1140
ctggcgaccc tgcctgagcc agcctccccg gggcgccagg cctgcggcag gaggcacaag 1200
aagaggacgt tcctgcggcc acgtatcatc ggcggctcct cctcgctgcc cggctcgcac 1260
ccctggctgg ccgccatcta catcggggac agcttctgcg ccgggagcct ggtccacacc 1320
tgctgggtgg tgtcggccgc ccactgcttc tcccacagcc cccccaggga cagcgtctcc 1380
gtggtgctgg gccagcactt cttcaaccgc acgacggacg tgacgcagac cttcggcatc 1440
gagaagtaca tcccgtacac cctgtactcg gtgttcaacc ccagcgacca cgacctcgtc 1500
ctgatccggc tgaagaagaa aggggaccgc tgtgccacac gctcgcagtt cgtgcagccc 1560
atctgcctgc ccgagcccgg cagcaccttc cccgcaggac acaagtgcca gattgcgggc 1620
tggggccact tggatgagaa cgtgagcggc tactccagct ccctgcggga ggccctggtc 1680
cccctggtcg ccgaccacaa gtgcagcagc cctgaggtct acggcgccga catcagcccc 1740
aacatgctct gtgccggcta cttcgactgc aagtccgacg cctgccaggg ggactcaggg 1800
gggcccctgg cctgcgagaa gaacggcgtg gcttacctct acggcatcat cagctggggt 1860
gacggctgcg ggcggctcca caagccgggg gtctacaccc gcgtggccaa ctatgtggac 1920
tggatcaacg accggatacg gcctcccagg cggcttgtgg ctccctcctg accctccagc 1980
gggacaccct ggttcccacc attccctgcc ttgctgacaa taaagatatt tccaagaa 2038

<210> 189
<211> 655
<212> PRT
<213> Homo sapiens

<220>
<223> hepatocyte growth factor activator

<400> 189
Met Gly Arg Trp Ala Trp Val Pro Ser Pro Trp Pro Pro Pro Gly Leu
 1   5   10   15
Gly Pro Phe Leu Leu Leu Leu Leu Leu Leu Leu Leu Leu Pro Arg Gly
            20   25   30
Phe Gln Pro Gln Pro Gly Gly Asn Arg Thr Glu Ser Pro Glu Pro Asn
        35   40   45
Ala Thr Ala Thr Pro Ala Ile Pro Thr Ile Leu Val Thr Ser Val Thr
    50   55   60
Ser Glu Thr Pro Ala Thr Ser Ala Pro Glu Ala Glu Gly Pro Gln Ser
65   70   75   80
Gly Gly Leu Pro Pro Pro Pro Arg Ala Val Pro Ser Ser Ser Ser Pro
                85   90   95
Gln Ala Gln Ala Leu Thr Glu Asp Gly Arg Pro Cys Arg Phe Pro Phe
            100   105   110
Arg Tyr Gly Gly Arg Met Leu His Ala Cys Thr Ser Glu Gly Ser Ala
        115   120   125
His Arg Lys Trp Cys Ala Thr Thr His Asn Tyr Asp Arg Asp Arg Ala
    130   135   140
Trp Gly Tyr Cys Val Glu Ala Thr Pro Pro Pro Gly Gly Pro Ala Ala

```
145                 150                 155                 160
Leu Asp Pro Cys Ala Ser Gly Pro Cys Leu Asn Gly Gly Ser Cys Ser
                165                 170                 175
Asn Thr Gln Asp Pro Gln Ser Tyr His Cys Ser Cys Pro Arg Ala Phe
            180                 185                 190
Thr Gly Lys Asp Cys Gly Thr Glu Lys Cys Phe Asp Glu Thr Arg Tyr
        195                 200                 205
Glu Tyr Leu Glu Gly Gly Asp Arg Trp Ala Arg Val Arg Gln Gly His
    210                 215                 220
Val Glu Gln Cys Glu Cys Phe Gly Gly Arg Thr Trp Cys Glu Gly Thr
225                 230                 235                 240
Arg His Thr Ala Cys Leu Ser Ser Pro Cys Leu Asn Gly Gly Thr Cys
                245                 250                 255
His Leu Ile Val Ala Thr Gly Thr Thr Val Cys Ala Cys Pro Pro Gly
            260                 265                 270
Phe Ala Gly Arg Leu Cys Asn Ile Glu Pro Asp Glu Arg Cys Phe Leu
        275                 280                 285
Gly Asn Gly Thr Gly Tyr Arg Gly Val Ala Ser Thr Ser Ala Ser Gly
    290                 295                 300
Leu Ser Cys Leu Ala Trp Asn Ser Asp Leu Leu Tyr Gln Glu Leu His
305                 310                 315                 320
Val Asp Ser Val Gly Ala Ala Ala Leu Leu Gly Leu Gly Pro His Ala

                325                 330                 335
Tyr Cys Arg Asn Pro Asp Asn Asp Glu Arg Pro Trp Cys Tyr Val Val
            340                 345                 350
Lys Asp Ser Ala Leu Ser Trp Glu Tyr Cys Arg Leu Glu Ala Cys Glu
        355                 360                 365
Ser Leu Thr Arg Val Gln Leu Ser Pro Asp Leu Leu Ala Thr Leu Pro
    370                 375                 380
Glu Pro Ala Ser Pro Gly Arg Gln Ala Cys Gly Arg Arg His Lys Lys
385                 390                 395                 400
Arg Thr Phe Leu Arg Pro Arg Ile Ile Gly Gly Ser Ser Ser Leu Pro
                405                 410                 415
Gly Ser His Pro Trp Leu Ala Ala Ile Tyr Ile Gly Asp Ser Phe Cys
            420                 425                 430
Ala Gly Ser Leu Val His Thr Cys Trp Val Val Ser Ala Ala His Cys
        435                 440                 445
Phe Ser His Ser Pro Pro Arg Asp Ser Val Ser Val Val Leu Gly Gln
    450                 455                 460
His Phe Phe Asn Arg Thr Thr Asp Val Thr Gln Thr Phe Gly Ile Glu
465                 470                 475                 480
Lys Tyr Ile Pro Tyr Thr Leu Tyr Ser Val Phe Asn Pro Ser Asp His
                485                 490                 495
Asp Leu Val Leu Ile Arg Leu Lys Lys Lys Gly Asp Arg Cys Ala Thr
            500                 505                 510
Arg Ser Gln Phe Val Gln Pro Ile Cys Leu Pro Glu Pro Gly Ser Thr
        515                 520                 525
Phe Pro Ala Gly His Lys Cys Gln Ile Ala Gly Trp Gly His Leu Asp
    530                 535                 540
Glu Asn Val Ser Gly Tyr Ser Ser Ser Leu Arg Glu Ala Leu Val Pro
545                 550                 555                 560
Leu Val Ala Asp His Lys Cys Ser Ser Pro Glu Val Tyr Gly Ala Asp
                565                 570                 575
Ile Ser Pro Asn Met Leu Cys Ala Gly Tyr Phe Asp Cys Lys Ser Asp
            580                 585                 590
Ala Cys Gln Gly Asp Ser Gly Gly Pro Leu Ala Cys Glu Lys Asn Gly
```

```
        595                 600                 605
Val Ala Tyr Leu Tyr Gly Ile Ile Ser Trp Gly Asp Gly Cys Gly Arg
    610                 615                 620
Leu His Lys Pro Gly Val Tyr Thr Arg Val Ala Asn Tyr Val Asp Trp
625                 630                 635                 640
Ile Asn Asp Arg Ile Arg Pro Pro Arg Arg Leu Val Ala Pro Ser
                645                 650                 655
```

<210> 190
<211> 2360
<212> DNA
<213> Homo sapiens

<220>
<223> u-plasminogen activator (uPA)

<400> 190

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acagtgcgga gaccgcagcc ccggagcccg ggccagggtc cacctgtccc cgcagcgccg 60
gctcgcgccc tcctgccgca gccaccgagc cgccgtctag cgccccgacc tcgccaccat 120
gagagccctg ctggcgcgcc tgcttctctg cgtcctggtc gtgagcgact ccaaaggcag 180
caatgaactt catcaagttc atcgaactg tgactgtcta aatggaggaa catgtgtgtc 240
caacaagtac ttctccaaca ttcactggtg caactgccca aagaaattcg gagggcagca 300
ctgtgaaata gataagtcaa aaacctgcta tgaggggaat ggtcacttt accgaggaaa 360
ggccagcact gacaccatgg gccggccctg cctgccctgg aactctgcca ctgtccttca 420
gcaaacgtac catgcccaca gatctgatgc tcttcagctg ggcctgggga aacataatta 480
ctgcaggaac ccagacaacc ggaggcgacc ctggtgctat gtgcaggtgg gcctaaagcc 540
gcttgtccaa gagtgcatgg tgcatgactg cgcagatgga aaaaagccct cctctcctcc 600
agaagaatta aaatttcagt gtggccaaaa gactctgagg ccccgcttta agattattgg 660
gggagaattc accaccatcg agaaccagcc ctggtttgcg gccatctaca ggaggcaccg 720
gggggctct gtcacctacg tgtgtggagg cagcctcatc agcccttgct gggtgatcag 780
cgccacacac tgcttcattg attacccaaa gaaggaggac tacatcgtct acctgggtcg 840
ctcaaggctt aactccaaca cgcaagggga gatgaagttt gaggtggaaa acctcatcct 900
acacaaggac tacagcgctg acacgcttgc tcaccacaac gacattgcct tgctgaagat 960
ccgttccaag gagggcaggt gtgcgcagcc atcccggact atacagacca tctgcctgcc 1020
ctcgatgtat aacgatcccc agtttggcac aagctgtgag atcactggct ttggaaaaga 1080
gaattctacc gactatctct atccggagca gctgaaaatg actgttgtga agctgatttc 1140
ccaccgggag tgtcagcagc cccactacta cggctctgaa gtcaccacca aaatgctgtg 1200
tgctgctgac ccacagtgga aaacagattc ctgccaggga gactcagggg gacccctcgt 1260
ctgttccctc caaggccgca tgactttgac tggaattgtg agctggggcc gtggatgtgc 1320
cctgaaggac aagccaggcg tctacacgag agtctcacac ttcttaccct ggatccgcag 1380
tcacaccaag gaagagaatg gcctggccct ctgagggtcc ccagggagga aacgggcacc 1440
acccgctttc ttgctggttg tcatttttgc agtagagtca tctccatcag ctgtaagaag 1500
agactgggaa gataggctct gcacagatgg atttgcctgt gccacccacc agggcgaacg 1560
acaatagctt taccctcagg cataggcctg ggtgctggct gcccagaccc ctctggccag 1620
gatggagggg tggtcctgac tcaacatgtt actgaccagc aacttgtctt tttctggact 1680
gaagcctgca ggagttaaaa agggcagggc atctcctgtg catgggtgaa gggagagcca 1740
gctcccccga cggtgggcat ttgtgaggcc catggttgag aaatgaataa tttcccaatt 1800
aggaagtgta acagctgagg tctcttgagg gagcttagcc aatgtgggag cagcggtttg 1860
gggagcagag acactaacga cttcagggca gggctctgat attccatgaa tgtatcagga 1920
aatatatatg tgtgtgtatg tttgcacact tgtgtgtggg ctgtgagtgt aagtgtgagt 1980
aagagctggt gtctgattgt taagtctaaa tatttcctta aactgtgtgg actgtgatgc 2040
cacacagagt ggtctttctg gagaggttat aggtcactcc tggggcctct tgggtccccc 2100
acgtgacagt gcctgggaat gtattattct gcagcatgac ctgtgaccag cactgtctca 2160
gtttcacttt cacatagatg tccctttctt ggccagttat cccttccttt tagcctagtt 2220
catccaatcc tcactgggtg gggtgaggac cactcctgta cactgaatat ttatatttca 2280
ctatttttat ttatattttt gtaatttaa ataaaagtga tcaataaaat gtgatttttc 2340
```

tgatgaaaaa aaaaaaaaaa 2360

<210> 191
<211> 431
<212> PRT
<213> Homo sapiens

<220>
<223> u-plasminogen activator (uPA)

<400> 191
Met Arg Ala Leu Leu Ala Arg Leu Leu Leu Cys Val Leu Val Val Ser
1 5 10 15
Asp Ser Lys Gly Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp
20 25 30
Cys Leu Asn Gly Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile
35 40 45
His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile
50 55 60
Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly
65 70 75 80
Lys Ala Ser Thr Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser
85 90 95
Ala Thr Val Leu Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu
100 105 110
Gln Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg
115 120 125
Arg Arg Pro Trp Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln
130 135 140
Glu Cys Met Val His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro
145 150 155 160
Pro Glu Glu Leu Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg
165 170 175
Phe Lys Ile Ile Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp
180 185 190
Phe Ala Ala Ile Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val
195 200 205
Cys Gly Gly Ser Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His
210 215 220
Cys Phe Ile Asp Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly
225 230 235 240
Arg Ser Arg Leu Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val
245 250 255
Glu Asn Leu Ile Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His
260 265 270
His Asn Asp Ile Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys
275 280 285
Ala Gln Pro Ser Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr
290 295 300
Asn Asp Pro Gln Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys
305 310 315 320
Glu Asn Ser Thr Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val
325 330 335
Val Lys Leu Ile Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly
340 345 350
Ser Glu Val Thr Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys
355 360 365

```
Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu
    370                 375                 380
Gln Gly Arg Met Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys
385                 390                 395                 400
Ala Leu Lys Asp Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu
                405                 410                 415
Pro Trp Ile Arg Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
            420                 425                 430
```

<210> 192
<211> 2653
<212> DNA
<213> Homo sapiens

<220>
<223> t-plasminogen activator (tPA) transcript variant 1

<400> 192

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atggccctgt ccactgagca tcctcccgcc acacagaaac ccgcccagcc ggggccaccg 60
accccacccc ctgcctggaa acttaaggag gccggagctg tggggagctc agagctgaga 120
tcctacagga gtccagggct ggagagaaaa cctctgcgag gaaagggaag gagcaagccg 180
tgaatttaag ggacgctgtg aagcaatcat ggatgcaatg aagagagggc tctgctgtgt 240
gctgctgctg tgtggagcag tcttcgtttc gcccagccag gaaatccatg cccgattcag 300
aagaggagcc agatcttacc aagtgatctg cagagatgaa aaaacgcaga tgatatacca 360
gcaacatcag tcatggctgc gccctgtgct cagaagcaac cgggtggaat attgctggtg 420
caacagtggc agggcacagt gccactcagt gcctgtcaaa agttgcagcg agccaaggtg 480
tttcaacggg ggcacctgcc agcaggccct gtacttctca gatttcgtgt gccagtgccc 540
cgaaggattt gctgggaagt gctgtgaaat agataccagg gccacgtgct acgaggacca 600
gggcatcagc tacaggggca cgtggagcac agcggagagt ggcgccgagt gcaccaactg 660
gaacagcagc gcgttggccc agaagcccta cagcgggcgg aggccagacg ccatcaggct 720
gggcctgggg aaccacaact actgcagaaa cccagatcga gactcaaagc cctggtgcta 780
cgtctttaag gcggggaagt acagctcaga gttctgcagc acccctgcct gctctgaggg 840
aaacagtgac tgctactttg ggaatgggtc agcctaccgt ggcacgcaca gcctcaccga 900
gtcgggtgcc tcctgcctcc cgtggaattc catgatcctg ataggcaagg tttacacagc 960
acagaacccc agtgcccagg cactgggcct gggcaaacat aattactgcc ggaatcctga 1020
tggggatgcc aagccctggt gccacgtgct gaagaaccgc aggctgacgt gggagtactg 1080
tgatgtgccc tcctgctcca cctgcggcct gagacagtac agccagcctc agtttcgcat 1140
caaaggaggg ctcttcgccg acatcgcctc ccacccctgg caggctgcca tctttgccaa 1200
gcacaggagg tcgcccggag agcggttcct gtgcgggggc atactcatca gctcctgctg 1260
gattctctct gccgcccact gcttccagga gaggtttccg ccccaccacc tgacggtgat 1320
cttgggcaga acataccggg tggtccctgg cgaggaggag cagaaatttg aagtcgaaaa 1380
atacattgtc cataaggaat tcgatgatga cacttacgac aatgacattg cgctgctgca 1440
gctgaaatcg gattcgtccc gctgtgccca ggagagcagc gtggtccgca ctgtgtgcct 1500
tcccccggcg gacctgcagc tgccggactg gacggagtgt gagctctccg gctacggcaa 1560
gcatgaggcc ttgtctcctt tctattcgga gcggctgaag gaggctcatg tcagactgta 1620
cccatccagc cgctgcacat cacaacattt acttaacaga acagtcaccg acaacatgct 1680
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cgattcggga ggccccctgg tgtgtctgaa cgatggccgc atgactttgg tgggcatcat 1800
cagctggggc ctgggctgtg gacagaagga tgtcccgggt gtgtacacca aggttaccaa 1860
ctacctagac tggattcgtg acaacatgcg accgtgacca ggaacacccg actcctcaaa 1920
agcaaatgag atcccgcctc ttcttcttca gaagacactg caaaggcgca gtgcttctct 1980
acagacttct ccagacccac cacaccgcag aagcgggacg agaccctaca ggagagggaa 2040
gagtgcattt tcccagatac ttcccatttt ggaagttttc aggacttggt ctgatttcag 2100
gatactctgt cagatgggaa gacatgaatg cacactagcc tctccaggaa tgcctcctcc 2160
ctgggcagaa agtggccatg ccaccctgtt ttcagctaaa gcccaacctc ctgacctgtc 2220
accgtgagca gctttggaaa caggaccaca aaaatgaaag catgtctcaa tagtaaaaga 2280
```

```
taacaagatc tttcaggaaa gacggattgc attagaaata gacagtatat ttatagtcac 2340
aagagcccag cagggcctca aagttggggc aggctggctg gcccgtcatg ttcctcaaaa 2400
gcacccttga cgtcaagtct ccttcccctt tccccactcc ctggctctca gaaggtattc 2460
cttttgtgta cagtgtgtaa agtgtaaatc ctttttcttt ataaacttta gagtagcatg 2520
agagaattgt atcatttgaa caactaggct tcagcatatt tatagcaatc catgttagtt 2580
tttactttct gttgccacaa ccctgtttta tactgtactt aataaattca gatatatttt 2640
tcacagtttt tcc                                                    2653
```

<210> 193
<211> 562
<212> PRT
<213> Homo sapiens

<220>
<223> t-plasminogen activator (tPA) isoform 1

<400> 193

```
Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 1               5                  10                  15
Ala Val Phe Val Ser Pro Ser Gln Glu Ile His Ala Arg Phe Arg Arg
            20                  25                  30
Gly Ala Arg Ser Tyr Gln Val Ile Cys Arg Asp Glu Lys Thr Gln Met
        35                  40                  45
Ile Tyr Gln Gln His Gln Ser Trp Leu Arg Pro Val Leu Arg Ser Asn
    50                  55                  60
Arg Val Glu Tyr Cys Trp Cys Asn Ser Gly Arg Ala Gln Cys His Ser
65                  70                  75                  80
Val Pro Val Lys Ser Cys Ser Glu Pro Arg Cys Phe Asn Gly Gly Thr
                85                  90                  95
Cys Gln Gln Ala Leu Tyr Phe Ser Asp Phe Val Cys Gln Cys Pro Glu
            100                 105                 110
Gly Phe Ala Gly Lys Cys Cys Glu Ile Asp Thr Arg Ala Thr Cys Tyr
        115                 120                 125
Glu Asp Gln Gly Ile Ser Tyr Arg Gly Thr Trp Ser Thr Ala Glu Ser
    130                 135                 140
Gly Ala Glu Cys Thr Asn Trp Asn Ser Ser Ala Leu Ala Gln Lys Pro
145                 150                 155                 160
Tyr Ser Gly Arg Arg Pro Asp Ala Ile Arg Leu Gly Leu Gly Asn His
                165                 170                 175
Asn Tyr Cys Arg Asn Pro Asp Arg Asp Ser Lys Pro Trp Cys Tyr Val
            180                 185                 190
Phe Lys Ala Gly Lys Tyr Ser Ser Glu Phe Cys Ser Thr Pro Ala Cys
        195                 200                 205
Ser Glu Gly Asn Ser Asp Cys Tyr Phe Gly Asn Gly Ser Ala Tyr Arg
    210                 215                 220
Gly Thr His Ser Leu Thr Glu Ser Gly Ala Ser Cys Leu Pro Trp Asn
225                 230                 235                 240
Ser Met Ile Leu Leu Ile Gly Lys Val Tyr Thr Ala Gln Asn Pro Ser Ala
                245                 250                 255
Gln Ala Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Gly
            260                 265                 270
Asp Ala Lys Pro Trp Cys His Val Leu Lys Asn Arg Arg Leu Thr Trp
        275                 280                 285
Glu Tyr Cys Asp Val Pro Ser Cys Ser Thr Cys Gly Leu Arg Gln Tyr
    290                 295                 300
Ser Gln Pro Gln Phe Arg Ile Lys Gly Gly Leu Phe Ala Asp Ile Ala
305                 310                 315                 320
```

```
Ser His Pro Trp Gln Ala Ala Ile Phe Ala Lys His Arg Arg Ser Pro
                325                 330                 335
Gly Glu Arg Phe Leu Cys Gly Gly Ile Leu Ile Ser Ser Cys Trp Ile
            340                 345                 350
Leu Ser Ala Ala His Cys Phe Gln Glu Arg Phe Pro Pro His His Leu
        355                 360                 365
Thr Val Ile Leu Gly Arg Thr Tyr Arg Val Val Pro Gly Glu Glu Glu
    370                 375                 380
Gln Lys Phe Glu Val Glu Lys Tyr Ile Val His Lys Glu Phe Asp Asp
385                 390                 395                 400
Asp Thr Tyr Asp Asn Asp Ile Ala Leu Leu Gln Leu Lys Ser Asp Ser
                405                 410                 415
Ser Arg Cys Ala Gln Glu Ser Ser Val Val Arg Thr Val Cys Leu Pro
            420                 425                 430
Pro Ala Asp Leu Gln Leu Pro Asp Trp Thr Glu Cys Glu Leu Ser Gly
        435                 440                 445
Tyr Gly Lys His Glu Ala Leu Ser Pro Phe Tyr Ser Glu Arg Leu Lys
    450                 455                 460
Glu Ala His Val Arg Leu Tyr Pro Ser Ser Arg Cys Thr Ser Gln His
465                 470                 475                 480
Leu Leu Asn Arg Thr Val Thr Asp Asn Met Leu Cys Ala Gly Asp Thr
                485                 490                 495
Arg Ser Gly Gly Pro Gln Ala Asn Leu His Asp Ala Cys Gln Gly Asp
            500                 505                 510
Ser Gly Gly Pro Leu Val Cys Leu Asn Asp Gly Arg Met Thr Leu Val
        515                 520                 525
Gly Ile Ile Ser Trp Gly Leu Gly Cys Gly Gln Lys Asp Val Pro Gly
    530                 535                 540
Val Tyr Thr Lys Val Thr Asn Tyr Leu Asp Trp Ile Arg Asp Asn Met
545                 550                 555                 560
Arg Pro
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<210> 194
<211> 2160
<212> DNA
<213> Homo sapiens

<220>
<223> t-plasminogen activator (tPA) transcript variant 2

<400> 194

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atggccctgt ccactgagca tcctcccgcc acacagaaac ccgcccagcc ggggccaccg 60
accccacccc ctgcctggaa acttaaggag gccggagctg tggggagctc agagctgaga 120
tcctacagga gtccagggct ggagagaaaa cctctgcgag gaaagggaag gagcaagccg 180
tgaatttaag ggacgctgtg aagcaatcat ggatgcaatg aagagagggc tctgctgtgt 240
gctgctgctg tgtggagcag tcttcgtttc gcccagccag gaaatccatg cccgattcag 300
aagaggagcc agatcttacc aagtgatctg cagagatgaa aaaacgcaga tgatatacca 360
gcaacatcag tcatggctgc gccctgtgct cagaagcaac cgggtggaat attgctggtg 420
caacagtggc agggcacagt gccactcagt gcctgtcaaa agttgcagcg agccaaggtg 480
tttcaacggg ggcacctgcc agcaggccct gtacttctca gatttcgtgt gccagtgccc 540
cgaaggattt gctgggaagt gctgtgaaat agataccagg gccacgtgct acgaggacca 600
gggcatcagc tacaggggca cgtggagcac agcggagagt ggcgccgagt gcaccaactg 660
gaacagcagc gcgttggccc agaagcccta cagcgggcgg aggccagacg ccatcaggct 720
gggcctgggg aaccacaact actgcagaaa cccagatcga gactcaaagc cctggtgcta 780
cgtctttaag gcggggaagt acagctcaga gttctgcagc acccctgcct gctctgaggg 840
```

```
aaacagtgac tgctactttg ggaatgggtc agcctaccgt ggcacgcaca gcctcaccga 900
gtcgggtgcc tcctgcctcc cgtggaattc catgatcctg ataggcaagg tttacacagc 960
acagaacccc agtgcccagg cactgggcct gggcaaacat aattactgcc ggactggacg 1020
gagtgtgagc tctccggcta cggcaagcat gaggccttgt ctcctttcta ttcggagcgg 1080
ctgaaggagg ctcatgtcag actgtaccca tccagccgct gcacatcaca acatttactt 1140
aacagaacag tcaccgacaa catgctgtgt gctggagaca ctcggagcgg cgggccccag 1200
gcaaacttgc acgacgcctg ccagggcgat tcgggaggcc ccctggtgtg tctgaacgat 1260
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ccgggtgtgt acaccaaggt taccaactac ctagactgga ttcgtgacaa catgcgaccg 1380
tgaccaggaa cacccgactc ctcaaaagca aatgagatcc cgcctcttct tcttcagaag 1440
acactgcaaa ggcgcagtgc ttctctacag acttctccag acccaccaca ccgcagaagc 1500
gggacgagac cctacaggag agggaagagt gcattttccc agatacttcc cattttggaa 1560
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ctagcctctc caggaatgcc tcctccctgg gcagaaagtg gccatgccac cctgttttca 1680
gctaaagccc aacctcctga cctgtcaccg tgagcagctt tggaaacagg accacaaaaa 1740
tgaaagcatg tctcaatagt aaaagataac aagatctttc aggaaagacg gattgcatta 1800
gaaatagaca gtatatttat agtcacaaga gcccagcagg gcctcaaagt tggggcaggc 1860
tggctggccc gtcatgttcc tcaaaagcac ccttgacgtc aagtctcctt ccccttccc 1920
cactccctgg ctctcagaag gtattccttt tgtgtacagt gtgtaaagtg taaatccttt 1980
ttctttataa actttagagt agcatgagag aattgtatca tttgaacaac taggcttcag 2040
catatttata gcaatccatg ttagttttta ctttctgttg ccacaaccct gttttatact 2100
gtacttaata aattcagata tatttttcac agtttttcca aaaaaaaaaa aaaaaaaaaa 2160
```

<210> 195
<211> 291
<212> PRT
<213> Homo sapiens

<220>
<223> t-plasminogen activator (tPA) isoform 2

<400> 195

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Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 1               5                  10                  15
Ala Val Phe Val Ser Pro Ser Gln Glu Ile His Ala Arg Phe Arg Arg
            20                  25                  30
Gly Ala Arg Ser Tyr Gln Val Ile Cys Arg Asp Glu Lys Thr Gln Met
        35                  40                  45
Ile Tyr Gln Gln His Gln Ser Trp Leu Arg Pro Val Leu Arg Ser Asn
    50                  55                  60
Arg Val Glu Tyr Cys Trp Cys Asn Ser Gly Arg Ala Gln Cys His Ser
65                  70                  75                  80
Val Pro Val Lys Ser Cys Ser Glu Pro Arg Cys Phe Asn Gly Gly Thr
                85                  90                  95
Cys Gln Gln Ala Leu Tyr Phe Ser Asp Phe Val Cys Gln Cys Pro Glu
            100                 105                 110
Gly Phe Ala Gly Lys Cys Cys Glu Ile Asp Thr Arg Ala Thr Cys Tyr
        115                 120                 125
Glu Asp Gln Gly Ile Ser Tyr Arg Gly Thr Trp Ser Thr Ala Glu Ser
    130                 135                 140
Gly Ala Glu Cys Thr Asn Trp Asn Ser Ser Ala Leu Ala Gln Lys Pro
145                 150                 155                 160
Tyr Ser Gly Arg Arg Pro Asp Ala Ile Arg Leu Gly Leu Gly Asn His
                165                 170                 175
Asn Tyr Cys Arg Asn Pro Asp Arg Asp Ser Lys Pro Trp Cys Tyr Val
            180                 185                 190
```

```
Phe Lys Ala Gly Lys Tyr Ser Ser Glu Phe Cys Ser Thr Pro Ala Cys
        195                 200                 205
Ser Glu Gly Asn Ser Asp Cys Tyr Phe Gly Asn Gly Ser Ala Tyr Arg
    210                 215                 220
Gly Thr His Ser Leu Thr Glu Ser Gly Ala Ser Cys Leu Pro Trp Asn
225                 230                 235                 240
Ser Met Ile Leu Ile Gly Lys Val Tyr Thr Ala Gln Asn Pro Ser Ala
                245                 250                 255
Gln Ala Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Thr Gly Arg Ser
            260                 265                 270
Val Ser Ser Pro Ala Thr Ala Ser Met Arg Pro Cys Leu Leu Ser Ile
        275                 280                 285
Arg Ser Gly
    290
```

<210> 196
<211> 2534
<212> DNA
<213> Homo sapiens

<220>
<223> t-plasminogen activator (tPA) transcript variant 3

<400> 196

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atggccctgt ccactgagca tcctcccgcc acacagaaac ccgcccagcc ggggccaccg 60
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tcctacagga gtccagggct ggagagaaaa cctctgcgag gaaagggaag gagcaagccg 180
tgaatttaag ggacgctgtg aagcaatcat ggatgcaatg aagagagggc tctgctgtgt 240
gctgctgctg tgtggagcag tcttcgtttc gcccagccag gaaatccatg cccgattcag 300
aagaggagcc agatcttacc aaggttgcag cgagccaagg tgtttcaacg ggggcacctg 360
ccagcaggcc ctgtacttct cagatttcgt gtgccagtgc cccgaaggat ttgctgggaa 420
gtgctgtgaa atagatacca gggccacgtg ctacgaggac cagggcatca gctacagggg 480
cacgtggagc acagcggaga gtggcgccga gtgcaccaac tggaacagca gcgcgttggc 540
ccagaagccc tacagcgggc ggaggccaga cgccatcagg ctgggcctgg ggaaccacaa 600
ctactgcaga aacccagatc gagactcaaa gccctggtgc tacgtcttta aggcggggaa 660
gtacagctca gagttctgca gcacccctgc ctgctctgag ggaaacagtg actgctactt 720
tgggaatggg tcagcctacc gtggcacgca cagcctcacc gagtcgggtg cctcctgcct 780
cccgtggaat tccatgatcc tgataggcaa ggtttacaca gcacagaacc ccagtgccca 840
ggcactgggc ctgggcaaac ataattactg ccggaatcct gatggggatg ccaagccctg 900
gtgccacgtg ctgaagaacc gcaggctgac gtgggagtac tgtgatgtgc cctcctgctc 960
cacctgcggc ctgagacagt acagccagcc tcagtttcgc atcaaaggag ggctcttcgc 1020
cgacatcgcc tcccaccccc ggcaggctgc catctttgcc aagcacagga ggtcgcccgg 1080
agagcggttc ctgtgcgggg gcatactcat cagctcctgc tggattctct ctgccgccca 1140
ctgcttccag gagaggtttc cgccccacca cctgacggtg atcttgggca gaacataccg 1200
ggtggtccct ggcgaggagg agcagaaatt tgaagtcgaa aaatacattg tccataagga 1260
attcgatgat gacacttacg acaatgacat tgcgctgctg cagctgaaat cggattcgtc 1320
ccgctgtgcc caggagagca gcgtggtccg cactgtgtgc cttcccccgg cggacctgca 1380
gctgccggac tggacggagt gtgagctctc cggctacggc aagcatgagg ccttgtctcc 1440
tttctattcg gagcggctga aggaggctca tgtcagactg tacccatcca gccgctgcac 1500
atcacaacat ttacttaaca gaacagtcac cgacaacatg ctgtgtgctg gagacactcg 1560
gagcggcggg ccccaggcaa acttgcacga cgcctgccag ggcgattcgg gaggcccct 1620
ggtgtgtctg aacgatggcc gcatgacttt ggtgggcatc atcagctggg gcctgggctg 1680
tggacagaag gatgtcccgg gtgtgtacac caaggttacc aactacctag actggattcg 1740
tgacaacatg cgaccgtgac caggaacacc cgactcctca aaagcaaatg agatcccgcc 1800
tcttcttctt cagaagacac tgcaaaggcg cagtgcttct ctacagactt ctccagaccc 1860
accacaccgc agaagcggga cgagacccta caggagaggg aagagtgcat tttcccagat 1920
```

```
acttcccatt ttggaagttt tcaggacttg gtctgatttc aggatactct gtcagatggg 1980
aagacatgaa tgcacactag cctctccagg aatgcctcct ccctgggcag aaagtggcca 2040
tgccaccctg ttttcagcta aagcccaacc tcctgacctg tcaccgtgag cagctttgga 2100
aacaggacca caaaaatgaa agcatgtctc aatagtaaaa gataacaaga tctttcagga 2160
aagacggatt gcattagaaa tagacagtat atttatagtc acaagagccc agcagggcct 2220
caaagttggg gcaggctggc tggcccgtca tgttcctcaa aagcaccctt gacgtcaagt 2280
ctccttcccc tttccccact ccctggctct cagaaggtat tccttttgtg tacagtgtgt 2340
aaagtgtaaa tccttttttct ttataaactt tagagtagca tgagagaatt gtatcatttg 2400
aacaactagg cttcagcata tttatagcaa tccatgttag tttttacttt ctgttgccac 2460
aaccctgttt tatactgtac ttaataaatt cagatatatt tttcacagtt tttccaaaaa 2520
aaaaaaaaaa aaaa                                                   2534
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<210> 197
<211> 516
<212> PRT
<213> Homo sapiens

<220>
<223> t-plasminogen activator (tPA) isoform 3

<400> 197

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Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
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Ala Val Phe Val Ser Pro Ser Gln Glu Ile His Ala Arg Phe Arg Arg
            20                  25                  30
Gly Ala Arg Ser Tyr Gln Gly Cys Ser Glu Pro Arg Cys Phe Asn Gly
        35                  40                  45
Gly Thr Cys Gln Gln Ala Leu Tyr Phe Ser Asp Phe Val Cys Gln Cys
    50                  55                  60
Pro Glu Gly Phe Ala Gly Lys Cys Cys Glu Ile Asp Thr Arg Ala Thr
65                  70                  75                  80
Cys Tyr Glu Asp Gln Gly Ile Ser Tyr Arg Gly Thr Trp Ser Thr Ala
                85                  90                  95
Glu Ser Gly Ala Glu Cys Thr Asn Trp Asn Ser Ser Ala Leu Ala Gln
            100                 105                 110
Lys Pro Tyr Ser Gly Arg Arg Pro Asp Ala Ile Arg Leu Gly Leu Gly
        115                 120                 125
Asn His Asn Tyr Cys Arg Asn Pro Asp Arg Asp Ser Lys Pro Trp Cys
    130                 135                 140
Tyr Val Phe Lys Ala Gly Lys Tyr Ser Ser Glu Phe Cys Ser Thr Pro
145                 150                 155                 160
Ala Cys Ser Glu Gly Asn Ser Asp Cys Tyr Phe Gly Asn Gly Ser Ala
                165                 170                 175
Tyr Arg Gly Thr His Ser Leu Thr Glu Ser Gly Ala Ser Cys Leu Pro
            180                 185                 190
Trp Asn Ser Met Ile Leu Ile Gly Lys Val Tyr Thr Ala Gln Asn Pro
        195                 200                 205
Ser Ala Gln Ala Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro
    210                 215                 220
Asp Gly Asp Ala Lys Pro Trp Cys His Val Leu Lys Asn Arg Arg Leu
225                 230                 235                 240
Thr Trp Glu Tyr Cys Asp Val Pro Ser Cys Ser Thr Cys Gly Leu Arg
                245                 250                 255
Gln Tyr Ser Gln Pro Gln Phe Arg Ile Lys Gly Gly Leu Phe Ala Asp
            260                 265                 270
Ile Ala Ser His Pro Trp Gln Ala Ala Ile Phe Ala Lys His Arg Arg
        275                 280                 285
```

```
Ser Pro Gly Glu Arg Phe Leu Cys Gly Gly Ile Leu Ile Ser Ser Cys
    290                 295                 300
Trp Ile Leu Ser Ala Ala His Cys Phe Gln Glu Arg Phe Pro Pro His
305                 310                 315                 320
His Leu Thr Val Ile Leu Gly Arg Thr Tyr Arg Val Val Pro Gly Glu
                325                 330                 335
Glu Glu Gln Lys Phe Glu Val Glu Lys Tyr Ile Val His Lys Glu Phe
            340                 345                 350
Asp Asp Asp Thr Tyr Asp Asn Asp Ile Ala Leu Leu Gln Leu Lys Ser
        355                 360                 365
Asp Ser Ser Arg Cys Ala Gln Glu Ser Ser Val Val Arg Thr Val Cys
    370                 375                 380
Leu Pro Pro Ala Asp Leu Gln Leu Pro Asp Trp Thr Glu Cys Glu Leu
385                 390                 395                 400
Ser Gly Tyr Gly Lys His Glu Ala Leu Ser Pro Phe Tyr Ser Glu Arg
                405                 410                 415
Leu Lys Glu Ala His Val Arg Leu Tyr Pro Ser Ser Arg Cys Thr Ser
            420                 425                 430
Gln His Leu Leu Asn Arg Thr Val Thr Asp Asn Met Leu Cys Ala Gly
        435                 440                 445
Asp Thr Arg Ser Gly Gly Pro Gln Ala Asn Leu His Asp Ala Cys Gln
    450                 455                 460
Gly Asp Ser Gly Gly Pro Leu Val Cys Leu Asn Asp Gly Arg Met Thr
465                 470                 475                 480
Leu Val Gly Ile Ile Ser Trp Gly Leu Gly Cys Gly Gln Lys Asp Val
                485                 490                 495
Pro Gly Val Tyr Thr Lys Val Thr Asn Tyr Leu Asp Trp Ile Arg Asp
            500                 505                 510
Asn Met Arg Pro
        515
```

<210> 198
<211> 2732
<212> DNA
<213> Homo sapiens

<220>
<223> Plasmin

<400> 198

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cataaggaag tggttcttct acttctttta tttctgaaat caggtcaagg agagcctctg 120
gatgactatg tgaataccca gggggcttca ctgttcagtg tcactaagaa gcagctggga 180
gcaggaagta tagaagaatg tgcagcaaaa tgtgaggagg acgaagaatt cacctgcagg 240
gcattccaat atcacagtaa agagcaacaa tgtgtgataa tggctgaaaa caggaagtcc 300
tccataatca ttaggatgag agatgtagtt ttatttgaaa agaaagtgta tctctcagag 360
tgcaagactg ggaatggaaa gaactacaga gggacgatgt ccaaaacaaa aaatggcatc 420
acctgtcaaa aatggagttc cacttctccc cacagaccta gattctcacc tgctacacac 480
ccctcagagg gactggagga gaactactgc aggaatccag acaacgatcc gcaggggccc 540
tggtgctata ctactgatcc agaaaagaga tatgactact gcgacattct tgagtgtgaa 600
gaggaatgta tgcattgcag tggagaaaac tatgacggca aaatttccaa gaccatgtct 660
ggactggaat gccaggcctg ggactctcag agcccacacg ctcatggata cattccttcc 720
aaatttccaa acaagaacct gaagaagaat tactgtcgta accccgatag ggagctgcgg 780
ccttggtgtt tcaccaccga ccccaacaag cgctgggaac tttgcgacat cccccgctgc 840
acaacacctc caccatcttc tggtcccacc taccagtgtc tgaagggaac aggtgaaaac 900
tatcgcggga atgtggctgt taccgtttcc gggcacacct gtcagcactg gagtgcacag 960
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```
acccctcaca cacataacag gacaccagaa aacttcccct gcaaaaattt ggatgaaaac 1020
tactgccgca atcctgacgg aaaaagggcc ccatggtgcc atacaaccaa cagccaagtg 1080
cggtgggagt actgtaagat accgtcctgt gactcctccc cagtatccac ggaacaattg 1140
gctcccacag caccacctga gctaacccct gtggtccagg actgctacca tggtgatgga 1200
cagagctacc gaggcacatc ctccaccacc accacaggaa agaagtgtca gtcttggtca 1260
tctatgacac cacaccggca ccagaagacc ccagaaaact acccaaatgc tggcctgaca 1320
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agcgtcaggt gggagtactg caacctgaaa aaatgctcag gaacagaagc gagtgttgta 1440
gcacctccgc ctgttgtcct gcttccagat gtagagactc cttccgaaga agactgtatg 1500
tttgggaatg ggaaaggata ccgaggcaag agggcgacca ctgttactgg gacgccatgc 1560
caggactggg ctgcccagga gccccataga cacagcattt tcactccaga gacaaatcca 1620
cgggcgggtc tggaaaaaaa ttactgccgt aaccctgatg gtgatgtagg tggtccctgg 1680
tgctacacga caaatccaag aaaactttac gactactgtg atgtccctca gtgtgcggcc 1740
ccttcatttg attgtgggaa gcctcaagtg gagccgaaga aatgtcctgg aagggttgtg 1800
gggggtgtgg tggcccaccc acattcctgg ccctggcaag tcagtcttag aacaaggttt 1860
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tgcttggaga agtccccaag gccttcatcc tacaaggtca tcctgggtgc acaccaagaa 1980
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gaagacactg tccccagcta ccagctacgc caaacctcgg catttttttgt gttattttct 2640
gactgctgga ttctgtagta aggtgacata gctatgacat ttgttaaaaa taaactctgt 2700
acttaacttt gatttgagta aattttggtt tt                              2732
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<210> 199
<211> 810
<212> PRT
<213> Homo sapiens

<220>
<223> Plasmin

<400> 199

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Met Glu His Lys Glu Val Val Leu Leu Leu Leu Leu Phe Leu Lys Ser
 1               5                  10                  15
Gly Gln Gly Glu Pro Leu Asp Asp Tyr Val Asn Thr Gln Gly Ala Ser
            20                  25                  30
Leu Phe Ser Val Thr Lys Lys Gln Leu Gly Ala Gly Ser Ile Glu Glu
        35                  40                  45
Cys Ala Ala Lys Cys Glu Glu Asp Glu Glu Phe Thr Cys Arg Ala Phe
    50                  55                  60
Gln Tyr His Ser Lys Glu Gln Gln Cys Val Ile Met Ala Glu Asn Arg
65                  70                  75                  80
Lys Ser Ser Ile Ile Ile Arg Met Arg Asp Val Val Leu Phe Glu Lys
                85                  90                  95
Lys Val Tyr Leu Ser Glu Cys Lys Thr Gly Asn Gly Lys Asn Tyr Arg
            100                 105                 110
Gly Thr Met Ser Lys Thr Lys Asn Gly Ile Thr Cys Gln Lys Trp Ser
        115                 120                 125
Ser Thr Ser Pro His Arg Pro Arg Phe Ser Pro Ala Thr His Pro Ser
```

```
    130                 135                 140
Glu Gly Leu Glu Glu Asn Tyr Cys Arg Asn Pro Asp Asn Asp Pro Gln
145                 150                 155                 160
Gly Pro Trp Cys Tyr Thr Thr Asp Pro Glu Lys Arg Tyr Asp Tyr Cys
                165                 170                 175
Asp Ile Leu Glu Cys Glu Glu Glu Cys Met His Cys Ser Gly Glu Asn
            180                 185                 190
Tyr Asp Gly Lys Ile Ser Lys Thr Met Ser Gly Leu Glu Cys Gln Ala
        195                 200                 205
Trp Asp Ser Gln Ser Pro His Ala His Gly Tyr Ile Pro Ser Lys Phe
    210                 215                 220
Pro Asn Lys Asn Leu Lys Lys Asn Tyr Cys Arg Asn Pro Asp Arg Glu
225                 230                 235                 240
Leu Arg Pro Trp Cys Phe Thr Thr Asp Pro Asn Lys Arg Trp Glu Leu
                245                 250                 255
Cys Asp Ile Pro Arg Cys Thr Thr Pro Pro Pro Ser Ser Gly Pro Thr
            260                 265                 270
Tyr Gln Cys Leu Lys Gly Thr Gly Glu Asn Tyr Arg Gly Asn Val Ala
        275                 280                 285
Val Thr Val Ser Gly His Thr Cys Gln His Trp Ser Ala Gln Thr Pro
    290                 295                 300
His Thr His Asn Arg Thr Pro Glu Asn Phe Pro Cys Lys Asn Leu Asp
305                 310                 315                 320
Glu Asn Tyr Cys Arg Asn Pro Asp Gly Lys Arg Ala Pro Trp Cys His
                325                 330                 335
Thr Thr Asn Ser Gln Val Arg Trp Glu Tyr Cys Lys Ile Pro Ser Cys
            340                 345                 350
Asp Ser Ser Pro Val Ser Thr Glu Gln Leu Ala Pro Thr Ala Pro Pro
        355                 360                 365
Glu Leu Thr Pro Val Val Gln Asp Cys Tyr His Gly Asp Gly Gln Ser
    370                 375                 380
Tyr Arg Gly Thr Ser Ser Thr Thr Thr Thr Gly Lys Lys Cys Gln Ser
385                 390                 395                 400
Trp Ser Ser Met Thr Pro His Arg His Gln Lys Thr Pro Glu Asn Tyr
                405                 410                 415
Pro Asn Ala Gly Leu Thr Met Asn Tyr Cys Arg Asn Pro Asp Ala Asp
            420                 425                 430
Lys Gly Pro Trp Cys Phe Thr Thr Asp Pro Ser Val Arg Trp Glu Tyr
        435                 440                 445
Cys Asn Leu Lys Lys Cys Ser Gly Thr Glu Ala Ser Val Val Ala Pro
    450                 455                 460
Pro Pro Val Val Leu Leu Pro Asp Val Glu Thr Pro Ser Glu Glu Asp
465                 470                 475                 480
Cys Met Phe Gly Asn Gly Lys Gly Tyr Arg Gly Lys Arg Ala Thr Thr
                485                 490                 495
Val Thr Gly Thr Pro Cys Gln Asp Trp Ala Ala Gln Glu Pro His Arg
            500                 505                 510
His Ser Ile Phe Thr Pro Glu Thr Asn Pro Arg Ala Gly Leu Glu Lys
        515                 520                 525
Asn Tyr Cys Arg Asn Pro Asp Gly Asp Val Gly Gly Pro Trp Cys Tyr
    530                 535                 540
Thr Thr Asn Pro Arg Lys Leu Tyr Asp Tyr Cys Asp Val Pro Gln Cys
545                 550                 555                 560
Ala Ala Pro Ser Phe Asp Cys Gly Lys Pro Gln Val Glu Pro Lys Lys
                565                 570                 575
Cys Pro Gly Arg Val Val Gly Gly Cys Val Ala His Pro His Ser Trp
            580                 585                 590
```

```
Pro Trp Gln Val Ser Leu Arg Thr Arg Phe Gly Met His Phe Cys Gly
        595                 600                 605
Gly Thr Leu Ile Ser Pro Glu Trp Val Leu Thr Ala Ala His Cys Leu
    610                 615                 620
Glu Lys Ser Pro Arg Pro Ser Ser Tyr Lys Val Ile Leu Gly Ala His
625                 630                 635                 640
Gln Glu Val Asn Leu Glu Pro His Val Gln Glu Ile Glu Val Ser Arg
                645                 650                 655
Leu Phe Leu Glu Pro Thr Arg Lys Asp Ile Ala Leu Leu Lys Leu Ser
            660                 665                 670
Ser Pro Ala Val Ile Thr Asp Lys Val Ile Pro Ala Cys Leu Pro Ser
        675                 680                 685
Pro Asn Tyr Val Val Ala Asp Arg Thr Glu Cys Phe Ile Thr Gly Trp
    690                 695                 700
Gly Glu Thr Gln Gly Thr Phe Gly Ala Gly Leu Leu Lys Glu Ala Gln
705                 710                 715                 720
Leu Pro Val Ile Glu Asn Lys Val Cys Asn Arg Tyr Glu Phe Leu Asn
                725                 730                 735
Gly Arg Val Gln Ser Thr Glu Leu Cys Ala Gly His Leu Ala Gly Gly
            740                 745                 750
Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Phe Glu
        755                 760                 765
Lys Asp Lys Tyr Ile Leu Gln Gly Val Thr Ser Trp Gly Leu Gly Cys
    770                 775                 780
Ala Arg Pro Asn Lys Pro Gly Val Tyr Val Arg Val Ser Arg Phe Val
785                 790                 795                 800
Thr Trp Ile Glu Gly Val Met Arg Asn Asn
                805                 810
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<210> 200
<211> 1527
<212> DNA
<213> Homo sapiens

<220>
<223> Neurosin transcript variant A

<400> 200
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ctggctcgct ctctcctggg gacacagagg tcggcaggca gcacacagag ggacctacgg 180
gcagctgttc cttccccga ctcaagaatc cccggaggcc cggaggcctg cagcaggagc 240
ggccatgaag aagctgatgg tggtgctgag tctgattgct gcagcctggg cagaggagca 300
gaataagttg gtgcatggcg gaccctgcga caagacatct cacccctacc aagctgccct 360
ctacacctcg ggccacttgc tctgtggtgg ggtccttatc catccactgt gggtcctcac 420
agctgcccac tgcaaaaaac cgaatcttca ggtcttcctg gggaagcata accttcggca 480
aagggagagt tcccaggagc agagttctgt tgtccgggct gtgatccacc ctgactatga 540
tgccgccagc catgaccagg acatcatgct gttgcgcctg gcacgcccag ccaaactctc 600
tgaactcatc cagccccttc ccctggagag ggactgctca gccaacacca ccagctgcca 660
catcctgggc tggggcaaga cagcagatgg tgatttccct gacaccatcc agtgtgcata 720
catccacctg gtgtcccgtg aggagtgtga gcatgcctac cctggccaga tcacccagaa 780
catgttgtgt gctggggatg agaagtacgg gaaggattcc tgccagggtg attctggggg 840
tccgctggta tgtggagacc acctccgagg ccttgtgtca tggggtaaca tcccctgtgg 900
atcaaaggag aagccaggag tctacaccaa cgtctgcaga tacacgaact ggatccaaaa 960
aaccattcag gccaagtgac cctgacatgt gacatctacc tcccgaccta ccacccccact 1020
ggctggttcc agaacgtctc tcacctagac cttgcctccc ctcctctcct gcccagctct 1080

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gaccctgatg cttaataaac gcagcgacgt gagggtcctg attctccctg gttttacccc 1140
agctccatcc ttgcatcact ggggaggacg tgatgagtga ggacttgggt cctcggtctt 1200
acccccacca ctaagagaat acaggaaaat ccccttctagg catctcctct ccccaaccct 1260
tccacacgtt tgatttcttc ctgcagaggc ccagccacgt gtctggaatc ccagctccgc 1320
tgcttactgt cggtgtcccc ttgggatgta cctttcttca ctgcagattt ctcacctgta 1380
agatgaagat aaggatgata cagtctccat aaggcagtgg ctgttggaaa gatttaaggt 1440
ttcacaccta tgacatacat ggaatagcac ctgggccacc atgcactcaa taaagaatga 1500
attttattat gaaaaaaaaa aaaaaaa                                     1527

<210> 201
<211> 244
<212> PRT
<213> Homo sapiens

<220>
<223> Neurosin isoform A

<400> 201
Met Lys Lys Leu Met Val Val Leu Ser Leu Ile Ala Ala Ala Trp Ala
 1               5                  10                  15
Glu Glu Gln Asn Lys Leu Val His Gly Gly Pro Cys Asp Lys Thr Ser
            20                  25                  30
His Pro Tyr Gln Ala Ala Leu Tyr Thr Ser Gly His Leu Leu Cys Gly
        35                  40                  45
Gly Val Leu Ile His Pro Leu Trp Val Leu Thr Ala Ala His Cys Lys
    50                  55                  60
Lys Pro Asn Leu Gln Val Phe Leu Gly Lys His Asn Leu Arg Gln Arg
65                  70                  75                  80
Glu Ser Ser Gln Glu Gln Ser Ser Val Val Arg Ala Val Ile His Pro
                85                  90                  95
Asp Tyr Asp Ala Ala Ser His Asp Gln Asp Ile Met Leu Leu Arg Leu
            100                 105                 110
Ala Arg Pro Ala Lys Leu Ser Glu Leu Ile Gln Pro Leu Pro Leu Glu
        115                 120                 125
Arg Asp Cys Ser Ala Asn Thr Thr Ser Cys His Ile Leu Gly Trp Gly
    130                 135                 140
Lys Thr Ala Asp Gly Asp Phe Pro Asp Thr Ile Gln Cys Ala Tyr Ile
145                 150                 155                 160
His Leu Val Ser Arg Glu Glu Cys Glu His Ala Tyr Pro Gly Gln Ile
                165                 170                 175
Thr Gln Asn Met Leu Cys Ala Gly Asp Glu Lys Tyr Gly Lys Asp Ser
            180                 185                 190
Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Gly Asp His Leu Arg
        195                 200                 205
Gly Leu Val Ser Trp Gly Asn Ile Pro Cys Gly Ser Lys Glu Lys Pro
    210                 215                 220
Gly Val Tyr Thr Asn Val Cys Arg Tyr Thr Asn Trp Ile Gln Lys Thr
225                 230                 235                 240
Ile Gln Ala Lys


<210> 202
<211> 1527
<212> DNA
<213> Homo sapiens
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<220>
<223> Neurosin transcript variant B

<400> 202
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ggctctgcca ctgcatctga gtgtcttctc tcctcacggc tccccgcatt tctaactctt 180
tctgcctcct cgtctcaaag ctgttccttc ccccgactca agaatccccg gaggcccgga 240
ggcctgcagc aggagcggcc atgaagaagc tgatggtggt gctgagtctg attgctgcag 300
cctgggcaga ggagcagaat aagttggtgc atggcggacc ctgcgacaag acatctcacc 360
cctaccaagc tgccctctac acctcgggcc acttgctctg tggtggggtc cttatccatc 420
cactgtgggt cctcacagct gcccactgca aaaaaccgaa tcttcaggtc ttcctgggga 480

agcataacct tcggcaaagg gagagttccc aggagcagag ttctgttgtc cgggctgtga 540
tccaccctga ctatgatgcc gccagccatg accaggacat catgctgttg cgcctggcac 600
gcccagccaa actctctgaa ctcatccagc cccttccccc ggagagggac tgctcagcca 660
acaccaccag ctgccacatc ctgggctggg gcaagacagc agatggtgat ttccctgaca 720
ccatccagtg tgcatacatc cacctggtgt cccgtgagga gtgtgagcat gcctaccctg 780
gccagatcac ccagaacatg ttgtgtgctg gggatgagaa gtacgggaag gattcctgcc 840
agggtgattc tgggggtccg ctggtatgtg gagaccacct ccgaggcctt gtgtcatggg 900
gtaacatccc ctgtggatca aaggagaagc caggagtcta caccaacgtc tgcagataca 960
cgaactggat ccaaaaaacc attcaggcca agtgaccctg acatgtgaca tctacctccc 1020
gacctaccac cccactggct ggttccagaa cgtctctcac ctagaccttg cctcccctcc 1080
tctcctgccc agctctgacc ctgatgctta ataaacgcag cgacgtgagg gtcctgattc 1140
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ttgggtcctc ggtcttaccc ccaccactaa gagaatacag gaaaatccct tctaggcatc 1260
tcctctcccc aacccttcca cacgtttgat ttcttcctgc agaggcccag ccacgtgtct 1320
ggaatcccag ctccgctgct tactgtcggt gtccccttgg gatgtacctt tcttcactgc 1380
agatttctca cctgtaagat gaagataagg atgatacagt ctccataagg cagtggctgt 1440
tggaaagatt taaggtttca cacctatgac atacatggaa tagcacctgg gccaccatgc 1500
actcaataaa gaatgaattt tattatg 1527

<210> 203
<211> 244
<212> PRT
<213> Homo sapiens

<220>
<223> Neurosin isoform A preprotein

<400> 203
Met Lys Lys Leu Met Val Val Leu Ser Leu Ile Ala Ala Ala Trp Ala
 1   5   10   15
Glu Glu Gln Asn Lys Leu Val His Gly Gly Pro Cys Asp Lys Thr Ser
            20   25   30
His Pro Tyr Gln Ala Ala Leu Tyr Thr Ser Gly His Leu Leu Cys Gly
        35   40   45
Gly Val Leu Ile His Pro Leu Trp Val Leu Thr Ala Ala His Cys Lys
    50   55   60
Lys Pro Asn Leu Gln Val Phe Leu Gly Lys His Asn Leu Arg Gln Arg
65   70   75   80
Glu Ser Ser Gln Glu Gln Ser Ser Val Val Arg Ala Val Ile His Pro
                85   90   95
Asp Tyr Asp Ala Ala Ser His Asp Gln Asp Ile Met Leu Leu Arg Leu
            100   105   110
Ala Arg Pro Ala Lys Leu Ser Glu Leu Ile Gln Pro Leu Pro Leu Glu
        115   120   125

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Arg Asp Cys Ser Ala Asn Thr Thr Ser Cys His Ile Leu Gly Trp Gly
    130                 135                 140
Lys Thr Ala Asp Gly Asp Phe Pro Asp Thr Ile Gln Cys Ala Tyr Ile
145                 150                 155                 160
His Leu Val Ser Arg Glu Glu Cys Glu His Ala Tyr Pro Gly Gln Ile
                165                 170                 175
Thr Gln Asn Met Leu Cys Ala Gly Asp Glu Lys Tyr Gly Lys Asp Ser
            180                 185                 190
Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Gly Asp His Leu Arg
        195                 200                 205
Gly Leu Val Ser Trp Gly Asn Ile Pro Cys Gly Ser Lys Glu Lys Pro
    210                 215                 220
Gly Val Tyr Thr Asn Val Cys Arg Tyr Thr Asn Trp Ile Gln Lys Thr
225                 230                 235                 240
Ile Gln Ala Lys
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<210> 204
<211> 1495
<212> DNA
<213> Homo sapiens

<220>
<223> Neurosin transcript variant C

<400> 204
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ggctctgcca ctgcatctga gtgtcttctc tcctcacggc tccccgcatt tctaactctt 180
tctgcctcct cgtctcaaag ctgttccttc ccccgactca agaatccccg gaggcccgga 240
ggcctgcagc agcctgggca gaggagcaga ataagttggt gcatggcgga ccctgcgaca 300
agacatctca cccctaccaa gctgccctct acacctcggg ccacttgctc tgtggtgggg 360
tccttatcca tccactgtgg gtcctcacag ctgcccactg caaaaaaccg aatcttcagg 420
tcttcctggg gaagcataac cttcggcaaa gggagagttc ccaggagcag agttctgttg 480
tccgggctgt gatccaccct gactatgatg ccgccagcca tgaccaggac atcatgctgt 540
tgcgcctggc acgcccagcc aaactctctg aactcatcca gccccttccc ctggagaggg 600
actgctcagc caacaccacc agctgccaca tcctgggctg gggcaagaca gcagatggtg 660
atttccctga caccatccag tgtgcataca tccacctggt gtcccgtgag gagtgtgagc 720
atgcctaccc tggccagatc acccagaaca tgttgtgtgc tggggatgag aagtacggga 780
aggattcctg ccagggtgat tctgggggtc cgctggtatg tggagaccac ctccgaggcc 840
ttgtgtcatg gggtaacatc ccctgtggat caaaggagaa gccaggagtc tacaccaacg 900
tctgcagata cacgaactgg atccaaaaaa ccattcaggc caagtgaccc tgacatgtga 960
catctacctc ccgacctacc accccactgg ctggttccag aacgtctctc acctagacct 1020
tgcctccccc cctctcctgc ccagctctga ccctgatgct taataaacgc agcgacgtga 1080
gggtcctgat tctccctggt tttaccccag ctccatcctt gcatcactgg ggaggacgtg 1140
atgagtgagg acttgggtcc tcggtcttac ccccaccact aagagaatac aggaaaatcc 1200
cttctaggca tctcctctcc ccaacccttc cacacgtttg atttcttcct gcagaggccc 1260
agccacgtgt ctggaatccc agctccgctg cttactgtcg gtgtcccctt gggatgtacc 1320
tttcttcact gcagatttct cacctgtaag atgaagataa ggatgataca gtctccataa 1380
ggcagtggct gttggaaaga tttaaggttt cacacctatg acatacatgg aatagcacct 1440
gggccaccat gcactcaata aagaatgaat tttattatga aaaaaaaaaa aaaaa      1495
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<210> 205
<211> 137
<212> PRT
<213> Homo sapiens

<220>
<223> Neurosin isoform B

<400> 205
Met Leu Leu Arg Leu Ala Arg Pro Ala Lys Leu Ser Glu Leu Ile Gln
 1   5   10   15
Pro Leu Pro Leu Glu Arg Asp Cys Ser Ala Asn Thr Thr Ser Cys His
            20   25   30
Ile Leu Gly Trp Gly Lys Thr Ala Asp Gly Asp Phe Pro Asp Thr Ile
        35   40   45
Gln Cys Ala Tyr Ile His Leu Val Ser Arg Glu Glu Cys Glu His Ala
    50   55   60
Tyr Pro Gly Gln Ile Thr Gln Asn Met Leu Cys Ala Gly Asp Glu Lys
65   70   75   80
Tyr Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys
                85   90   95
Gly Asp His Leu Arg Gly Leu Val Ser Trp Gly Asn Ile Pro Cys Gly
            100   105   110
Ser Lys Glu Lys Pro Gly Val Tyr Thr Asn Val Cys Arg Tyr Thr Asn
        115   120   125
Trp Ile Gln Lys Thr Ile Gln Ala Lys
    130   135

<210> 206
<211> 1386
<212> DNA
<213> Homo sapiens

<220>
<223> Neurosin transcript variant D

<400> 206
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ggctctgcca ctgcatctga gtgtcttctc tcctcacggc tccccgcatt tctaactctt 180
tctgcctcct cgtctcaaag ctgttccttc ccccgactca agaatccccg gaggcccgga 240
ggcctgcagc aggagcggcc atgaagaagc tgatggtggt gctgagtctg attgctgcag 300
gaatcttcag gtcttcctgg ggaagcataa ccttcggcaa agggagagtt cccaggagca 360
gagttctgtt gtccgggctg tgatccaccc tgactatgat gccgccagcc atgaccagga 420
catcatgctg ttgcgcctgg cacgcccagc caaactctct gaactcatcc agccccttcc 480
cctggagagg gactgctcag ccaacaccac cagctgccac atcctgggct ggggcaagac 540
agcagatggt gatttccctg acaccatcca gtgtgcatac atccacctgg tgtcccgtga 600
ggagtgtgag catgcctacc ctggccagat cacccagaac atgttgtgtg ctggggatga 660
gaagtacggg aaggattcct gccagggtga ttctgggggt ccgctggtat gtggagacca 720
cctccgaggc cttgtgtcat ggggtaacat cccctgtgga tcaaaggaga agccaggagt 780
ctacaccaac gtctgcagat acacgaactg gatccaaaaa accattcagg ccaagtgacc 840
ctgacatgtg acatctacct cccgacctac caccccactg gctggttcca gaacgtctct 900
cacctagacc ttgcctcccc tcctctcctg cccagctctg accctgatgc ttaataaacg 960
cagcgacgtg agggtcctga ttctccctgg ttttacccca gctccatcct tgcatcactg 1020
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caggaaaatc ccttctaggc atctcctctc cccaaccctt ccacacgttt gatttcttcc 1140
tgcagaggcc cagccacgtg tctggaatcc cagctccgct gcttactgtc ggtgtccccc 1200
tgggatgtac ctttcttcac tgcagatttc tcacctgtaa gatgaagata aggatgatac 1260
agtctccata aggcagtggc tgttggaaag atttaaggtt tcacacctat gacatacatg 1320
gaatagcacc tgggccacca tgcactcaat aaagaatgaa ttttattatg aaaaaaaaaa 1380

aaaaaa 1386

<210> 207
<211> 40
<212> PRT
<213> Homo sapiens

<220>
<223> Neurosin isoform C

<400> 207
Met Lys Lys Leu Met Val Val Leu Ser Leu Ile Ala Ala Gly Ile Phe
1 5 10 15
Arg Ser Ser Trp Gly Ser Ile Thr Phe Gly Lys Gly Arg Val Pro Arg
20 25 30
Ser Arg Val Leu Leu Ser Gly Leu
35 40

<210> 208
<211> 3351
<212> DNA
<213> Homo sapiens

<220>
<223> Neurotrypsin

<400> 208
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gcttcgtgct agccctgatg ttaggggcgc tccccgaagt ggtcggcttt gattctgtcc 120
tcaatgattc cctccaccac agccaccgcc attcgccccc tgcgggtccg cactaccccc 180
attaccttcc cacccagcag cggcccccga cgacgcgtcc gccgccgcct ctcccgcgct 240
tcccgcgccc cccgcgggcg ctccctgccc agcgcccgca cgccctccag gccgggcaca 300
cgccccggcc gcacccctgg ggctgccccg ccggcgagcc atgggtcagc gtgacggact 360
tcggcgcccc gtgtctgcgg tgggcggagg tgccaccctt cctggagcgg tcgcccccag 420
cgagctgggc tcagctgcga ggacagcgcc acaacttttg tcggagcccc gacggcgcgg 480
gcagaccctg gtgtttctac ggagacgccc gtggcaaggt ggactggggc tactgcgact 540
gcagacacgg atcagtacga cttcgtggcg gcaaaaatga gtttgaaggc acagtggaag 600
tatatgcaag tggagtttgg ggcactgtct gtagcagcca ctgggatgat tctgatgcat 660
cagtcatttg tcaccagctg cagctgggag gaaaaggaat agcaaaacaa accccgtttt 720
ctggactggg ccttattccc atttattgga gcaatgtccg ttgccgagga gatgaagaaa 780
atatactgct ttgtgaaaaa gacatctggc agggtggggt gtgtcctcag aagatggcag 840
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gcagcagtgt gcatgaaggc cgggtggagc tctaccatgc tggccagtgg ggaaccgttt 960
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atgaagtacg ctgcactggg aatgagcttt caattgagca gtgtccaaag agctcctggg 1140
gagagcataa ctgtggccat aaagaagatg ctggagtgtc ctgtacccct ctaacagatg 1200
gggtcatcag acttgcaggt gggaaaggca gccatgaggg tcgcttggag gtatattaca 1260
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cagggcccat atggttggat gacgtcagct gctcaggaaa ggaaaccaga tttcttcagt 1440
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gctaccctgg cggcgaggga cacaggctct ctctgggttt tcctgtcaga ctgatggatg 1560
gagaaaataa gaaagaagga cgagtggagg tttttatcaa tggccagtgg ggaacaatct 1620
gtgatgatgg atggactgat aaggatgcag ctgtgatctg tcgtcagctt ggctacaagg 1680
gtcctgccag agcaagaacc atggcttact ttggagaagg aaaaggaccc atccatgtgg 1740

ataatgtgaa gtgcacagga aatgagaggt ccttggctga ctgtatcaag caagatattg 1800
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aagaaattgg agttcaacag attgtgattc atcgggagta tcgacccgac cgcagtgatt 2220
atgacatagc cctggttaga ttacaaggac cagaagagca atgtgccaga ttcagcagcc 2280
atgttttgcc agcctgttta ccactctgga gagagaggcc acagaaaaca gcatccaact 2340
gttacataac aggatggggt gacacaggac gagcctattc aagaacacta caacaagcag 2400
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gaatgctttg tgctggaaac ctccatgaac acaaacgcgt ggacagctgc cagggagaca 2520
gcggaggacc actcatgtgt gaacggcccg gagagagctg ggtggtgtat ggggtgacct 2580
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aacccctttt aattgaatca gtggtgtctg aaatcatatt aaatacccac atttgacata 3060
aatgcggtac cctttactac actcatgagt ggcatattta tgcttaggtc ttttcaaaag 3120
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aagaattcca ctataaactt ttaggcctga ataggagtag taaagcctca aggacatctg 3240
cctgtcacaa tatattctca aagtgatctg atatttggaa acaagtatcc ttgttgagta 3300
ccaagtgcta cagaaaccat aagataaaaa tactttctac ctacagcgtg c 3351

<210> 209
<211> 875
<212> PRT
<213> Homo sapiens

<220>
<223> Neurotrypsin

<400> 209
Met Thr Leu Ala Arg Phe Val Leu Ala Leu Met Leu Gly Ala Leu Pro
1 5 10 15
Glu Val Val Gly Phe Asp Ser Val Leu Asn Asp Ser Leu His His Ser
20 25 30
His Arg His Ser Pro Pro Ala Gly Pro His Tyr Pro Tyr Tyr Leu Pro
35 40 45
Thr Gln Gln Arg Pro Pro Thr Thr Arg Pro Pro Pro Pro Leu Pro Arg
50 55 60
Phe Pro Arg Pro Pro Arg Ala Leu Pro Ala Gln Arg Pro His Ala Leu
65 70 75 80
Gln Ala Gly His Thr Pro Arg Pro His Pro Trp Gly Cys Pro Ala Gly
85 90 95
Glu Pro Trp Val Ser Val Thr Asp Phe Gly Ala Pro Cys Leu Arg Trp
100 105 110
Ala Glu Val Pro Pro Phe Leu Glu Arg Ser Pro Pro Ala Ser Trp Ala
115 120 125
Gln Leu Arg Gly Gln Arg His Asn Phe Cys Arg Ser Pro Asp Gly Ala
130 135 140
Gly Arg Pro Trp Cys Phe Tyr Gly Asp Ala Arg Gly Lys Val Asp Trp
145 150 155 160

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Gly Tyr Cys Asp Cys Arg His Gly Ser Val Arg Leu Arg Gly Gly Lys
                165                 170                 175
Asn Glu Phe Glu Gly Thr Val Glu Val Tyr Ala Ser Gly Val Trp Gly
            180                 185                 190
Thr Val Cys Ser Ser His Trp Asp Asp Ser Asp Ala Ser Val Ile Cys
        195                 200                 205
His Gln Leu Gln Leu Gly Gly Lys Gly Ile Ala Lys Gln Thr Pro Phe
    210                 215                 220
Ser Gly Leu Gly Leu Ile Pro Ile Tyr Trp Ser Asn Val Arg Cys Arg
225                 230                 235                 240
Gly Asp Glu Glu Asn Ile Leu Leu Cys Glu Lys Asp Ile Trp Gln Gly
                245                 250                 255
Gly Val Cys Pro Gln Lys Met Ala Ala Ala Val Thr Cys Ser Phe Ser
            260                 265                 270
His Gly Pro Thr Phe Pro Ile Ile Arg Leu Ala Gly Gly Ser Ser Val
        275                 280                 285
His Glu Gly Arg Val Glu Leu Tyr His Ala Gly Gln Trp Gly Thr Val
    290                 295                 300
Cys Asp Asp Gln Trp Asp Asp Ala Asp Ala Glu Val Ile Cys Arg Gln
305                 310                 315                 320
Leu Gly Leu Ser Gly Ile Ala Lys Ala Trp His Gln Ala Tyr Phe Gly
                325                 330                 335
Glu Gly Ser Gly Pro Val Met Leu Asp Glu Val Arg Cys Thr Gly Asn
            340                 345                 350
Glu Leu Ser Ile Glu Gln Cys Pro Lys Ser Ser Trp Gly Glu His Asn
        355                 360                 365
Cys Gly His Lys Glu Asp Ala Gly Val Ser Cys Thr Pro Leu Thr Asp
    370                 375                 380
Gly Val Ile Arg Leu Ala Gly Gly Lys Gly Ser His Glu Gly Arg Leu
385                 390                 395                 400
Glu Val Tyr Tyr Arg Gly Gln Trp Gly Thr Val Cys Asp Asp Gly Trp
                405                 410                 415
Thr Glu Leu Asn Thr Tyr Val Val Cys Arg Gln Leu Gly Phe Lys Tyr
            420                 425                 430
Gly Lys Gln Ala Ser Ala Asn His Phe Glu Glu Ser Thr Gly Pro Ile
        435                 440                 445
Trp Leu Asp Asp Val Ser Cys Ser Gly Lys Glu Thr Arg Phe Leu Gln
    450                 455                 460
Cys Ser Arg Arg Gln Trp Gly Arg His Asp Cys Ser His Arg Glu Asp
465                 470                 475                 480
Val Ser Ile Ala Cys Tyr Pro Gly Gly Glu Gly His Arg Leu Ser Leu
                485                 490                 495
Gly Phe Pro Val Arg Leu Met Asp Gly Glu Asn Lys Lys Glu Gly Arg
            500                 505                 510
Val Glu Val Phe Ile Asn Gly Gln Trp Gly Thr Ile Cys Asp Asp Gly
        515                 520                 525
Trp Thr Asp Lys Asp Ala Ala Val Ile Cys Arg Gln Leu Gly Tyr Lys
    530                 535                 540
Gly Pro Ala Arg Ala Arg Thr Met Ala Tyr Phe Gly Glu Gly Lys Gly
545                 550                 555                 560
Pro Ile His Val Asp Asn Val Lys Cys Thr Gly Asn Glu Arg Ser Leu
                565                 570                 575
Ala Asp Cys Ile Lys Gln Asp Ile Gly Arg His Asn Cys Arg His Ser
            580                 585                 590
Glu Asp Ala Gly Val Ile Cys Asp Tyr Phe Gly Lys Lys Ala Ser Gly
        595                 600                 605
Asn Ser Asn Lys Glu Ser Leu Ser Ser Val Cys Gly Leu Arg Leu Leu
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    610                 615                 620
His Arg Arg Gln Lys Arg Ile Ile Gly Gly Lys Asn Ser Leu Arg Gly
625                 630                 635                 640
Gly Trp Pro Trp Gln Val Ser Leu Arg Leu Lys Ser Ser His Gly Asp
                645                 650                 655
Gly Arg Leu Leu Cys Gly Ala Thr Leu Leu Ser Ser Cys Trp Val Leu
            660                 665                 670
Thr Ala Ala His Cys Phe Lys Arg Tyr Gly Asn Ser Thr Arg Ser Tyr
        675                 680                 685
Ala Val Arg Val Gly Asp Tyr His Thr Leu Val Pro Glu Glu Phe Glu
    690                 695                 700
Glu Glu Ile Gly Val Gln Gln Ile Val Ile His Arg Glu Tyr Arg Pro
705                 710                 715                 720
Asp Arg Ser Asp Tyr Asp Ile Ala Leu Val Arg Leu Gln Gly Pro Glu
                725                 730                 735
Glu Gln Cys Ala Arg Phe Ser Ser His Val Leu Pro Ala Cys Leu Pro
            740                 745                 750
Leu Trp Arg Glu Arg Pro Gln Lys Thr Ala Ser Asn Cys Tyr Ile Thr
        755                 760                 765
Gly Trp Gly Asp Thr Gly Arg Ala Tyr Ser Arg Thr Leu Gln Gln Ala
    770                 775                 780
Ala Ile Pro Leu Leu Pro Lys Arg Phe Cys Glu Glu Arg Tyr Lys Gly
785                 790                 795                 800
Arg Phe Thr Gly Arg Met Leu Cys Ala Gly Asn Leu His Glu His Lys
                805                 810                 815
Arg Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Met Cys Glu
            820                 825                 830
Arg Pro Gly Glu Ser Trp Val Val Tyr Gly Val Thr Ser Trp Gly Tyr
        835                 840                 845
Gly Cys Gly Val Lys Asp Ser Pro Gly Val Tyr Thr Lys Val Ser Ala
    850                 855                 860
Phe Val Pro Trp Ile Lys Ser Val Thr Lys Leu
865                 870                 875
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<210> 210
<211> 1165
<212> DNA
<213> Homo sapiens

<220>
<223> tryptase beta 2 (I)

<400> 210
agaaggaaca gggagcggcc aggatgctga atctgctgct gctggcgctg cccgtcctgg 60
cgagccgcgc ctacgcggcc cctgccccag gccaggccct gcagcgagtg ggcatcgttg 120
ggggtcagga ggccccccagg agcaagtggc cctggcaggt gagcctgaga gtccgcgacc 180
gatactggat gcacttctgc gggggctccc tcatccaccc ccagtgggtg ctgaccgcag 240
cgcactgcgt gggaccggac gtcaaggatc tggccgccct cagggtgcaa ctgcgggagc 300
agcacctcta ctaccaggac cagctgctgc cggtcagcag gatcatcgtg cacccacagt 360
tctacaccgc ccagatcgga gcggacatcg ccctgctgga gctggaggag ccggtgaacg 420
tctccagcca cgtccacacg gtcaccctgc cccctgcctc agagaccttc cccccgggga 480
tgccgtgctg ggtcactggc tggggcgatg tggacaatga tgagcgcctc ccaccgccat 540
ttcctctgaa gcaggtgaag gtccccataa tggaaaacca catttgtgac gcaaaatacc 600
accttggcgc ctacacggga gacgacgtcc gcatcgtccg tgacgacatg ctgtgtgccg 660
ggaacacccg gagggactca tgccagggcg actccggagg gcccctggtg tgcaaggtga 720
atggcacctg gctgcaggcg ggcgtggtca gctggggcga gggctgtgcc cagcccaacc 780

```
ggcctggcat ctacacccgt gtcacctact acttggactg gatccaccac tatgtcccca 840
aaaagccgtg agtcaggcct ggggtgtcca cctgggtcac tggagagcca gcccctcctg 900
tccaaaacac cactgcttcc tacccaggtg gcgactgccc cccacacctt ccctgccccg 960
tcctgagtgc cccttcctgt cctaagcccc ctgctctctt ctgagccccc tcccctgtcc 1020
tgaggaccct tccccatcct gagccccctt ccctgtccta agcctgacgc ctgcaccggg 1080
ccctccggcc ctcccctgcc caggcagctg gtggtgggcg ctaatcctcc tgagtgctgg 1140
acctcattaa agtgcatgga aatca                                      1165
```

<210> 211
<211> 275
<212> PRT
<213> Homo sapiens

<220>
<223> tryptase beta 2 (I)

<400> 211

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Met Leu Asn Leu Leu Leu Leu Ala Leu Pro Val Leu Ala Ser Arg Ala
 1               5                  10                  15
Tyr Ala Ala Pro Ala Pro Gly Gln Ala Leu Gln Arg Val Gly Ile Val
            20                  25                  30
Gly Gly Gln Glu Ala Pro Arg Ser Lys Trp Pro Trp Gln Val Ser Leu
        35                  40                  45
Arg Val Arg Asp Arg Tyr Trp Met His Phe Cys Gly Gly Ser Leu Ile
    50                  55                  60
His Pro Gln Trp Val Leu Thr Ala Ala His Cys Val Gly Pro Asp Val
65                  70                  75                  80
Lys Asp Leu Ala Ala Leu Arg Val Gln Leu Arg Glu Gln His Leu Tyr
                85                  90                  95
Tyr Gln Asp Gln Leu Leu Pro Val Ser Arg Ile Ile Val His Pro Gln
            100                 105                 110
Phe Tyr Thr Ala Gln Ile Gly Ala Asp Ile Ala Leu Leu Glu Leu Glu
        115                 120                 125
Glu Pro Val Asn Val Ser Ser His Val His Thr Val Thr Leu Pro Pro
    130                 135                 140
Ala Ser Glu Thr Phe Pro Pro Gly Met Pro Cys Trp Val Thr Gly Trp
145                 150                 155                 160
Gly Asp Val Asp Asn Asp Glu Arg Leu Pro Pro Pro Phe Pro Leu Lys
                165                 170                 175
Gln Val Lys Val Pro Ile Met Glu Asn His Ile Cys Asp Ala Lys Tyr
            180                 185                 190
His Leu Gly Ala Tyr Thr Gly Asp Asp Val Arg Ile Val Arg Asp Asp
        195                 200                 205
Met Leu Cys Ala Gly Asn Thr Arg Arg Asp Ser Cys Gln Gly Asp Ser
    210                 215                 220
Gly Gly Pro Leu Val Cys Lys Val Asn Gly Thr Trp Leu Gln Ala Gly
225                 230                 235                 240
Val Val Ser Trp Gly Glu Gly Cys Ala Gln Pro Asn Arg Pro Gly Ile
                245                 250                 255
Tyr Thr Arg Val Thr Tyr Tyr Leu Asp Trp Ile His His Tyr Val Pro
            260                 265                 270
Lys Lys Pro
        275
```

<210> 212
<211> 1013

<212> DNA
<213> Homo sapiens

<220>
<223> Neuropsin transcript variant 1

<400> 212
gttcccagaa gctccccagg ctctagtgca ggaggagaag gaggaggagc aggaggtgga 60
gattcccagt taaaaggctc cagaatcgtg taccaggcag agaactgaag tactggggcc 120
tcctccactg ggtccgaatc agtaggtgac cccgcccctg gattctggaa gacctcacca 180
tgggacgccc ccgacctcgt gcggccaaga cgtggatgtt cctgctcttg ctgggggggag 240
cctgggcagg acactccagg gcacaggagg acaaggtgct ggggggtcat gagtgccaac 300
cccattcgca gccttggcag gcggccttgt tccagggcca gcaactactc tgtggcggtg 360
tccttgtagg tggcaactgg gtccttacag ctgcccactg taaaaaaccg aaatacacag 420
tacgcctggg agaccacagc ctacagaata aagatggccc agagcaagaa atacctgtgg 480
ttcagtccat cccacacccc tgctacaaca gcagcgatgt ggaggaccac aaccatgatc 540
tgatgcttct tcaactgcgt gaccaggcat ccctggggtc caaagtgaag cccatcagcc 600
tggcagatca ttgcacccag cctggccaga agtgcaccgt ctcaggctgg ggcactgtca 660
ccagtccccg agagaatttt cctgacactc tcaactgtgc agaagtaaaa atctttcccc 720
agaagaagtg tgaggatgct tacccggggc agatcacaga tggcatggtc tgtgcaggca 780
gcagcaaagg ggctgacacg tgccagggcg attctggagg ccccctggtg tgtgatggtg 840
cactccaggg catcacatcc tggggctcag acccctgtgg gaggtccgac aaacctggcg 900
tctataccaa catctgccgc tacctggact ggatcaagaa gatcataggc agcaagggct 960
gattctagga taagcactag atctccctta ataaactcac aactctctgg ttc 1013

<210> 213
<211> 260
<212> PRT
<213> Homo sapiens

<220>
<223> Neuropsin isoform 1

<400> 213
Met Gly Arg Pro Arg Pro Arg Ala Ala Lys Thr Trp Met Phe Leu Leu
 1   5   10   15
Leu Leu Gly Gly Ala Trp Ala Gly His Ser Arg Ala Gln Glu Asp Lys
            20   25   30
Val Leu Gly Gly His Glu Cys Gln Pro His Ser Gln Pro Trp Gln Ala
        35   40   45
Ala Leu Phe Gln Gly Gln Gln Leu Leu Cys Gly Gly Val Leu Val Gly
    50   55   60
Gly Asn Trp Val Leu Thr Ala Ala His Cys Lys Lys Pro Lys Tyr Thr
65   70   75   80
Val Arg Leu Gly Asp His Ser Leu Gln Asn Lys Asp Gly Pro Glu Gln
                85   90   95
Glu Ile Pro Val Val Gln Ser Ile Pro His Pro Cys Tyr Asn Ser Ser
            100   105   110
Asp Val Glu Asp His Asn His Asp Leu Met Leu Leu Gln Leu Arg Asp
        115   120   125
Gln Ala Ser Leu Gly Ser Lys Val Lys Pro Ile Ser Leu Ala Asp His
    130   135   140
Cys Thr Gln Pro Gly Gln Lys Cys Thr Val Ser Gly Trp Gly Thr Val
145   150   155   160
Thr Ser Pro Arg Glu Asn Phe Pro Asp Thr Leu Asn Cys Ala Glu Val
                165   170   175
Lys Ile Phe Pro Gln Lys Lys Cys Glu Asp Ala Tyr Pro Gly Gln Ile

```
            180                 185                 190
Thr Asp Gly Met Val Cys Ala Gly Ser Ser Lys Gly Ala Asp Thr Cys
        195                 200                 205
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Asp Gly Ala Leu Gln Gly
    210                 215                 220
Ile Thr Ser Trp Gly Ser Asp Pro Cys Gly Arg Ser Asp Lys Pro Gly
225                 230                 235                 240
Val Tyr Thr Asn Ile Cys Arg Tyr Leu Asp Trp Ile Lys Lys Ile Ile
                245                 250                 255
Gly Ser Lys Gly
            260
```

<210> 214
<211> 1148
<212> DNA
<213> Homo sapiens

<220>
<223> Neuropsin transcript variant 2

<400> 214
gttcccagaa gctccccagg ctctagtgca ggaggagaag gaggaggagc aggaggtgga 60
gattcccagt taaaaggctc cagaatcgtg taccaggcag agaactgaag tactggggcc 120
tcctccactg ggtccgaatc agtaggtgac cccgcccctg gattctggaa gacctcacca 180
tgggacgccc ccgacctcgt gcggccaaga cgtggatgtt cctgctcttg ctgggggggag 240
cctgggcagc gtgtggaagc ctggacctcc tcactaagtt gtatgcggag aacttgccgt 300
gtgtccattt gaacccacag tggccttccc agccctcgca ctgccccaga gggtggcgat 360
ccaaccctct ccctcctgct gcaggacact ccagggcaca ggaggacaag gtgctggggg 420
gtcatgagtg ccaaccccat tcgcagcctt ggcaggcggc cttgttccag ggccagcaac 480
tactctgtgg cggtgtcctt gtaggtggca actgggtcct tacagctgcc cactgtaaaa 540
aaccgaaata cacagtacgc ctgggagacc acagcctaca gaataaagat ggcccagagc 600
aagaaatacc tgtggttcag tccatcccac acccctgcta caacagcagc gatgtggagg 660
accacaacca tgatctgatg cttcttcaac tgcgtgacca ggcatccctg gggtccaaag 720
tgaagcccat cagcctggca gatcattgca cccagcctgg ccagaagtgc accgtctcag 780
gctggggcac tgtcaccagt ccccgagaga attttcctga cactctcaac tgtgcagaag 840
taaaaatctt tccccagaag aagtgtgagg atgcttaccc ggggcagatc acagatggca 900
tggtctgtgc aggcagcagc aaaggggctg acacgtgcca gggcgattct ggaggccccc 960
tggtgtgtga tggtgcactc cagggcatca catcctgggg ctcagacccc tgtgggaggt 1020
ccgacaaacc tggcgtctat accaacatct gccgctacct ggactggatc aagaagatca 1080
taggcagcaa gggctgattc taggataagc actagatctc ccttaataaa ctcacaactc 1140
tctggttc   1148

<210> 215
<211> 305
<212> PRT
<213> Homo sapiens

<220>
<223> Neuropsin isoform 2

<400> 215
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Met Gly Arg Pro Arg Pro Arg Ala Ala Lys Thr Trp Met Phe Leu Leu
 1               5                  10                  15
Leu Leu Gly Gly Ala Trp Ala Ala Cys Gly Ser Leu Asp Leu Leu Thr
            20                  25                  30
Lys Leu Tyr Ala Glu Asn Leu Pro Cys Val His Leu Asn Pro Gln Trp
```

```
        35                  40                  45
Pro Ser Gln Pro Ser His Cys Pro Arg Gly Trp Arg Ser Asn Pro Leu
    50                  55                  60
Pro Pro Ala Ala Gly His Ser Arg Ala Gln Glu Asp Lys Val Leu Gly
65                  70                  75                  80
Gly His Glu Cys Gln Pro His Ser Gln Pro Trp Gln Ala Ala Leu Phe
                85                  90                  95
Gln Gly Gln Gln Leu Leu Cys Gly Gly Val Leu Val Gly Gly Asn Trp
            100                 105                 110
Val Leu Thr Ala Ala His Cys Lys Lys Pro Lys Tyr Thr Val Arg Leu
        115                 120                 125
Gly Asp His Ser Leu Gln Asn Lys Asp Gly Pro Glu Gln Glu Ile Pro
    130                 135                 140
Val Val Gln Ser Ile Pro His Pro Cys Tyr Asn Ser Ser Asp Val Glu
145                 150                 155                 160
Asp His Asn His Asp Leu Met Leu Leu Gln Leu Arg Asp Gln Ala Ser
                165                 170                 175
Leu Gly Ser Lys Val Lys Pro Ile Ser Leu Ala Asp His Cys Thr Gln
            180                 185                 190
Pro Gly Gln Lys Cys Thr Val Ser Gly Trp Gly Thr Val Thr Ser Pro
        195                 200                 205
Arg Glu Asn Phe Pro Asp Thr Leu Asn Cys Ala Glu Val Lys Ile Phe
    210                 215                 220
Pro Gln Lys Lys Cys Glu Asp Ala Tyr Pro Gly Gln Ile Thr Asp Gly
225                 230                 235                 240
Met Val Cys Ala Gly Ser Ser Lys Gly Ala Asp Thr Cys Gln Gly Asp
                245                 250                 255
Ser Gly Gly Pro Leu Val Cys Asp Gly Ala Leu Gln Gly Ile Thr Ser
            260                 265                 270
Trp Gly Ser Asp Pro Cys Gly Arg Ser Asp Lys Pro Gly Val Tyr Thr
        275                 280                 285
Asn Ile Cys Arg Tyr Leu Asp Trp Ile Lys Lys Ile Ile Gly Ser Lys
    290                 295                 300
Gly
305
```

<210> 216
<211> 590
<212> DNA
<213> Homo sapiens

<220>
<223> Neuropsin transcript variant 3

<400> 216
gttcccagaa gctccccagg ctctagtgca ggaggagaag gaggaggagc aggaggtgga 60
gattcccagt taaaaggctc cagaatcgtg taccaggcag agaactgaag tactggggcc 120
tcctccactg ggtccgaatc agtaggtgac cccgcccctg gattctggaa gacctcacca 180
tgggacgccc ccgacctcgt gcggccaaga cgtggatgtt cctgctcttg ctgggggggag 240
cctgggcaga gaattttcct gacactctca actgtgcaga agtaaaaatc tttccccaga 300
agaagtgtga ggatgcttac ccggggcaga tcacagatgg catggtctgt gcaggcagca 360
gcaaaggggc tgacacgtgc cagggcgatt ctggaggccc cctggtgtgt gatggtgcac 420
tccagggcat cacatcctgg ggctcagacc cctgtgggag gtccgacaaa cctggcgtct 480
ataccaacat ctgccgctac ctggactgga tcaagaagat cataggcagc aagggctgat 540
tctaggataa gcactagatc tcccttaata aactcacaac tctctggttc 590

<210> 217
<211> 119
<212> PRT
<213> Homo sapiens

<220>
<223> Neuropsin isoform 3

<400> 217
Met Gly Arg Pro Arg Pro Arg Ala Ala Lys Thr Trp Met Phe Leu Leu
 1   5   10   15
Leu Leu Gly Gly Ala Trp Ala Glu Asn Phe Pro Asp Thr Leu Asn Cys
            20   25   30
Ala Glu Val Lys Ile Phe Pro Gln Lys Lys Cys Glu Asp Ala Tyr Pro
        35   40   45
Gly Gln Ile Thr Asp Gly Met Val Cys Ala Gly Ser Ser Lys Gly Ala
    50   55   60
Asp Thr Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Asp Gly Ala
65   70   75   80
Leu Gln Gly Ile Thr Ser Trp Gly Ser Asp Pro Cys Gly Arg Ser Asp
                85   90   95
Lys Pro Gly Val Tyr Thr Asn Ile Cys Arg Tyr Leu Asp Trp Ile Lys
            100   105   110
Lys Ile Ile Gly Ser Lys Gly
        115

<210> 218
<211> 456
<212> DNA
<213> Homo sapiens

<220>
<223> Neuropsin transcript variant 4

<400> 218
gttcccagaa gctccccagg ctctagtgca ggaggagaag gaggaggagc aggaggtgga 60
gattcccagt taaaaggctc cagaatcgtg taccaggcag agaactgaag tactggggcc 120
tcctccactg ggtccgaatc agtaggtgac cccgcccctg gattctggaa gacctcacca 180
tgggacgccc ccgacctcgt gcggccaaga cgtggatgtt cctgctcttg ctgggggggag 240
cctgggcagg gcgattctgg aggcccccctg gtgtgtgatg gtgcactcca gggcatcaca 300
tcctggggct cagacccctg tgggaggtcc gacaaacctg gcgtctatac caacatctgc 360
cgctacctgg actggatcaa gaagatcata ggcagcaagg gctgattcta ggataagcac 420
tagatctccc ttaataaact cacaactctc tggttc   456

<210> 219
<211> 32
<212> PRT
<213> Homo sapiens

<220>
<223> Neuropsin isoform 4

<400> 219
Met Gly Arg Pro Arg Pro Arg Ala Ala Lys Thr Trp Met Phe Leu Leu
 1   5   10   15
Leu Leu Gly Gly Ala Trp Ala Gly Arg Phe Trp Arg Pro Pro Gly Val

20 25 30

<210> 220
<211> 1580
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK10 transcript variant 1

<400> 220
catcctgcca cccctagcct tgctggggac gtgaaccctc tccccgcgcc tgggaagcct 60
tcttggcacc gggacccgga gaatccccac ggaagccagt tccaaaaggg atgaaaaggg 120
ggcgtttcgg gcactgggag aagcctgtat tccagggccc ctcccagagc aggaatctgg 180
gacccaggag tgccagcctc acccacgcag atcctggcca tgagagctcc gcacctccac 240
ctctccgccg cctctggcgc ccgggctctg gcgaagctgc tgccgctgct gatggcgcaa 300
ctctgggccg cagaggcggc gctgctcccc caaaacgaca cgcgcttgga ccccgaagcc 360
tatggctccc cgtgcgcgcg cggctcgcag ccctggcagg tctcgctctt caacggcctc 420
tcgttccact gcgcgggtgt cctggtggac cagagttggg tgctgacggc cgcgcactgc 480
ggaaacaagc cactgtgggc tcgagtaggg gatgaccacc tgctgcttct tcagggagag 540
cagctccgcc ggaccactcg ctctgttgtc catcccaagt accaccaggg ctcaggcccc 600
atcctgccaa ggcgaacgga tgagcacgat ctcatgttgc tgaagctggc caggcccgta 660
gtgctggggc cccgcgtccg ggccctgcag cttccctacc gctgtgctca gcccggagac 720
cagtgccagg ttgctggctg gggcaccacg gccgcccgga gagtgaagta caacaagggc 780
ctgacctgct ccagcatcac tatcctgagc cctaaagagt gtgaggtctt ctaccctggc 840
gtggtcacca acaacatgat atgtgctgga ctggaccggg gccaggaccc ttgccagagt 900
gactctggag gccccctggt ctgtgacgag accctccaag gcatcctctc gtggggtgtt 960
taccccctgtg gctctgccca gcatccagct gtctacaccc agatctgcaa atacatgtcc 1020
tggatcaata aagtcatacg ctccaactga tccagatgct acgctccagc tgatccagat 1080
gttatgctcc tgctgatcca gatgcccaga ggctccatcg tccatcctct tcctccccag 1140
tcggctgaac tctccccttg tctgcactgt tcaaacctct gccgccctcc acacctctaa 1200
acatctcccc tctcacctca ttcccccacc tatccccatt ctctgcctgt actgaagctg 1260
aaatgcagga agtggtggca aaggtttatt ccagagaagc caggaagccg gtcatcaccc 1320
agcctctgag agcagttact ggggtcaccc aacctgactt cctctgccac tccctgctgt 1380
gtgactttgg gcaagccaag tgccctctct gaacctcagt ttcctcatct gcaaaatggg 1440
aacaatgacg tgcctacctc ttagacatgt tgtgaggaga ctatgatata acatgtgtat 1500
gtaaatcttc atggtgattg tcatgtaagg cttaacacag tgggtggtga gttctgacta 1560
aaggttacct gttgtcgtga 1580

<210> 221
<211> 276
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK10

<400> 221

Met Arg Ala Pro His Leu His Leu Ser Ala Ala Ser Gly Ala Arg Ala
1 5 10 15
Leu Ala Lys Leu Leu Pro Leu Leu Met Ala Gln Leu Trp Ala Ala Glu
20 25 30
Ala Ala Leu Leu Pro Gln Asn Asp Thr Arg Leu Asp Pro Glu Ala Tyr
35 40 45
Gly Ser Pro Cys Ala Arg Gly Ser Gln Pro Trp Gln Val Ser Leu Phe

```
     50                  55                  60
Asn Gly Leu Ser Phe His Cys Ala Gly Val Leu Val Asp Gln Ser Trp
65                  70                  75                  80
Val Leu Thr Ala Ala His Cys Gly Asn Lys Pro Leu Trp Ala Arg Val
                85                  90                  95
Gly Asp Asp His Leu Leu Leu Leu Gln Gly Glu Gln Leu Arg Arg Thr
            100                 105                 110
Thr Arg Ser Val Val His Pro Lys Tyr His Gln Gly Ser Gly Pro Ile
        115                 120                 125
Leu Pro Arg Arg Thr Asp Glu His Asp Leu Met Leu Leu Lys Leu Ala
    130                 135                 140
Arg Pro Val Val Leu Gly Pro Arg Val Arg Ala Leu Gln Leu Pro Tyr
145                 150                 155                 160
Arg Cys Ala Gln Pro Gly Asp Gln Cys Gln Val Ala Gly Trp Gly Thr
                165                 170                 175
Thr Ala Ala Arg Arg Val Lys Tyr Asn Lys Gly Leu Thr Cys Ser Ser
            180                 185                 190
Ile Thr Ile Leu Ser Pro Lys Glu Cys Glu Val Phe Tyr Pro Gly Val
        195                 200                 205
Val Thr Asn Asn Met Ile Cys Ala Gly Leu Asp Arg Gly Gln Asp Pro
    210                 215                 220
Cys Gln Ser Asp Ser Gly Gly Pro Leu Val Cys Asp Glu Thr Leu Gln
225                 230                 235                 240
Gly Ile Leu Ser Trp Gly Val Tyr Pro Cys Gly Ser Ala Gln His Pro
                245                 250                 255
Ala Val Tyr Thr Gln Ile Cys Lys Tyr Met Ser Trp Ile Asn Lys Val
            260                 265                 270
Ile Arg Ser Asn
        275
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<210> 222
<211> 1443
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK10 transcript variant 2

<400> 222
accagcggca gaccacaggc agggcagagg cacgtctggg tcccctccct ccttcctatc 60
ggcgactccc aggatcctgg ccatgagagc tccgcacctc cacctctccg ccgcctctgg 120
cgcccgggct ctggcgaagc tgctgccgct gctgatggcg caactctggg ccgcagaggc 180
ggcgctgctc ccccaaaacg acacgcgctt ggaccccgaa gcctatggct ccccgtgcgc 240
gcgcggctcg cagccctggc aggtctcgct cttcaacggc ctctcgttcc actgcgcggg 300
tgtcctggtg gaccagagtt gggtgctgac ggccgcgcac tgcggaaaca agccactgtg 360
ggctcgagta ggggatgacc acctgctgct tcttcaggga gagcagctcc gccggaccac 420
tcgctctgtt gtccatccca agtaccacca gggctcaggc cccatcctgc caaggcgaac 480
ggatgagcac gatctcatgt tgctgaagct ggccaggccc gtagtgctgg ggccccgcgt 540
ccgggccctg cagcttccct accgctgtgc tcagcccgga gaccagtgcc aggttgctgg 600
ctggggcacc acggccgccc ggagagtgaa gtacaacaag ggcctgacct gctccagcat 660
cactatcctg agccctaaag agtgtgaggt cttctaccct ggcgtggtca ccaacaacat 720
gatatgtgct ggactggacc ggggccagga cccttgccag agtgactctg gaggcccccc 780
ggtctgtgac gagaccctcc aaggcatcct ctcgtggggt gtttacccct gtggctctgc 840
ccagcatcca gctgtctaca cccagatctg caaatacatg tcctggatca ataaagtcat 900
acgctccaac tgatccagat gctacgctcc agctgatcca gatgttatgc tcctgctgat 960
ccagatgccc agaggctcca tcgtccatcc tcttcctccc cagtcggctg aactctcccc 1020

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ttgtctgcac tgttcaaacc tctgccgccc tccacacctc taaacatctc ccctctcacc 1080
tcattccccc acctatcccc attctctgcc tgtactgaag ctgaaatgca ggaagtggtg 1140
gcaaaggttt attccagaga agccaggaag ccggtcatca cccagcctct gagagcagtt 1200
actggggtca cccaacctga cttcctctgc cactccctgc tgtgtgactt tgggcaagcc 1260
aagtgccctc tctgaacctc agtttcctca tctgcaaaat gggaacaatg acgtgcctac 1320
ctcttagaca tgttgtgagg agactatgat ataacatgtg tatgtaaatc ttcatggtga 1380
ttgtcatgta aggcttaaca cagtgggtgg tgagttctga ctaaaggtta cctgttgtcg 1440
tga                                                               1443
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<210> 223
<211> 276
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK10

<400> 223

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Met Arg Ala Pro His Leu His Leu Ser Ala Ala Ser Gly Ala Arg Ala
 1               5                  10                  15
Leu Ala Lys Leu Leu Pro Leu Leu Met Ala Gln Leu Trp Ala Ala Glu
            20                  25                  30
Ala Ala Leu Leu Pro Gln Asn Asp Thr Arg Leu Asp Pro Glu Ala Tyr
        35                  40                  45
Gly Ser Pro Cys Ala Arg Gly Ser Gln Pro Trp Gln Val Ser Leu Phe
    50                  55                  60
Asn Gly Leu Ser Phe His Cys Ala Gly Val Leu Val Asp Gln Ser Trp
65                  70                  75                  80
Val Leu Thr Ala Ala His Cys Gly Asn Lys Pro Leu Trp Ala Arg Val
                85                  90                  95
Gly Asp Asp His Leu Leu Leu Leu Gln Gly Glu Gln Leu Arg Arg Thr

            100                 105                 110
Thr Arg Ser Val Val His Pro Lys Tyr His Gln Gly Ser Gly Pro Ile
        115                 120                 125
Leu Pro Arg Arg Thr Asp Glu His Asp Leu Met Leu Leu Lys Leu Ala
    130                 135                 140
Arg Pro Val Val Leu Gly Pro Arg Val Arg Ala Leu Gln Leu Pro Tyr
145                 150                 155                 160
Arg Cys Ala Gln Pro Gly Asp Gln Cys Gln Val Ala Gly Trp Gly Thr
                165                 170                 175
Thr Ala Ala Arg Arg Val Lys Tyr Asn Lys Gly Leu Thr Cys Ser Ser
            180                 185                 190
Ile Thr Ile Leu Ser Pro Lys Glu Cys Glu Val Phe Tyr Pro Gly Val
        195                 200                 205
Val Thr Asn Asn Met Ile Cys Ala Gly Leu Asp Arg Gly Gln Asp Pro
    210                 215                 220
Cys Gln Ser Asp Ser Gly Gly Pro Leu Val Cys Asp Glu Thr Leu Gln
225                 230                 235                 240
Gly Ile Leu Ser Trp Gly Val Tyr Pro Cys Gly Ser Ala Gln His Pro
                245                 250                 255
Ala Val Tyr Thr Gln Ile Cys Lys Tyr Met Ser Trp Ile Asn Lys Val
            260                 265                 270
Ile Arg Ser Asn
        275
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<210> 224
<211> 3226
<212> DNA
<213> Homo sapiens

<220>
<223> Epitheliasin

<400> 224
cgcgagctaa gcaggaggcg gaggcggagg cggagggcga ggggcgggga gcgccgcctg 60
gagcgcggca ggtcatattg aacattccag atacctatca ttactcgatg ctgttgataa 120
cagcaagatg gctttgaact cagggtcacc accagctatt ggaccttact atgaaaacca 180
tggataccaa ccggaaaacc cctatcccgc acagcccact gtggtcccca ctgtctacga 240
ggtgcatccg gctcagtact acccgtcccc cgtgccccag tacgccccga gggtcctgac 300
gcaggcttcc aaccccgtcg tctgcacgca gcccaaatcc ccatccggga cagtgtgcac 360
ctcaaagact aagaaagcac tgtgcatcac cttgaccctg gggaccttcc tcgtgggagc 420
tgcgctggcc gctggcctac tctggaagtt catgggcagc aagtgctcca actctgggat 480
agagtgcgac tcctcaggta cctgcatcaa cccctctaac tggtgtgatg gcgtgtcaca 540
ctgccccggc ggggaggacg agaatcggtg tgttcgcctc tacggaccaa acttcatcct 600
tcagatgtac tcatctcaga ggaagtcctg gcaccctgtg tgccaagacg actggaacga 660
gaactacggg cgggcggcct gcagggacat gggctataag aataatttt actctagcca 720
aggaatagtg gatgacagcg gatccaccag ctttatgaaa ctgaacacaa gtgccggcaa 780
tgtcgatatc tataaaaaac tgtaccacag tgatgcctgt tcttcaaaag cagtggtttc 840
tttacgctgt atagcctgcg gggtcaactt gaactcaagc cgccagagca ggatcgtggg 900
cggtgagagc gcgctcccgg gggcctggcc ctggcaggtc agcctgcacg tccagaacgt 960
ccacgtgtgc ggaggctcca tcatcacccc cgagtggatc gtgacagccg cccactgcgt 1020
ggaaaaacct cttaacaatc catggcattg gacggcattt gcggggattt tgagacaatc 1080
tttcatgttc tatggagccg gataccaagt agaaaaagtg atttctcatc caaattatga 1140
ctccaagacc aagaacaatg acattgcgct gatgaagctg cagaagcctc tgactttcaa 1200
cgacctagtg aaaccagtgt gtctgcccaa cccaggcatg atgctgcagc cagaacagct 1260
ctgctggatt tccgggtggg gggccaccga ggagaaaggg aagacctcag aagtgctgaa 1320
cgctgccaag gtgcttctca ttgagacaca gagatgcaac agcagatatg tctatgacaa 1380
cctgatcaca ccagccatga tctgtgccgg cttcctgcag gggaacgtcg attcttgcca 1440
gggtgacagt ggagggcctc tggtcacttc gaagaacaat atctggtggc tgatagggga 1500
tacaagctgg ggttctggct gtgccaaagc ttacagacca ggagtgtacg ggaatgtgat 1560
ggtattcacg gactggattt atcgacaaat gagggcagac ggctaatcca catggtcttc 1620
gtccttgacg tcgttttaca agaaaacaat ggggctggtt ttgcttcccc gtgcatgatt 1680
tactcttaga gatgattcag aggtcacttc atttttatta aacagtgaac ttgtctggct 1740
ttggcactct ctgccattct gtgcaggctg cagtggctcc cctgcccagc ctgctctccc 1800
taacccctg tccgcaaggg gtgatggccg gctggttgtg ggcactggcg gtcaagtgtg 1860
gaggagaggg gtggaggctg ccccattgag atcttcctgc tgagtccttt ccaggggcca 1920
attttggatg agcatggagc tgtcacctct cagctgctgg atgacttgag atgaaaaagg 1980
agagacatgg aaagggagac agccaggtgg cacctgcagc ggctgccctc tggggccact 2040
tggtagtgtc cccagcctac ctctccacaa ggggattttg ctgatgggtt cttagagcct 2100
tagcagccct ggatggtggc cagaaataaa gggaccagcc cttcatgggt ggtgacgtgg 2160
tagtcacttg taaggggaac agaaacattt ttgttcttat ggggtgagaa tatagacagt 2220
gcccttggtg cgagggaagc aattgaaaag gaacttgccc tgagcactcc tggtgcaggt 2280
ctccacctgc acattgggtg gggctcctgg gagggagact cagccttcct cctcatcctc 2340
cctgaccctg ctcctagcac cctggagagt gcacatgccc cttggtcctg gcagggcgcc 2400
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gggaaatcaa ggatgctcag tttaaggtac actgtttcca tgttatgttt ctacacattg 2520
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actctttgaa actgtatcac ctttgccaag taagagtggt ggcctatttc agctgctttg 2640
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atggtggcgg cgaagaagag aaagatgtgt tttgttttgg actctctgtg gtcccttcca 2760
atgctgtggg tttccaacca ggggaagggt ccctttgca ttgccaagtg ccataaccat 2820
gagcactact ctaccatggt tctgcctcct ggccaagcag gctggtttgc aagaatgaaa 2880

tgaatgattc tacagctagg acttaacctt gaaatggaaa gtcttgcaat cccatttgca 2940
ggatccgtct gtgcacatgc ctctgtagag agcagcattc ccagggacct tggaaacagt 3000
tggcactgta aggtgcttgc tccccaagac acatcctaaa aggtgttgta atggtgaaaa 3060
cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca actgtttgtc ttttttttgta 3120
tctttttttaa actgtaaagt tcaattgtga aaatgaatat catgcaaata aattatgcga 3180
ttttttttttc aaagcaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa 3226

<210> 225
<211> 492
<212> PRT
<213> Homo sapiens

<220>
<223> Epitheliasin

<400> 225
Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
1 5 10 15
Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
20 25 30
Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
35 40 45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
50 55 60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
65 70 75 80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
85 90 95
Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys
100 105 110
Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
115 120 125
Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
130 135 140
Glu Asn Arg Cys Val Arg Leu Tyr Gly Pro Asn Phe Ile Leu Gln Met
145 150 155 160
Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp
165 170 175
Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn
180 185 190
Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser
195 200 205
Phe Met Lys Leu Asn Thr Ser Ala Gly Asn Val Asp Ile Tyr Lys Lys
210 215 220
Leu Tyr His Ser Asp Ala Cys Ser Ser Lys Ala Val Val Ser Leu Arg
225 230 235 240
Cys Ile Ala Cys Gly Val Asn Leu Asn Ser Ser Arg Gln Ser Arg Ile
245 250 255
Val Gly Gly Glu Ser Ala Leu Pro Gly Ala Trp Pro Trp Gln Val Ser
260 265 270
Leu His Val Gln Asn Val His Val Cys Gly Gly Ser Ile Ile Thr Pro
275 280 285
Glu Trp Ile Val Thr Ala Ala His Cys Val Glu Lys Pro Leu Asn Asn
290 295 300
Pro Trp His Trp Thr Ala Phe Ala Gly Ile Leu Arg Gln Ser Phe Met
305 310 315 320
Phe Tyr Gly Ala Gly Tyr Gln Val Glu Lys Val Ile Ser His Pro Asn

```
                325                 330                 335
Tyr Asp Ser Lys Thr Lys Asn Asn Asp Ile Ala Leu Met Lys Leu Gln
            340                 345                 350
Lys Pro Leu Thr Phe Asn Asp Leu Val Lys Pro Val Cys Leu Pro Asn
        355                 360                 365
Pro Gly Met Met Leu Gln Pro Glu Gln Leu Cys Trp Ile Ser Gly Trp
    370                 375                 380
Gly Ala Thr Glu Glu Lys Gly Lys Thr Ser Glu Val Leu Asn Ala Ala
385                 390                 395                 400
Lys Val Leu Leu Ile Glu Thr Gln Arg Cys Asn Ser Arg Tyr Val Tyr
                405                 410                 415
Asp Asn Leu Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly
            420                 425                 430
Asn Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser
        435                 440                 445
Lys Asn Asn Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly
    450                 455                 460
Cys Ala Lys Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe
465                 470                 475                 480
Thr Asp Trp Ile Tyr Arg Gln Met Arg Ala Asp Gly
                485                 490
```

<210> 226
<211> 1280
<212> DNA
<213> Homo sapiens

<220>
<223> Prostase

<400> 226

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ggatctctcg tctctggtag ctgcagccaa atcataaacg gcgaggactg cagcccgcac 120
tcgcagccct ggcaggcggc actggtcatg gaaaacgaat tgttctgctc gggcgtcctg 180
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg 240
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc 300
ctctccgtac ggcacccaga gtacaacaga cccttgctcg ctaacgacct catgctcatc 360
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag 420
tgccctaccg cggggaactc ttgcctcgtt tctggctggg gtctgctggc gaacggcaga 480
atgcctaccg tgctgcagtg cgtgaacgtg tcggtggtgt ctgaggaggt ctgcagtaag 540
ctctatgacc cgctgtacca ccccagcatg ttctgcgccg gcggagggca agaccagaag 600
gactcctgca acggtgactc tgggggggccc ctgatctgca acgggtactt gcagggcctt 660
gtgtctttcg gaaaagcccc gtgtggccaa gttggcgtgc caggtgtcta caccaacctc 720
tgcaaattca ctgagtggat agagaaaacc gtccaggcca gttaactctg gggactggga 780
acccatgaaa ttgaccccca aatacatcct gcggaaggaa ttcaggaata tctgttccca 840
gcccctcctc cctcaggccc aggagtccag gcccccagcc cctcctccct caaaccaagg 900
gtacagatcc ccagcccctc ctccctcaga cccaggagtc cagacccccc agcccctcct 960
ccctcagacc caggagtcca gcccctcctc cctcagaccc aggagtccag acccccccagc 1020
ccctcctccc tcagacccag gggtccaggc ccccaacccc tcctccctca gactcagagg 1080
tccaagcccc caacccctcc ttccccagac ccagaggtcc aggtcccagc ccctcctccc 1140
tcagacccag cggtccaatg ccacctagac tctccctgta cacagtgccc ccttgtggca 1200
cgttgaccca accttaccag ttggtttttc atttttgtc cctttccccc agatccagaa 1260
ataaagtcta agagaagcgc                                              1280
```

<210> 227
<211> 254

<212> PRT
<213> Homo sapiens

<220>
<223> Prostase

<400> 227

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Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile
 1               5                  10                  15
Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile
            20                  25                  30
Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
        35                  40                  45
Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
    50                  55                  60
Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
65                  70                  75                  80
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
                85                  90                  95
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
            100                 105                 110
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
        115                 120                 125
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
    130                 135                 140
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
145                 150                 155                 160
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
                165                 170                 175
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
            180                 185                 190
Ala Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly
        195                 200                 205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
    210                 215                 220
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
225                 230                 235                 240
Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
                245                 250
```

<210> 228
<211> 1391
<212> DNA
<213> Homo sapiens

<220>
<223> Brain serine proteinase 2

<400> 228
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ccagccatgg tggtttctgg agcgccccca gccctgggtg ggggctgtct cggcaccttc 120
acctccctgc tgctgctggc gtcgacagcc atcctcaatg cggccaggat acctgttccc 180
ccagcctgtg ggaagcccca gcagctgaac cgggttgtgg gcggcgagga cagcactgac 240
agcgagtggc cctggatcgt gagcatccag aagaatggga cccaccactg cgcaggttct 300
ctgctcacca gccgctgggt gatcactgct gcccactgtt tcaaggacaa cctgaacaaa 360

```
ccatacctgt tctctgtgct gctgggggcc tggcagctgg ggaaccctgg ctctcggtcc 420
cagaaggtgg gtgttgcctg ggtggagccc caccctgtgt attcctggaa ggaaggtgcc 480
tgtgcagaca ttgccctggt gcgtctcgag cgctccatac agttctcaga gcgggtcctg 540
cccatctgcc tacctgatgc ctctatccac ctccctccaa acacccactg ctggatctca 600
ggctggggga gcatccaaga tggagttccc ttgccccacc ctcagaccct gcagaagctg 660
aaggttccta tcatcgactc ggaagtctgc agccatctgt actggcgggg agcaggacag 720
ggacccatca ctgaggacat gctgtgtgcc ggctacttgg agggggagcg ggatgcttgt 780
ctgggcgact ccgggggccc cctcatgtgc caggtggacg gcgcctggct gctggccggc 840
atcatcagct ggggcgaggg ctgtgccgag cgcaacaggc ccggggtcta catcagcctc 900
tctgcgcacc gctcctgggt ggagaagatc gtgcaagggg tgcagctccg cgggcgcgct 960

caggggggtg gggccctcag ggcaccgagc cagggctctg gggccgccgc gcgctcctag 1020
ggcgcagcgg gacgcggggc tcggatctga aaggcggcca gatccacatc tggatctgga 1080
tctgcggcgg cctcgggcgg tttcccccgc cgtaaatagg ctcatctacc tctacctctg 1140
ggggcccgga cggctgctgc ggaaaggaaa ccccctcccc gacccgcccg acggcctcag 1200
gccccgcctc caaggcatca ggccccgccc aacggcctca tgtccccgcc cccacgactt 1260
ccggccccgc cccgggcccc agcgcttttg tgtatataaa tgttaatgat ttttataggt 1320
atttgtaacc ctgcccacat atcttattta ttcctccaat ttcaataaat tatttattct 1380
ccagtgaaaa a                                                      1391

<210> 229
<211> 317
<212> PRT
<213> Homo sapiens

<220>
<223> Brain serine proteinase 2

<400> 229
Met Val Val Ser Gly Ala Pro Pro Ala Leu Gly Gly Gly Cys Leu Gly
 1               5                  10                  15
Thr Phe Thr Ser Leu Leu Leu Leu Ala Ser Thr Ala Ile Leu Asn Ala
            20                  25                  30
Ala Arg Ile Pro Val Pro Pro Ala Cys Gly Lys Pro Gln Gln Leu Asn
        35                  40                  45
Arg Val Val Gly Gly Glu Asp Ser Thr Asp Ser Glu Trp Pro Trp Ile
    50                  55                  60
Val Ser Ile Gln Lys Asn Gly Thr His His Cys Ala Gly Ser Leu Leu
65                  70                  75                  80
Thr Ser Arg Trp Val Ile Thr Ala Ala His Cys Phe Lys Asp Asn Leu
                85                  90                  95
Asn Lys Pro Tyr Leu Phe Ser Val Leu Leu Gly Ala Trp Gln Leu Gly
            100                 105                 110
Asn Pro Gly Ser Arg Ser Gln Lys Val Gly Val Ala Trp Val Glu Pro
        115                 120                 125
His Pro Val Tyr Ser Trp Lys Glu Gly Ala Cys Ala Asp Ile Ala Leu
    130                 135                 140
Val Arg Leu Glu Arg Ser Ile Gln Phe Ser Glu Arg Val Leu Pro Ile
145                 150                 155                 160
Cys Leu Pro Asp Ala Ser Ile His Leu Pro Pro Asn Thr His Cys Trp
                165                 170                 175
Ile Ser Gly Trp Gly Ser Ile Gln Asp Gly Val Pro Leu Pro His Pro
            180                 185                 190
Gln Thr Leu Gln Lys Leu Lys Val Pro Ile Ile Asp Ser Glu Val Cys
        195                 200                 205
Ser His Leu Tyr Trp Arg Gly Ala Gly Gln Gly Pro Ile Thr Glu Asp
    210                 215                 220
```

```
Met Leu Cys Ala Gly Tyr Leu Glu Gly Glu Arg Asp Ala Cys Leu Gly
225                 230                 235                 240
Asp Ser Gly Gly Pro Leu Met Cys Gln Val Asp Gly Ala Trp Leu Leu
                245                 250                 255
Ala Gly Ile Ile Ser Trp Gly Glu Gly Cys Ala Glu Arg Asn Arg Pro
            260                 265                 270
Gly Val Tyr Ile Ser Leu Ser Ala His Arg Ser Trp Val Glu Lys Ile
        275                 280                 285
Val Gln Gly Val Gln Leu Arg Gly Arg Ala Gln Gly Gly Gly Ala Leu
    290                 295                 300
Arg Ala Pro Ser Gln Gly Ser Gly Ala Ala Ala Arg Ser
305                 310                 315
```

<210> 230
<211> 1184
<212> DNA
<213> Homo sapiens

<220>
<223> Chymopasin

<400> 230
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gggctgcggc attcctgcca tcaaaccggc actgagcttc agccagagga ttgtcaacgg 120
ggagaatgca gtgttgggct cctggccctg gcaggtgtcc ctgcaggaca gcagcggctt 180
ccacttctgc ggtggttctc tcatcagcca gtcctgggtg gtcactgctg cccactgcaa 240
tgtcagccct ggccgccatt ttgttgtcct gggcgagtat gaccgatcat caaacgcaga 300
gcccttgcag gttctgtccg tctctcgggc cattacacac cctagctgga actctaccac 360
catgaacaat gacgtgacgc tgctgaagct cgcctcgcca gcccagtaca caacacgcat 420
ctcgccagtt tgcctggcat cctcaaacga ggctctgact gaaggcctca cgtgtgtcac 480
caccggctgg ggtcgcctca gtggcgtggg caatgtgaca ccagcacatc tgcagcaggt 540
ggctttgccc ctggtcactg tgaatcagtg ccggcagtac tggggctcaa gtatcactga 600
ctccatgatc tgtgcaggtg gcgcaggtgc ctcctcgtgc cagggtgact ccggaggccc 660
tcttgtctgc cagaagggaa acacatgggt gcttattggt attgtctcct ggggcaccaa 720
aaactgcaat gtgcgcgcac ctgctgtgta tactcgagtt agcaagttca gcacctggat 780
caaccaggtc atagcctaca actgagctca ccacaggccc tccccagctc aacccattaa 840
agacccaggc cctgtcccat catgcattca tgtctgtctt cctggctcag gagaaagaag 900
aggctgttga gggtccgact ccctacttgg acttctggca cagaaggggc tgagtgactc 960
cttgagtagc agtggctctt cctagagtag ccatgccgag gccggggccc ccacccctcc 1020
tccagggcaa ccccttggtc ctacagcaag aagccagaac tgttggaatg aatggcagcc 1080
ctccctggag aggcagcctg tttactgaat acagaggata cgtttacaaa ctgaatacgc 1140
ataataaata actgcacatt ctccatccaa aaaaaaaaaa aaaa   1184

<210> 231
<211> 264
<212> PRT
<213> Homo sapiens

<220>
<223> Chymopasin

<400> 231
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Met Leu Leu Leu Ser Leu Thr Leu Ser Leu Val Leu Leu Gly Ser Ser
 1               5                  10                  15
Trp Gly Cys Gly Ile Pro Ala Ile Lys Pro Ala Leu Ser Phe Ser Gln
            20                  25                  30
```

```
Arg Ile Val Asn Gly Glu Asn Ala Val Leu Gly Ser Trp Pro Trp Gln
        35                  40                  45
Val Ser Leu Gln Asp Ser Ser Gly Phe His Phe Cys Gly Gly Ser Leu
    50                  55                  60
Ile Ser Gln Ser Trp Val Val Thr Ala Ala His Cys Asn Val Ser Pro
65                  70                  75                  80
Gly Arg His Phe Val Val Leu Gly Glu Tyr Asp Arg Ser Ser Asn Ala
                85                  90                  95
Glu Pro Leu Gln Val Leu Ser Val Ser Arg Ala Ile Thr His Pro Ser
            100                 105                 110
Trp Asn Ser Thr Thr Met Asn Asn Asp Val Thr Leu Leu Lys Leu Ala
        115                 120                 125
Ser Pro Ala Gln Tyr Thr Thr Arg Ile Ser Pro Val Cys Leu Ala Ser
    130                 135                 140
Ser Asn Glu Ala Leu Thr Glu Gly Leu Thr Cys Val Thr Thr Gly Trp
145                 150                 155                 160
Gly Arg Leu Ser Gly Val Gly Asn Val Thr Pro Ala His Leu Gln Gln
                165                 170                 175
Val Ala Leu Pro Leu Val Thr Val Asn Gln Cys Arg Gln Tyr Trp Gly
            180                 185                 190
Ser Ser Ile Thr Asp Ser Met Ile Cys Ala Gly Gly Ala Gly Ala Ser
        195                 200                 205
Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Gln Lys Gly Asn
    210                 215                 220
Thr Trp Val Leu Ile Gly Ile Val Ser Trp Gly Thr Lys Asn Cys Asn
225                 230                 235                 240
Val Arg Ala Pro Ala Val Tyr Thr Arg Val Ser Lys Phe Ser Thr Trp
                245                 250                 255
Ile Asn Gln Val Ile Ala Tyr Asn
            260
```

<210> 232
<211> 1207
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 11 transcript variant 1

<400> 232
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ggagtgcagg cttggaaagc aggagagctc agcctacgtc tttaatcctc ctgcccaccc 60
cttggattct gtctccactg ggactcaaga gaggaacctg gggcccgctc ctccccctc 120
caggccatga ggattctgca gttaatcctg cttgctctgg caacagggct tgtaggggga 180
gagaccagga tcatcaaggg gttcgagtgc aagcctcact cccagccctg gcaggcagcc 240
ctgttcgaga agacgcggct actctgtggg gcgacgctca tcgcccccag atggctcctg 300
acagcagccc actgcctcaa gccccgctac atagttcacc tggggcagca caacctccag 360
aaggaggagg gctgtgagca gacccggaca gccactgagt ccttccccca ccccggcttc 420
aacaacagcc tccccaacaa agaccaccgc aatgacatca tgctggtgaa gatggcatcg 480
ccagtctcca tcacctgggc tgtgcgaccc ctcaccctct cctcacgctg tgtcactgct 540
ggcaccagct gcctcatttc cggctggggc agcacgtcca gcccccagtt acgcctgcct 600
cacaccttgc gatgcgccaa catcaccatc attgagcacc agaagtgtga gaacgcctac 660
cccggcaaca tcacagacac catggtgtgt gccagcgtgc aggaaggggg caaggactcc 720
tgccagggtg actccggggg ccctctggtc tgtaaccagt ctcttcaagg cattatctcc 780
tggggccagg atccgtgtgc gatcacccga aagcctggtg tctacacgaa agtctgcaaa 840
tatgtggact ggatccagga gacgatgaag aacaattaga ctggacccac ccaccacagc 900
ccatcaccct ccatttccac ttggtgtttg gttcctgttc actctgttaa taagaaaccc 960
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taagccaaga ccctctacga acattctttg ggcctcctgg actacaggag atgctgtcac 1020
ttaataatca acctggggtt cgaaatcagt gagacctgga ttcaaattct gccttgaaat 1080
attgtgactc tgggaatgac aacacctggt ttgttctctg ttgtatcccc agccccaaag 1140
acagctcctg gccatatatc aaggtttcaa taaatatttg ctaaatgagt gaaaaaaaaa 1200
aaaaaaa 1207

<210> 233
<211> 250
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 11 isoform 1

<400> 233
Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val
1 5 10 15
Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser
20 25 30
Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly
35 40 45
Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu
50 55 60
Lys Pro Arg Tyr Ile Val His Leu Gly Gln His Asn Leu Gln Lys Glu
65 70 75 80
Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro
85 90 95
Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp His Arg Asn Asp Ile Met
100 105 110
Leu Val Lys Met Ala Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro
115 120 125
Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile
130 135 140
Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr
145 150 155 160
Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn
165 170 175
Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln
180 185 190
Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val
195 200 205
Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys
210 215 220
Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val
225 230 235 240
Asp Trp Ile Gln Glu Thr Met Lys Asn Asn
245 250

<210> 234
<211> 1289
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein 11 transcript variant 2

<400> 234
ctgccttgct ccacacctgg tcaggggaga gaggggagga aagccaaggg aagggaccta 60
actgaaaaca aacaagctgg gagaagcagg aatctgcgct cgggttccgc agatgcagag 120
gttgaggtgg ctgcgggact ggaagtcatc gggcagaggt ctcacagcag ccaaggaacc 180
tggggcccgc tcctcccccc tccaggccat gaggattctg cagttaatcc tgcttgctct 240
ggcaacaggg cttgtagggg gagagaccag gatcatcaag gggttcgagt gcaagcctca 300
ctcccagccc tggcaggcag ccctgttcga gaagacgcgg ctactctgtg gggcgacgct 360
catcgccccc agatggctcc tgacagcagc ccactgcctc aagccccgct acatagttca 420
cctggggcag cacaacctcc agaaggagga gggctgtgag cagacccgga cagccactga 480
gtccttcccc caccccggct tcaacaacag cctccccaac aaagaccacc gcaatgacat 540
catgctggtg aagatggcat cgccagtctc catcacctgg gctgtgcgac ccctcaccct 600
ctcctcacgc tgtgtcactg ctggcaccag ctgcctcatt tccggctggg gcagcacgtc 660
cagcccccag ttacgcctgc ctcacacctt gcgatgcgcc aacatcacca tcattgagca 720
ccagaagtgt gagaacgcct accccggcaa catcacagac accatggtgt gtgccagcgt 780
gcaggaaggg ggcaaggact cctgccaggg tgactccggg ggccctctgg tctgtaacca 840
gtctcttcaa ggcattatct cctggggcca ggatccgtgt gcgatcaccc gaaagcctgg 900
tgtctacacg aaagtctgca aatatgtgga ctggatccag gagacgatga agaacaatta 960
gactggaccc acccaccaca gcccatcacc ctccatttcc acttggtgtt tggttcctgt 1020
tcactctgtt aataagaaac cctaagccaa gaccctctac gaacattctt tgggcctcct 1080
ggactacagg agatgctgtc acttaataat caacctgggg ttcgaaatca gtgagacctg 1140
gattcaaatt ctgccttgaa atattgtgac tctgggaatg acaacacctg gtttgttctc 1200
tgttgtatcc ccagccccaa agacagctcc tggccatata tcaaggtttc aataaatatt 1260
tgctaaatga gtgaaaaaaa aaaaaaaaa 1289

<210> 235
<211> 282
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein 11 isoform 2

<400> 235
Met Gln Arg Leu Arg Trp Leu Arg Asp Trp Lys Ser Ser Gly Arg Gly
 1   5   10   15
Leu Thr Ala Ala Lys Glu Pro Gly Ala Arg Ser Ser Pro Leu Gln Ala
            20   25   30
Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val
        35   40   45
Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser
    50   55   60
Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly
65   70   75   80
Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu
                85   90   95
Lys Pro Arg Tyr Ile Val His Leu Gly Gln His Asn Leu Gln Lys Glu
            100   105   110
Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro
        115   120   125
Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp His Arg Asn Asp Ile Met
    130   135   140
Leu Val Lys Met Ala Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro
145   150   155   160
Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile
                165   170   175
Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr
            180   185   190

```
Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn
        195                 200                 205
Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln
    210                 215                 220
Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val
225                 230                 235                 240
Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys
                245                 250                 255
Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val
            260                 265                 270
Asp Trp Ile Gln Glu Thr Met Lys Asn Asn
        275                 280
```

<210> 236
<211> 802
<212> DNA
<213> Homo sapiens

<220>
<223> anionic trypsin (II)

<400> 236
accaccatga atctacttct gatccttacc tttgttgcag ctgctgttgc tgccccctttt 60
gatgatgatg acaagatcgt tgggggctac atctgtgagg agaattctgt cccctaccag 120
gtgtccttga attctggcta ccacttctgc ggtggctccc tcatcagcga acagtgggtg 180
gtgtcagcag gtcactgcta caagtcccgc atccaggtga gactgggaga gcacaacatc 240
gaagtcctgg aggggaatga acagttcatc aatgcagcca agatcatccg ccaccccaaa 300
tacaacagcc ggactctgga caatgacatc ctgctgatca agctctcctc acctgccgtc 360
atcaattccc gcgtgtccgc catctctctg cccactgccc ctccagctgc tggcaccgag 420
tccctcatct ccggctgggg caacactctg agttctggtg ccgactaccc agacgagctg 480
cagtgcctgg atgctcctgt gctgagccag gctgagtgtg aagcctccta ccctggaaag 540
attaccaaca acatgttctg tgtgggcttc ctcgagggag gcaaggattc ctgccagggt 600
gattctggtg gccctgtggt ctccaatgga gagctccaag gaattgtctc ctggggctat 660
ggctgtgccc agaagaacag gcctggagtc tacaccaagg tctacaacta tgtggactgg 720
attaaggaca ccatagctgc caacagctaa agcccctggt ccctctgcag tctctatacc 780
aataaagtga ccctgctctc ac 802

<210> 237
<211> 247
<212> PRT
<213> Homo sapiens

<220>
<223> anionic trypsin (II)

<400> 237
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Met Asn Leu Leu Leu Ile Leu Thr Phe Val Ala Ala Ala Val Ala Ala
 1               5                  10                  15
Pro Phe Asp Asp Asp Asp Lys Ile Val Gly Gly Tyr Ile Cys Glu Glu
            20                  25                  30
Asn Ser Val Pro Tyr Gln Val Ser Leu Asn Ser Gly Tyr His Phe Cys
        35                  40                  45
Gly Gly Ser Leu Ile Ser Glu Gln Trp Val Val Ser Ala Gly His Cys
    50                  55                  60
Tyr Lys Ser Arg Ile Gln Val Arg Leu Gly Glu His Asn Ile Glu Val
65                  70                  75                  80
```

```
Leu Glu Gly Asn Glu Gln Phe Ile Asn Ala Ala Lys Ile Ile Arg His
                85                  90                  95
Pro Lys Tyr Asn Ser Arg Thr Leu Asp Asn Asp Ile Leu Leu Ile Lys
            100                 105                 110
Leu Ser Ser Pro Ala Val Ile Asn Ser Arg Val Ser Ala Ile Ser Leu
        115                 120                 125
Pro Thr Ala Pro Pro Ala Ala Gly Thr Glu Ser Leu Ile Ser Gly Trp
    130                 135                 140
Gly Asn Thr Leu Ser Ser Gly Ala Asp Tyr Pro Asp Glu Leu Gln Cys
145                 150                 155                 160
Leu Asp Ala Pro Val Leu Ser Gln Ala Glu Cys Glu Ala Ser Tyr Pro
                165                 170                 175
Gly Lys Ile Thr Asn Asn Met Phe Cys Val Gly Phe Leu Glu Gly Gly
            180                 185                 190
Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Val Val Ser Asn Gly
        195                 200                 205
Glu Leu Gln Gly Ile Val Ser Trp Gly Tyr Gly Cys Ala Gln Lys Asn
    210                 215                 220
Arg Pro Gly Val Tyr Thr Lys Val Tyr Asn Tyr Val Asp Trp Ile Lys
225                 230                 235                 240
Asp Thr Ile Ala Ala Asn Ser
                245
```

<210> 238
<211> 1475
<212> DNA
<213> Homo sapiens

<220>
<223> LOC144757 peptidase

<400> 238
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acctgccgcc atcttgctca ccagcctcca aaatgcggct ggggctcctg agcgtggcgc 60
tgttgtttgt ggggagctct cacttatact cagaccacta ctcgccctct ggaaggcaca 120
ggctcggccc ctcgccggaa ccggcggcta gttcccagca ggctgaggcc gtccgcaaga 180
ggctccggcg gcggagggag ggaggggcgc atgcaaagga ttgtggaaca gcaccgctta 240
aggatgtgtt gcaagggtct cggattatag ggggcaccga agcacaagct ggcgcatggc 300
cgtgggtggt gagcctgcag attaaatatg gccgtgttct tgttcatgta tgtgggggaa 360
ccctagtgag agagaggtgg gtcctcacag ctgcccactg cactaaagac gctagcgatc 420
ctttaatgtg gacagctgtg attggaacta ataatataca tggacgctat cctcatacca 480
agaagataaa aattaaagca atcattattc atccaaactt cattttggaa tcttatgtaa 540
atgatattgc acttttcac ttaaaaaaag cagtgaggta taatgactat attcagccta 600
tttgcctacc ttttgatgtt ttccaaatcc tggacggaaa cacaaagtgt tttataagtg 660
gctggggaag aacaaaagaa gaaggtaacg ctacaaatat tttacaagat gcagaagtgc 720
attatatttc tcgagagatg tgtaattctg agaggagtta tgggggaata attcctaaca 780
cttcattttg tgcaggtgat gaagatggag cttttgatac ttgcaggggt gacagtgggg 840
gaccattaat gtgctactta ccagaatata aaagattttt tgtaatggga attaccagtt 900
acggacatgg ctgtggtcga agaggttttc ctggtgtcta tattgggcca tccttctacc 960
aaaagtggct gacagagcat ttcttccatg caagcactca aggcatactt actataaata 1020
ttttacgtgg ccagatcctc atagctttat gttttgtcat cttactagca acaacataaa 1080
gaaattctga aggctttcat atctttattt tgcattgtgt ccctttctat gttctatata 1140
atgaacatca tttattcttc tagcaattaa ttgcctacat tagagatttc atgtgaacat 1200
tttatgggct ataagtattg tgacagatat acaattgtaa ttttggcact gaatcacatg 1260
tctccttgaa atatcttgat tattttataa tcataattct gtatctggaa tactcataga 1320
gtttgtacaa aatattcagt taaacatata tgtgtataaa tgccaaataa tagtttataa 1380
ttaaaatgaa agctgtcatt tggttaaatt aataaaaatt ctttcttaga ttttattcta 1440
```

aaaaaaaaaa aaaaaaaaga aaaaaaaaaa aaaaa 1475

<210> 239
<211> 348
<212> PRT
<213> Homo sapiens

<220>
<223> LOC144757 peptidase

<400> 239
Met Arg Leu Gly Leu Leu Ser Val Ala Leu Leu Phe Val Gly Ser Ser
1 5 10 15
His Leu Tyr Ser Asp His Tyr Ser Pro Ser Gly Arg His Arg Leu Gly
20 25 30
Pro Ser Pro Glu Pro Ala Ala Ser Ser Gln Gln Ala Glu Ala Val Arg
35 40 45
Lys Arg Leu Arg Arg Arg Arg Glu Gly Gly Ala His Ala Lys Asp Cys
50 55 60
Gly Thr Ala Pro Leu Lys Asp Val Leu Gln Gly Ser Arg Ile Ile Gly
65 70 75 80
Gly Thr Glu Ala Gln Ala Gly Ala Trp Pro Trp Val Val Ser Leu Gln
85 90 95
Ile Lys Tyr Gly Arg Val Leu Val His Val Cys Gly Gly Thr Leu Val
100 105 110
Arg Glu Arg Trp Val Leu Thr Ala Ala His Cys Thr Lys Asp Ala Ser
115 120 125
Asp Pro Leu Met Trp Thr Ala Val Ile Gly Thr Asn Asn Ile His Gly
130 135 140
Arg Tyr Pro His Thr Lys Lys Ile Lys Ile Lys Ala Ile Ile Ile His
145 150 155 160
Pro Asn Phe Ile Leu Glu Ser Tyr Val Asn Asp Ile Ala Leu Phe His
165 170 175
Leu Lys Lys Ala Val Arg Tyr Asn Asp Tyr Ile Gln Pro Ile Cys Leu
180 185 190
Pro Phe Asp Val Phe Gln Ile Leu Asp Gly Asn Thr Lys Cys Phe Ile
195 200 205
Ser Gly Trp Gly Arg Thr Lys Glu Glu Gly Asn Ala Thr Asn Ile Leu
210 215 220
Gln Asp Ala Glu Val His Tyr Ile Ser Arg Glu Met Cys Asn Ser Glu
225 230 235 240
Arg Ser Tyr Gly Gly Ile Ile Pro Asn Thr Ser Phe Cys Ala Gly Asp
245 250 255
Glu Asp Gly Ala Phe Asp Thr Cys Arg Gly Asp Ser Gly Gly Pro Leu
260 265 270
Met Cys Tyr Leu Pro Glu Tyr Lys Arg Phe Phe Val Met Gly Ile Thr
275 280 285
Ser Tyr Gly His Gly Cys Gly Arg Arg Gly Phe Pro Gly Val Tyr Ile
290 295 300
Gly Pro Ser Phe Tyr Gln Lys Trp Leu Thr Glu His Phe Phe His Ala
305 310 315 320

Ser Thr Gln Gly Ile Leu Thr Ile Asn Ile Leu Arg Gly Gln Ile Leu
325 330 335
Ile Ala Leu Cys Phe Val Ile Leu Leu Ala Thr Thr
340 345

<210> 240
<211> 1164
<212> DNA
<213> Homo sapiens

<220>
<223> Mername-AA169 peptidase

<400> 240
atgattgccg ttctcattgt gttgtccctg acagtggtgg cagtgaccat aggtctcctg 60
gttcacttcc tagtatttga ccaaaaaaag gagtactatc atggctcctt taaaatttta 120
gatccacaaa tcaataacaa tttcggacaa agcaacacat atcaacttaa ggacttacga 180
gagacgaccg aaaatttggt ggatgagata tttatagatt cagcctggaa gaaaaattat 240
atcaagaacc aagtagtcag actgactcca gaggaagatg gtgtgaaagt agatgtcatt 300
atggtgttcc agttcccctc tactgaacaa agggcagtaa gagagaagaa aatccaaagc 360
atcttaaatc agaagataag gaatttaaga gccttgccaa taaatgcctc atcagttcaa 420
gttaatggtt gtggtaaacg agttgttcca ttaaacgtca acagaatagc atctggagtc 480
attgcaccca aggcggcctg gccttggcaa gcttcccttc agtatgataa catccatcag 540
tgtggggcca ccttgattag taacacatgg cttgtcactg cagcacactg cttccagaag 600
tataaaaatc cacatcaatg gactgttagt tttggaacaa aaatcaaccc tcccttaatg 660
aaaagaaatg tcagaagatt tattatccat gagaagtacc gctctgcagc aagagagtac 720
gacattgctg ttgtgcaggt ctcttccaga gtcacctttt cggatgacat acgccagatt 780
tgtttgccag aagcctctgc atccttccaa ccaaatttga ctgtccacat cacaggattt 840
ggagcacttt actatggtgg ggaatcccaa aatgatctcc gagaagccag agtgaaaatc 900
ataagtgatg atgtctgcaa gcaaccacag gtgtatggca atgatataaa acctggaatg 960
ttctgtgccg gatatatgga aggaatttat gatgcctgca ggggtgattc tgggggacct 1020
ttagtcacaa gggatctgaa agatacgtgg tatctcattg gaattgtaag ctggggagat 1080
aactgtggtc aaaaggacaa gcctggagtc tacacacaag tgacttatta ccgaaactgg 1140
attgcttcaa aaacaggcat ctaa 1164

<210> 241
<211> 387
<212> PRT
<213> Homo sapiens

<220>
<223> Mername-AA169 peptidase

<400> 241
Met Ile Ala Val Leu Ile Val Leu Ser Leu Thr Val Val Ala Val Thr
 1   5   10   15
Ile Gly Leu Leu Val His Phe Leu Val Phe Asp Gln Lys Lys Glu Tyr
            20   25   30
Tyr His Gly Ser Phe Lys Ile Leu Asp Pro Gln Ile Asn Asn Asn Phe
        35   40   45
Gly Gln Ser Asn Thr Tyr Gln Leu Lys Asp Leu Arg Glu Thr Thr Glu
    50   55   60
Asn Leu Val Asp Glu Ile Phe Ile Asp Ser Ala Trp Lys Lys Asn Tyr
65   70   75   80
Ile Lys Asn Gln Val Val Arg Leu Thr Pro Glu Glu Asp Gly Val Lys
                85   90   95
Val Asp Val Ile Met Val Phe Gln Phe Pro Ser Thr Glu Gln Arg Ala
            100   105   110
Val Arg Glu Lys Lys Ile Gln Ser Ile Leu Asn Gln Lys Ile Arg Asn
        115   120   125
Leu Arg Ala Leu Pro Ile Asn Ala Ser Ser Val Gln Val Asn Gly Cys

```
    130                 135                 140
Gly Lys Arg Val Val Pro Leu Asn Val Asn Arg Ile Ala Ser Gly Val
145                 150                 155                 160
Ile Ala Pro Lys Ala Ala Trp Pro Trp Gln Ala Ser Leu Gln Tyr Asp
                165                 170                 175
Asn Ile His Gln Cys Gly Ala Thr Leu Ile Ser Asn Thr Trp Leu Val
            180                 185                 190
Thr Ala Ala His Cys Phe Gln Lys Tyr Lys Asn Pro His Gln Trp Thr
        195                 200                 205
Val Ser Phe Gly Thr Lys Ile Asn Pro Pro Leu Met Lys Arg Asn Val
    210                 215                 220
Arg Arg Phe Ile Ile His Glu Lys Tyr Arg Ser Ala Ala Arg Glu Tyr
225                 230                 235                 240
Asp Ile Ala Val Val Gln Val Ser Ser Arg Val Thr Phe Ser Asp Asp
                245                 250                 255
Ile Arg Gln Ile Cys Leu Pro Glu Ala Ser Ala Ser Phe Gln Pro Asn
            260                 265                 270
Leu Thr Val His Ile Thr Gly Phe Gly Ala Leu Tyr Tyr Gly Gly Glu
        275                 280                 285
Ser Gln Asn Asp Leu Arg Glu Ala Arg Val Lys Ile Ile Ser Asp Asp
    290                 295                 300
Val Cys Lys Gln Pro Gln Val Tyr Gly Asn Asp Ile Lys Pro Gly Met
305                 310                 315                 320
Phe Cys Ala Gly Tyr Met Glu Gly Ile Tyr Asp Ala Cys Arg Gly Asp
                325                 330                 335
Ser Gly Gly Pro Leu Val Thr Arg Asp Leu Lys Asp Thr Trp Tyr Leu
            340                 345                 350
Ile Gly Ile Val Ser Trp Gly Asp Asn Cys Gly Gln Lys Asp Lys Pro
        355                 360                 365
Gly Val Tyr Thr Gln Val Thr Tyr Tyr Arg Asn Trp Ile Ala Ser Lys
    370                 375                 380
Thr Gly Ile
385
```

<210> 242
<211> 431
<212> PRT
<213> Rattus norvegicus

<220>
<223> Mername-AA171 peptidase

<400> 242

```
Met Ala Arg Gly Gln Pro Arg Arg Ser Glu Glu Pro Trp Thr Ala Leu
 1               5                  10                  15
Arg Asn Arg Thr Glu Cys Lys Thr Lys Ile Lys Leu Thr Lys Cys Gly
            20                  25                  30
Lys Ile Thr Leu Gly Ile Leu Thr Ala Val Ile Ala Ala Val Val Ile
        35                  40                  45
Gly Leu Ile Ala Tyr Phe Ala Ala Cys Gly Lys Thr Pro Phe Tyr Tyr
    50                  55                  60
His Val Ser Phe Lys Val Asn Asn Ile Asp Tyr Asp Ser Lys Phe Ala
65                  70                  75                  80
Lys Pro Tyr Ser Gln Glu Tyr Met Asp Leu Asn Lys Arg Ile Val Ser
                85                  90                  95
Leu Met Asn Glu Thr Phe His Glu Ser Lys Leu Arg Lys Gln Tyr Val
```

```
            100                 105                 110
Lys Ala His Thr Val Gln Val Ser Lys Ala Lys Gly Lys Val Val Ile
        115                 120                 125
His Gly Val Leu Lys Phe Lys Ser Cys Tyr Lys Asn Asn Val Glu Lys
    130                 135                 140
Phe Trp Asp Ser Val Glu Thr Ile Leu Tyr Gln Lys Leu Lys Ser Gln
145                 150                 155                 160
Thr Arg Leu Leu Ile Asp Ser Ser Ser Phe Lys Phe Ser Asp Ile Ala
                165                 170                 175
Met Pro Ile Ala Glu Asp Leu Leu Asn Thr Cys Cys Gly Arg Arg Thr
            180                 185                 190
Ile Thr Pro Gly Gly His Lys Val Ala Gly Gly Gln Asp Ala Glu Glu
        195                 200                 205
Gly Glu Trp Pro Trp Gln Ala Ser Leu Gln Gln Asn Asn Val His Arg
    210                 215                 220
Cys Gly Ala Thr Leu Ile Ser Asn Ser Trp Leu Ile Thr Ala Ala His
225                 230                 235                 240
Cys Phe Val Arg Ser Ala Asn Pro Lys Asp Trp Lys Val Ser Phe Gly
                245                 250                 255
Phe Leu Leu Ser Lys Pro Gln Ala Gln Arg Ala Val Lys Ser Ile Val
            260                 265                 270
Ile His Glu Asn Tyr Ser Tyr Pro Ala His Asn Asn Asp Ile Ala Val
        275                 280                 285
Val Arg Leu Ser Ser Pro Val Leu Tyr Glu Asn Asn Ile Arg Arg Ala
    290                 295                 300
Cys Leu Pro Glu Ala Thr Gln Lys Phe Pro Pro Asn Ser Asp Val Val
305                 310                 315                 320
Val Thr Gly Trp Gly Thr Leu Lys Ser Asp Gly Asp Ser Pro Asn Ile
                325                 330                 335
Leu Gln Lys Gly Arg Val Lys Ile Ile Asp Asn Lys Thr Cys Asn Ser
            340                 345                 350
Gly Lys Ala Tyr Gly Gly Val Ile Thr Pro Gly Met Leu Cys Ala Gly
        355                 360                 365
Phe Leu Glu Gly Arg Val Asp Ala Cys Gln Gly Asp Ser Gly Gly Pro
    370                 375                 380
Leu Val Ser Glu Asp Ser Lys Gly Ile Trp Phe Leu Ala Gly Ile Val
385                 390                 395                 400
Ser Trp Gly Asp Glu Cys Ala Leu Pro Asn Lys Pro Gly Val Tyr Thr
                405                 410                 415
Arg Val Thr His Tyr Arg Asp Trp Ile Ser Ser Lys Thr Gly Leu
            420                 425                 430
```

<210> 243
<211> 247
<212> PRT
<213> Homo sapiens

<220>
<223> Mername-AA174 peptidase

<400> 243

```
Met Asn Pro Leu Leu Ile Leu Ala Phe Val Gly Ala Ala Val Ala Val
 1               5                  10                  15
Pro Phe Asp Asp Asp Asp Lys Ile Val Gly Gly Tyr Thr Cys Glu Glu
            20                  25                  30
Asn Ser Val Pro Tyr Gln Val Ser Leu Asn Ser Gly Ser His Phe Cys
```

```
        35                  40                  45
Gly Gly Ser Leu Ile Ser Glu Gln Trp Val Val Ser Ala Gly His Cys
    50                  55                  60
Tyr Lys Pro His Ile Gln Val Arg Leu Gly Glu His Asn Ile Glu Val
65                  70                  75                  80
Leu Glu Gly Asn Glu Gln Phe Ile Asn Ala Ala Lys Ile Ile Arg His
                85                  90                  95
Pro Lys Tyr Asn Arg Ile Thr Leu Asn Asn Asp Ile Met Leu Ile Lys
            100                 105                 110
Leu Ser Thr Pro Ala Val Ile Asn Ala His Val Ser Thr Ile Ser Leu
        115                 120                 125
Pro Thr Ala Pro Pro Ala Ala Gly Thr Glu Cys Leu Ile Ser Gly Trp
    130                 135                 140
Gly Asn Thr Leu Ser Ser Gly Ala Asp Tyr Pro Asp Glu Leu Gln Cys
145                 150                 155                 160
Leu Asp Ala Pro Val Leu Thr Gln Ala Lys Cys Lys Ala Ser Tyr Pro
                165                 170                 175
Leu Lys Ile Thr Ser Lys Met Phe Cys Val Gly Phe Leu Glu Gly Gly
            180                 185                 190
Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Val Val Cys Asn Gly
        195                 200                 205
Gln Leu Gln Gly Ile Val Ser Trp Gly Tyr Gly Cys Ala Gln Lys Arg
    210                 215                 220
Arg Pro Gly Val Tyr Thr Lys Val Tyr Asn Tyr Val Asp Trp Ile Lys
225                 230                 235                 240
Asp Thr Ile Ala Ala Asn Ser
                245
```

<210> 244
<211> 1099
<212> DNA
<213> Homo sapiens

<220>
<223> Mername-AA175 peptidase

<400> 244
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gcacagccca gggccatgct cctgttctca gtgttgctgc tcctgtccct ggtcacggga 60
actcagctcg gtccacggac tcctctccca gaggctggag tggctatcct aggcagggct 120
aggggagccc accgccctca gccccgtcat ccccccagcc cagtcagtga atgtggtgac 180
agatctattt tcgagggaag aactcggtat tccagaatca caggggggat ggaggcggag 240
gtgggtgagt ttccgtggca ggtgagtatt caggcaagaa gtgaaccttt ctgtggcggc 300
tccatcctca acaagtggtg gattctcact gcggctcact gcttatattc cgaggagctg 360
tttccagaag aactgagtgt cgtgctgggg accaacgact taactagccc atccatggaa 420
ataaaggagg tcgccagcat cattcttcac aaagacttta agagagccaa catggacaat 480
gacattgcct tgctgctgct ggcttcgccc atcaagctcg atgacctgaa ggtgcccatc 540
tgcctcccca cgcagcccgg ccctgccaca tggcgcgaat gctgggtggc aggttggggc 600
cagaccaatg ctgctgacaa aaactctgtg aaaacggatc tgatgaaagt gccaatggtc 660
atcatggact gggaggagtg ttcaaagatg tttccaaaac ttaccaaaaa tatgctgtgt 720
gccggataca agaatgagag ctatgatgcc tgcaagggtg acagtggggg gcctctggtc 780
tgcaccccag agcctggtga gaagtggtac caggtgggca tcatcagctg gggaaagagc 840
tgtggagaga agaacacccc agggatatac acctcgttgg tgaactacaa cctctggatc 900
gagaaagtga cccagctaga gggcaggccc ttcaatgcag agaaaaggag gacttctgtc 960
aaacagaaac ctatgggctc cccagtctcg ggagtcccag agccaggcag ccccagatcc 1020
tggctcctgc tctgtccccc gtcccatgtg ttgttcagag ctattttgta ctgataataa 1080
aatagaggct attctttca                                              1099
```

<210> 245
<211> 352
<212> PRT
<213> Homo sapiens

<220>
<223> Mername-AA175 peptidase

<400> 245
Met Leu Leu Phe Ser Val Leu Leu Leu Leu Ser Leu Val Thr Gly Thr
 1   5   10   15
Gln Leu Gly Pro Arg Thr Pro Leu Pro Glu Ala Gly Val Ala Ile Leu
            20   25   30
Gly Arg Ala Arg Gly Ala His Arg Pro Gln Pro Arg His Pro Pro Ser
        35   40   45
Pro Val Ser Glu Cys Gly Asp Arg Ser Ile Phe Glu Gly Arg Thr Arg
    50   55   60
Tyr Ser Arg Ile Thr Gly Gly Met Glu Ala Glu Val Gly Glu Phe Pro
65   70   75   80
Trp Gln Val Ser Ile Gln Ala Arg Ser Glu Pro Phe Cys Gly Gly Ser
                85   90   95
Ile Leu Asn Lys Trp Trp Ile Leu Thr Ala Ala His Cys Leu Tyr Ser
            100   105   110
Glu Glu Leu Phe Pro Glu Glu Leu Ser Val Val Leu Gly Thr Asn Asp
        115   120   125
Leu Thr Ser Pro Ser Met Glu Ile Lys Glu Val Ala Ser Ile Ile Leu
    130   135   140
His Lys Asp Phe Lys Arg Ala Asn Met Asp Asn Asp Ile Ala Leu Leu
145   150   155   160
Leu Leu Ala Ser Pro Ile Lys Leu Asp Asp Leu Lys Val Pro Ile Cys
                165   170   175
Leu Pro Thr Gln Pro Gly Pro Ala Thr Trp Arg Glu Cys Trp Val Ala
            180   185   190
Gly Trp Gly Gln Thr Asn Ala Ala Asp Lys Asn Ser Val Lys Thr Asp
        195   200   205
Leu Met Lys Val Pro Met Val Ile Met Asp Trp Glu Glu Cys Ser Lys
    210   215   220
Met Phe Pro Lys Leu Thr Lys Asn Met Leu Cys Ala Gly Tyr Lys Asn
225   230   235   240
Glu Ser Tyr Asp Ala Cys Lys Gly Asp Ser Gly Gly Pro Leu Val Cys
                245   250   255
Thr Pro Glu Pro Gly Glu Lys Trp Tyr Gln Val Gly Ile Ile Ser Trp
            260   265   270
Gly Lys Ser Cys Gly Glu Lys Asn Thr Pro Gly Ile Tyr Thr Ser Leu
        275   280   285
Val Asn Tyr Asn Leu Trp Ile Glu Lys Val Thr Gln Leu Glu Gly Arg
    290   295   300
Pro Phe Asn Ala Glu Lys Arg Arg Thr Ser Val Lys Gln Lys Pro Met
305   310   315   320
Gly Ser Pro Val Ser Gly Val Pro Glu Pro Gly Ser Pro Arg Ser Trp
                325   330   335
Leu Leu Leu Cys Pro Leu Ser His Val Leu Phe Arg Ala Ile Leu Tyr
            340   345   350

<210> 246

<211> 1927
<212> DNA
<213> Homo sapiens

<220>
<223> stratum corneum chymotryptic enzyme transcript variant 1

<400> 246
tgccagccca agtcggaact tggatcacat cagatcctct cgagctccag caggagaggc 60
ccttcctcgc ctggcagccc ctgagcggct cagcagggca ccatggcaag atcccttctc 120
ctgcccctgc agatcttact gctatcctta gccttggaaa ctgcaggaga agaagcccag 180
ggtgacaaga ttattgatgg cgccccatgt gcaagaggct cccacccatg gcaggtggcc 240
ctgctcagtg gcaatcagct ccactgcgga ggcgtcctgg tcaatgagcg ctgggtgctc 300
actgccgccc actgcaagat gaatgagtac accgtgcacc tgggcagtga tacgctgggc 360
gacaggagag ctcagaggat caaggcctcg aagtcattcc gccacccccgg ctactccaca 420
cagacccatg ttaatgacct catgctcgtg aagctcaata gccaggccag gctgtcatcc 480
atggtgaaga aagtcaggct gccctcccgc tgcgaacccc ctggaaccac ctgtactgtc 540
tccggctggg gcactaccac gagcccagat gtgacctttc cctctgacct catgtgcgtg 600
gatgtcaagc tcatctcccc ccaggactgc acgaaggttt acaaggactt actggaaaat 660
tccatgctgt gcgctggcat ccccgactcc aagaaaaacg cctgcaatgg tgactcaggg 720
ggaccgttgg tgtgcagagg taccctgcaa ggtctggtgt cctggggaac tttcccttgc 780
ggccaaccca atgacccagg agtctacact caagtgtgca agttcaccaa gtggataaat 840
gacaccatga aaaagcatcg ctaacgccac actgagttaa ttaactgtgt gcttccaaca 900
gaaaatgcac aggagtgagg acgccgatga cctatgaagt caaatttgac tttacctttc 960
ctcaaagata tatttaaacc aacctcatgc cctgttgata aaccaatcaa attggtaaag 1020
acctaaaacc aaaacaaata aagaaacaca aaaccctcag tgctggagaa gagtcagtga 1080
gaccagcact ctcaaacact ggaactggac gttcgtacag tctttacgga agacacttgg 1140
tcaacgtaca ccgagaccct tattcaccac ctttgaccca gtaactctaa tcttaggaag 1200
aacctactga aacaaaaaaa atccaaaatg tagaacaaga cttgaattta ccatgatatt 1260
atttatcaca gaaatgaagt gaaaccatca aacatgttcc aaaagtacca gatggcttaa 1320
ataatagtct ggcttggcac aacgatgttt tttttctttg agacagagtc tctgttgctt 1380
gggctgcaat gcagtgatgc aatcttggct cactgcaacc tccgcctcct gggttcaagt 1440
gattctcgtg cttcagcctc ccaagtacct gggactacag gtgtgcacca ccacaccagg 1500
ctaatttttt gtgtattttt actagagaca gggtttcacc atgttggcca gcgtggtctt 1560
gaacgcctga cctcagatga tccacccacc ttggcctccc aaagtgctgg gattacaggc 1620
atgagccacc acggccagcc cacaatgata ttacaaacct attaaaaatg atacttagac 1680
agaattgtca gtattattca agaacattta ggctatagga tgttaaatga caaaaggaag 1740
gacaaaaata tatatgtatg tgaccctacc cataaaaaat gaaatattca cagaatcaga 1800
tctgaaaaca catgtcccag actgcatact ggggtcgtca tgaggtgtct ccttccttct 1860
gtgtactttt ccttgaatgt gcacttttat aacatgaaaa ataaaggtgg ggaaaaaagt 1920
ctgaaga 1927

<210> 247
<211> 253
<212> PRT
<213> Homo sapiens

<220>
<223> stratum corneum chymotryptic enzyme transcript variant 1

<400> 247
Met Ala Arg Ser Leu Leu Leu Pro Leu Gln Ile Leu Leu Leu Ser Leu
 1   5   10   15
Ala Leu Glu Thr Ala Gly Glu Glu Ala Gln Gly Asp Lys Ile Ile Asp
            20   25   30
Gly Ala Pro Cys Ala Arg Gly Ser His Pro Trp Gln Val Ala Leu Leu
        35   40   45

```
Ser Gly Asn Gln Leu His Cys Gly Gly Val Leu Val Asn Glu Arg Trp
    50                  55                  60
Val Leu Thr Ala Ala His Cys Lys Met Asn Glu Tyr Thr Val His Leu
65                  70                  75                  80
Gly Ser Asp Thr Leu Gly Asp Arg Arg Ala Gln Arg Ile Lys Ala Ser
                85                  90                  95
Lys Ser Phe Arg His Pro Gly Tyr Ser Thr Gln Thr His Val Asn Asp
            100                 105                 110
Leu Met Leu Val Lys Leu Asn Ser Gln Ala Arg Leu Ser Ser Met Val
        115                 120                 125
Lys Lys Val Arg Leu Pro Ser Arg Cys Glu Pro Pro Gly Thr Thr Cys
    130                 135                 140
Thr Val Ser Gly Trp Gly Thr Thr Thr Ser Pro Asp Val Thr Phe Pro
145                 150                 155                 160
Ser Asp Leu Met Cys Val Asp Val Lys Leu Ile Ser Pro Gln Asp Cys
                165                 170                 175
Thr Lys Val Tyr Lys Asp Leu Leu Glu Asn Ser Met Leu Cys Ala Gly
            180                 185                 190
Ile Pro Asp Ser Lys Lys Asn Ala Cys Asn Gly Asp Ser Gly Gly Pro
        195                 200                 205
Leu Val Cys Arg Gly Thr Leu Gln Gly Leu Val Ser Trp Gly Thr Phe
    210                 215                 220
Pro Cys Gly Gln Pro Asn Asp Pro Gly Val Tyr Thr Gln Val Cys Lys
225                 230                 235                 240
Phe Thr Lys Trp Ile Asn Asp Thr Met Lys Lys His Arg
                245                 250
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<210> 248
<211> 1927
<212> DNA
<213> Homo sapiens

<220>
<223> stratum corneum chymotryptic enzyme transcript variant 2

<400> 248
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ccttcctcgc ctggcagccc ctgagcggct cagcagggca ccatggcaag atcccttctc 120
ctgcccctgc agatcttact gctatcctta gccttggaaa ctgcaggaga agaagcccag 180
ggtgacaaga ttattgatgg cgccccatgt gcaagaggct cccacccatg gcaggtggcc 240
ctgctcagtg gcaatcagct ccactgcgga ggcgtcctgg tcaatgagcg ctgggtgctc 300
actgccgccc actgcaagat gaatgagtac accgtgcacc tgggcagtga tacgctgggc 360
gacaggagag ctcagaggat caaggcctcg aagtcattcc gccaccccgg ctactccaca 420
cagacccatg ttaatgacct catgctcgtg aagctcaata gccaggccag gctgtcatcc 480
atggtgaaga aagtcaggct gccctcccgc tgcgaacccc ctggaaccac ctgtactgtc 540
tccggctggg gcactaccac gagcccagat gtgacctttc cctctgacct catgtgcgtg 600
gatgtcaagc tcatctcccc ccaggactgc acgaaggttt acaaggactt actggaaaat 660
tccatgctgt gcgctggcat ccccgactcc aagaaaaacg cctgcaatgg tgactcaggg 720
ggaccgttgg tgtgcagagg taccctgcaa ggtctggtgt cctggggaac tttcccttgc 780
ggccaaccca atgacccagg agtctacact caagtgtgca agttcaccaa gtggataaat 840
gacaccatga aaaagcatcg ctaacgccac actgagttaa ttaactgtgt gcttccaaca 900
gaaaatgcac aggagtgagg acgccgatga cctatgaagt caaatttgac tttacctttc 960
ctcaaagata tatttaaacc aacctcatgc cctgttgata aaccaatcaa attggtaaag 1020
acctaaaacc aaaacaaata aagaaacaca aaaccctcag tgctggagaa gagtcagtga 1080
gaccagcact ctcaaacact ggaactggac gttcgtacag tctttacgga agacacttgg 1140
tcaacgtaca ccgagaccct tattcaccac ctttgaccca gtaactctaa tcttaggaag 1200
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aacctactga aacaaaaaaa atccaaaatg tagaacaaga cttgaattta ccatgatatt 1260
atttatcaca gaaatgaagt gaaaccatca aacatgttcc aaaagtacca gatggcttaa 1320
ataatagtct ggcttggcac aacgatgttt tttttctttg agacagagtc tctgttgctt 1380
gggctgcaat gcagtgatgc aatcttggct cactgcaacc tccgcctcct gggttcaagt 1440
gattctcgtg cttcagcctc ccaagtacct gggactacag gtgtgcacca ccacaccagg 1500
ctaatttttt gtgtattttt actagagaca gggtttcacc atgttggcca gcgtggtctt 1560
gaacgcctga cctcagatga tccacccacc ttggcctccc aaagtgctgg gattacaggc 1620
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agaattgtca gtattattca agaacattta ggctatagga tgttaaatga caaaaggaag 1740
gacaaaaata tatatgtatg tgaccctacc cataaaaaat gaaatattca cagaatcaga 1800
tctgaaaaca catgtcccag actgcatact ggggtcgtca tgaggtgtct ccttccttct 1860
gtgtactttt ccttgaatgt gcacttttat aacatgaaaa ataaaggtgg ggaaaaaagt 1920
ctgaaga                                                          1927

<210> 249
<211> 253
<212> PRT
<213> Homo sapiens

<220>
<223> stratum corneum chymotryptic enzyme

<400> 249
Met Ala Arg Ser Leu Leu Leu Pro Leu Gln Ile Leu Leu Leu Ser Leu
 1               5                  10                  15
Ala Leu Glu Thr Ala Gly Glu Glu Ala Gln Gly Asp Lys Ile Ile Asp
            20                  25                  30
Gly Ala Pro Cys Ala Arg Gly Ser His Pro Trp Gln Val Ala Leu Leu
        35                  40                  45
Ser Gly Asn Gln Leu His Cys Gly Gly Val Leu Val Asn Glu Arg Trp
    50                  55                  60
Val Leu Thr Ala Ala His Cys Lys Met Asn Glu Tyr Thr Val His Leu
65                  70                  75                  80
Gly Ser Asp Thr Leu Gly Asp Arg Arg Ala Gln Arg Ile Lys Ala Ser
                85                  90                  95
Lys Ser Phe Arg His Pro Gly Tyr Ser Thr Gln Thr His Val Asn Asp
            100                 105                 110
Leu Met Leu Val Lys Leu Asn Ser Gln Ala Arg Leu Ser Ser Met Val
        115                 120                 125
Lys Lys Val Arg Leu Pro Ser Arg Cys Glu Pro Pro Gly Thr Thr Cys
    130                 135                 140
Thr Val Ser Gly Trp Gly Thr Thr Thr Ser Pro Asp Val Thr Phe Pro
145                 150                 155                 160
Ser Asp Leu Met Cys Val Asp Val Lys Leu Ile Ser Pro Gln Asp Cys
                165                 170                 175
Thr Lys Val Tyr Lys Asp Leu Leu Glu Asn Ser Met Leu Cys Ala Gly
            180                 185                 190
Ile Pro Asp Ser Lys Lys Asn Ala Cys Asn Gly Asp Ser Gly Gly Pro
        195                 200                 205
Leu Val Cys Arg Gly Thr Leu Gln Gly Leu Val Ser Trp Gly Thr Phe
    210                 215                 220
Pro Cys Gly Gln Pro Asn Asp Pro Gly Val Tyr Thr Gln Val Cys Lys
225                 230                 235                 240
Phe Thr Lys Trp Ile Asn Asp Thr Met Lys Lys His Arg
                245                 250
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<210> 250
<211> 2800
<212> DNA
<213> Homo sapiens

<220>
<223> trypsin-like enzyme, respiratory

<400> 250
atttgagtgg gaatctcaaa gcagttgagt aggcagaaaa aagaacctct tcattaagga 60
ttaaaatgta taggccagca cgtgtaactt cgacttcaag atttctgaat ccatatgtag 120
tatgtttcat tgtcgtcgca ggggtagtga tcctggcagt caccatagct ctacttgttt 180
acttttagc ttttgatcaa aaatcttact tttataggag cagttttcaa ctcctaaatg 240
ttgaatataa tagtcagtta aattcaccag ctacacagga atacaggact ttgagtggaa 300
gaattgaatc tctgattact aaaacattca aagaatcaaa tttaagaaat cagttcatca 360
gagctcatgt tgccaaactg aggcaagatg gtagtggtgt gagagcggat gttgtcatga 420
aatttcaatt cactagaaat aacaatggag catcaatgaa aagcagaatt gagtctgttt 480
tacgacaaat gctgaataac tctggaaacc tggaaataaa cccttcaact gagataacat 540
cacttactga ccaggctgca gcaaattggc ttattaatga atgtggggcc ggtccagacc 600
taataacatt gtctgagcag agaatccttg gaggcactga ggctgaggag ggaagctggc 660
cgtggcaagt cagtctgcgg ctcaataatg cccaccactg tggaggcagc ctgatcaata 720
acatgtggat cctgacagca gctcactgct tcagaagcaa ctctaatcct cgtgactgga 780
ttgccacgtc tggtatttcc acaacatttc ctaaactaag aatgagagta agaaatattt 840
taattcataa caattataaa tctgcaactc atgaaaatga cattgcactt gtgagacttg 900
agaacagtgt caccttacc aaagatatcc atagtgtgtg tctcccagct gctacccaga 960
atattccacc tggctctact gcttatgtaa caggatgggg cgctcaagaa tatgctggcc 1020
acacagttcc agagctaagg caaggacagg tcagaataat aagtaatgat gtatgtaatg 1080
caccacatag ttataatgga gccatcttgt ctggaatgct gtgtgctgga gtacctcaag 1140
gtggagtgga cgcatgtcag ggtgactctg gtggcccact agtacaagaa gactcacggc 1200
ggctttggtt tattgtgggg atagtaagct ggggagatca gtgtggcctg ccggataagc 1260
caggagtgta tactcgagtg acagcctacc ttgactggat taggcaacaa actgggatct 1320
agtgcaacaa gtgcatccct gttgcaaagt ctgtatgcag gtgtgcctgt cttaaattcc 1380
aaagctttac atttcaactg aaaaagaaac tagaaatgtc ctaatttaac atcttgttac 1440
ataaatatgg tttaacaaac actgtttaac ctttctttat tattaaaggt tttctatttt 1500
ctccagagaa ctatatgaat gttgcatagt actgtggctg tgtaacagaa gaaacacact 1560
aaactaatta caaagttaac aatttcatta cagttgtgct aaatgcccgt agtgagaaga 1620
acaggaacct tgagcatgta tagtagagga acctgcacag gtctgatggg tcagaggggt 1680
cttctctggg tttcactgag gatgagaagt aagcaaactg tggaaacatg caaaggaaaa 1740
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ttaaaatttt tggttactca atatcttata cttagtatga gtcctaaaat taaaaatgtg 1860
aaactgttgt actatacgta taacctaacc ttaattattc tgtaagaaca tgcttccata 1920
ggaaatagtg gataattttc agctatttaa ggcaaaagct aaaatagttc actcctcaac 1980
tgagacccaa agaattatag atatttttca tgatgaccca tgaaaaatat cactcatcta 2040
cataaaggag agactatatc tattttatag agaagctaag aaatatacct acacaaactt 2100
gtcaggtgct ttacaactac atagtacttt ttaacaacaa aataataatt ttaagaatga 2160
aaaatttaat catcgggaag aacgtcccac tacagacttc ctatcactgg cagttatatt 2220
tttgagcgta aaagggtcgt caaacgctaa atctaagtaa cgaattgaaa gtttaaagag 2280
ggggaagagt tggtttgcaa aggaaaagtt taaatagctt aatatcaata gaatgatcct 2340
gaagacagaa aaaactttgt cactcttcct ctctcatttt ctttctctct ctctcccctt 2400
ctcatacaca tgcctccccc accaaagaat ataatgtaaa ttaaatccac taaaatgtaa 2460
tggcatgaaa atctctgtag tctgaatcac taatattcct gagtttttat gagctcctag 2520
tacagctaaa gtttgcctat gcatgatcat ctatgcgtca gagcttcctc cttctacaag 2580
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ttcctgatgt aaaattgtgc aaacacctac aataaagcca tctactttta gggaaaggga 2700
gttgaaaatg caaccaactc ttggcgaact gtacaaacaa atctttgcta tactttattt 2760
caaataaatt ctttttaaaa taaaaaaaaa aaaaaaaaaa 2800

<210> 251
<211> 418
<212> PRT
<213> Homo sapiens

<220>
<223> trypsin-like enzyme, respiratory

<400> 251
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Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
20 25 30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
130 135 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145 150 155 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
165 170 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
180 185 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
195 200 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
210 215 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225 230 235 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
245 250 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
260 265 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
275 280 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
290 295 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305 310 315 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
325 330 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
340 345 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
355 360 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
370 375 380

```
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
                405                 410                 415
Gly Ile
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<210> 252
<211> 3149
<212> DNA
<213> Homo sapiens

<220>
<223> Matripase

<400> 252

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gcggaggggg cccgaaggac ttcggcgcgg gactcaagta caactcccgg cacgagaaag 120
tgaatggctt ggaggaaggc gtggagttcc tgccagtcaa caacgtcaag aaggtggaaa 180
agcatggccc ggggcgctgg gtggtgctgg cagccgtgct gatcggcctc ctcttggtct 240
tgctggggat cggcttcctg gtgtggcatt tgcagtaccg ggacgtgcgt gtccagaagg 300
tcttcaatgg ctacatgagg atcacaaatg agaattttgt ggatgcctac gagaactcca 360
actccactga gtttgtaagc ctggccagca aggtgaagga cgcgctgaag ctgctgtaca 420
gcggagtccc attcctgggc ccctaccaca aggagtcggc tgtgacggcc ttcagcgagg 480
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gggggacgc cgactcagtg ctgagcctca ccttccgcag ctttgacctt gcgtcctgcg 840
acgagcgcgg cagcgacctg gtgacggtgt acaacaccct gagccccatg gagccccacg 900
ccctggtgca gttgtgtggc acctaccctc cctcctacaa cctgaccttc cactcctccc 960
agaacgtcct gctcatcaca ctgataacca acactgagcg gcggcatccc ggctttgagg 1020
ccaccttctt ccagctgcct aggatgagca gctgtggagg ccgcttacgt aaagcccagg 1080
ggacattcaa cagcccctac tacccaggcc actacccacc caacattgac tgcacatgga 1140
acattgaggt gcccaacaac cagcatgtga aggtgcgctt caaattcttc tacctgctgg 1200
agcccggcgt gcctgcgggc acctgcccca aggactacgt ggagatcaat ggggagaaat 1260
actgcggaga gaggtcccag ttcgtcgtca ccagcaacag caacaagatc acagttcgct 1320
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ccagtgaccc atgcccgggg cagttcacgt gccgcacggg gcggtgtatc cggaaggagc 1440
tgcgctgtga tggctgggcc gactgcaccg accacagcga tgagctcaac tgcagttgcg 1500
acgccggcca ccagttcacg tgcaagaaca agttctgcaa gcccctcttc tgggtctgcg 1560
acagtgtgaa cgactgcgga gacaacagcg acgagcaggg gtgcagttgt ccggcccaga 1620
ccttcaggtg ttccaatggg aagtgcctct cgaaaagcca gcagtgcaat gggaaggacg 1680
actgtgggga cgggtccgac gaggcctcct gccccaaggt gaacgtcgtc acttgtacca 1740
aacacaccta ccgctgcctc aatgggctct gcttgagcaa gggcaaccct gagtgtgacg 1800
ggaaggagga ctgtagcgac ggctcagatg agaaggactg cgactgtggg ctgcggtcat 1860
tcacgagaca ggctcgtgtt gttgggggca cggatgcgga tgagggcgag tggccctggc 1920
aggtaagcct gcatgctctg ggccagggcc acatctgcgg tgcttccctc atctctccca 1980
actggctggt ctctgccgca cactgctaca tcgatgacag aggattcagg tactcagacc 2040
ccacgcagtg gacggccttc ctgggcttgc acgaccagag ccagcgcagc gcccctgggg 2100
tgcaggagcg caggctcaag cgcatcatct cccacccctt cttcaatgac ttcaccttcg 2160
actatgacat cgcgctgctg gagctggaga aaccggcaga gtacagctcc atggtgcggc 2220
ccatctgcct gccggacgcc tcccatgtct tccctgccgg caaggccatc tgggtcacgg 2280
gctggggaca cacccagtat ggaggcactg gcgcgctgat cctgcaaaag ggtgagatcc 2340
gcgtcatcaa ccagaccacc tgcgagaacc tcctgccgca gcagatcacg ccgcgcatga 2400
tgtgcgtggg cttcctcagc ggcggcgtgg actcctgcca gggtgattcc gggggacccc 2460
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tgtccagcgt ggaggcggat gggcggatct tccaggccgg tgtggtgagc tggggagacg 2520
gctgcgctca gaggaacaag ccaggcgtgt acacaaggct ccctctgttt cgggactgga 2580
tcaaagagaa cactggggta taggggccgg ggccacccaa atgtgtacac ctgcggggcc 2640
acccatcgtc caccccagtg tgcacgcctg caggctggag actggaccgc tgactgcacc 2700
agcgccccca gaacatacac tgtgaactca atctccaggg ctccaaatct gcctagaaaa 2760
cctctcgctt cctcagcctc caaagtggag ctgggaggta gaaggggagg acactggtgg 2820
ttctactgac ccaactgggg gcaaaggttt gaagacacag cctcccccgc cagccccaag 2880
ctgggccgag gcgcgtttgt gtatatctgc ctcccctgtc tgtaaggagc agcgggaacg 2940
gagcttcgga gcctcctcag tgaaggtggt ggggctgccg gatctgggct gtggggccct 3000
tgggccacgc tcttgaggaa gcccaggctc ggaggaccct ggaaaacaga cgggtctgag 3060
actgaaaatg gtttaccagc tcccaggtga cttcagtgtg tgtattgtgt aaatgagtaa 3120
aacattttat ttctttttaa aaaaaaaaa                                   3149

<210> 253
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Matripase

<400> 253
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
```

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        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
```

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His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 254
<211> 1258
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK13

<400> 254
tcaggccccg cccgccctgc cctcccctcc cgatcccgga gccatgtggc ccctggccct 60
agtgatcgcc tccctgacct tggccttgtc aggaggtgtc tcccaggagt cttccaaggt 120
tctcaacacc aatgggacca gtgggtttct cccaggtggc tacacctgct tcccccactc 180
tcagccctgg caggctgccc tactagtgca agggcggcta ctctgtgggg gagtcctggt 240
ccaccccaaa tgggtcctca ctgccgcaca ctgtctaaag gaggggctca aagtttacct 300
aggcaagcac gccctagggc gtgtggaagc tggtgagcag gtgagggaag ttgtccactc 360
tatcccccac cctgaatacc ggagaagccc cacccacctg aaccacgacc atgacatcat 420
gcttctggag ctgcagtccc cggtccagct cacaggctac atccaaaccc tgccccttc 480
ccacaacaac cgcctaaccc ctggcaccac ctgtcgggtg tctggctggg gcaccaccac 540
cagcccccag gtgaattacc ccaaaactct acaatgtgcc aacatccaac ttcgctcaga 600
tgaggagtgt cgtcaagtct acccaggaaa gatcactgac aacatgttgt gtgccggcac 660
aaaagagggt ggcaaagact cctgtgaggg tgactctggg ggccccctgg tctgtaacag 720
aacactgtat ggcatcgtct cctggggaga cttcccatgt gggcaacctg accggcctgg 780
tgtctacacc cgtgtctcaa gatacgtcct gtggatccgt gaaacaatcc gaaaatatga 840
aacccagcag caaaaatggt tgaagggccc acaataaaag ttgagaaatg taccggcttc 900
catcctgtca ccatgacttc ctcacatggt ctgcttagcc cttctctgct ccttattccc 960
agtgttccat ttgaaccagt gatccatgtc ctgaaaaatg ctcaatctca gctaacattc 1020
catgtttcag aagcattcag gcactgccag gcttgcagtc tcccagatgt tgcatccctg 1080
aaacatctca acaacctgaa tgtcccaacc cagacaatgg cccaggtctc tcaacttcat 1140
cagtgtggct tctatgagcc cagatcacca cctgaacgtt ctgtctgtgg cacattctta 1200
aatatttcca tcagcccatc tcaacaatat atgtcctata aatggaccat ccttgaca 1258

<210> 255
<211> 277
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK13

<400> 255
Met Trp Pro Leu Ala Leu Val Ile Ala Ser Leu Thr Leu Ala Leu Ser
 1   5   10   15
Gly Gly Val Ser Gln Glu Ser Ser Lys Val Leu Asn Thr Asn Gly Thr
            20   25   30
Ser Gly Phe Leu Pro Gly Gly Tyr Thr Cys Phe Pro His Ser Gln Pro
        35   40   45
Trp Gln Ala Ala Leu Leu Val Gln Gly Arg Leu Leu Cys Gly Gly Val
    50   55   60
Leu Val His Pro Lys Trp Val Leu Thr Ala Ala His Cys Leu Lys Glu
65   70   75   80

Gly Leu Lys Val Tyr Leu Gly Lys His Ala Leu Gly Arg Val Glu Ala
                85   90   95
Gly Glu Gln Val Arg Glu Val Val His Ser Ile Pro His Pro Glu Tyr
            100   105   110
Arg Arg Ser Pro Thr His Leu Asn His Asp His Asp Ile Met Leu Leu
        115   120   125
Glu Leu Gln Ser Pro Val Gln Leu Thr Gly Tyr Ile Gln Thr Leu Pro
    130   135   140
Leu Ser His Asn Asn Arg Leu Thr Pro Gly Thr Thr Cys Arg Val Ser
145   150   155   160
Gly Trp Gly Thr Thr Thr Ser Pro Gln Val Asn Tyr Pro Lys Thr Leu
                165   170   175
Gln Cys Ala Asn Ile Gln Leu Arg Ser Asp Glu Glu Cys Arg Gln Val
            180   185   190
Tyr Pro Gly Lys Ile Thr Asp Asn Met Leu Cys Ala Gly Thr Lys Glu
        195   200   205
Gly Gly Lys Asp Ser Cys Glu Gly Asp Ser Gly Gly Pro Leu Val Cys
    210   215   220
Asn Arg Thr Leu Tyr Gly Ile Val Ser Trp Gly Asp Phe Pro Cys Gly
225   230   235   240
Gln Pro Asp Arg Pro Gly Val Tyr Thr Arg Val Ser Arg Tyr Val Leu
                245   250   255
Trp Ile Arg Glu Thr Ile Arg Lys Tyr Glu Thr Gln Gln Gln Lys Trp
            260   265   270
Leu Lys Gly Pro Gln
        275

<210> 256
<211> 1438
<212> DNA
<213> Homo sapiens

<220>
<223> kallikrein hK9

<400> 256
catggaggag gaaggagatg gcatggctta ccataaagaa gcactggacg ccgggtgcac 60
gttccaggat ccaggtgccc aggggtcatg aagctgggac tcctctgtgc tctgctctct 120
ctgctggcag ggcatggctg ggcagacacc cgtgccatcg gggccgagga atgtcgcccc 180
aactcccagc cttggcaggc cggcctcttc caccttactc ggctcttctg tggggcgacc 240
ctcatcagtg accgctggct gctcacagct gcccactgcc gcaagccgta tctgtgggtc 300
cgccttggag agcaccacct ctggaaatgg gagggtccgg agcagctgtt ccgggttacg 360
gacttcttcc cccaccctgg cttcaacaag gacctcagcg ccaatgacca caatgatgac 420
atcatgctga tccgcctgcc caggcaggca cgtctgagtc ctgctgtgca gcccctcaac 480

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ctcagccaga cctgtgtctc cccaggcatg cagtgtctca tctcaggctg gggggccgtg 540
tccagcccca aggcgctgtt tccagtcaca ctgcagtgtg ccaacatcag catcctggag 600
aacaaactct gtcactgggc ataccctgga cacatctcgg acagcatgct ctgtgcgggc 660
ctgtgggagg ggggccgagg ttcctgccag ggtgactctg ggggccccct ggtttgcaat 720
ggaaccttgg caggcgtggt gtctgggggt gctgagccct gctccagacc ccggcgcccc 780
gcagtctaca ccagcgtatg ccactacctt gactggatcc aagaaatcat ggagaactga 840
gcccgcgcgc cacgggggca ccttggaaga ccaagagagg ccgaagggca cggggtaggg 900
ggttctcgta gggtcccagc ctcaatggtt cccgccctgg acctccagct gccctgactc 960
ccctctggac actaagactc cgcccctgag gctccgcccc ctcacgaggt caagcaagac 1020
acagtcgcgc cccctcggaa cggagcaggg acacgccctt cagagcccgt ctctatgacg 1080
tcaccgacag ccatcacctc cttcttggaa cagcacagcc tgtggctccg ccccaaggaa 1140
ccacttacac aaaatagctc cgcccctcgg aactttgccc agtgggactt cccctcggga 1200
ctccacccct tgtggccccg cctccttcac cagagatctc gcccctcgtg atgtcagggg 1260
cgcagtagct ccgcccacgt ggagctcggg cggtgtagag ctcagcccct tgtggccccg 1320
tcctgggcgt gtgctgggtt tgaatcctgg cggagacctg gggggaaatt gagggagggt 1380
ctggatacct ttagagccaa tgcaacggat gatttttcag taaacgcggg aaacctca   1438

<210> 257
<211> 250
<212> PRT
<213> Homo sapiens

<220>
<223> kallikrein hK9

<400> 257
Met Lys Leu Gly Leu Leu Cys Ala Leu Leu Ser Leu Leu Ala Gly His
 1               5                  10                  15
Gly Trp Ala Asp Thr Arg Ala Ile Gly Ala Glu Glu Cys Arg Pro Asn
            20                  25                  30
Ser Gln Pro Trp Gln Ala Gly Leu Phe His Leu Thr Arg Leu Phe Cys
        35                  40                  45
Gly Ala Thr Leu Ile Ser Asp Arg Trp Leu Leu Thr Ala Ala His Cys
    50                  55                  60
Arg Lys Pro Tyr Leu Trp Val Arg Leu Gly Glu His His Leu Trp Lys
65                  70                  75                  80
Trp Glu Gly Pro Glu Gln Leu Phe Arg Val Thr Asp Phe Phe Pro His
                85                  90                  95
Pro Gly Phe Asn Lys Asp Leu Ser Ala Asn Asp His Asn Asp Asp Ile
            100                 105                 110
Met Leu Ile Arg Leu Pro Arg Gln Ala Arg Leu Ser Pro Ala Val Gln
        115                 120                 125
Pro Leu Asn Leu Ser Gln Thr Cys Val Ser Pro Gly Met Gln Cys Leu
    130                 135                 140
Ile Ser Gly Trp Gly Ala Val Ser Ser Pro Lys Ala Leu Phe Pro Val
145                 150                 155                 160
Thr Leu Gln Cys Ala Asn Ile Ser Ile Leu Glu Asn Lys Leu Cys His
                165                 170                 175
Trp Ala Tyr Pro Gly His Ile Ser Asp Ser Met Leu Cys Ala Gly Leu
            180                 185                 190
Trp Glu Gly Gly Arg Gly Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu
        195                 200                 205
Val Cys Asn Gly Thr Leu Ala Gly Val Val Ser Gly Gly Ala Glu Pro
    210                 215                 220
Cys Ser Arg Pro Arg Arg Pro Ala Val Tyr Thr Ser Val Cys His Tyr
225                 230                 235                 240
Leu Asp Trp Ile Gln Glu Ile Met Glu Asn
```

245 250

<210> 258
<211> 3212
<212> DNA
<213> Homo sapiens

<220>
<223> Mername-AA035 peptidase

<400> 258
cttgagccag acccagtcca gctctggtgc ctgccctctg gtgcgagctg acctgagatg 60
cacttccctc ctctgtgagc tgtctcggca cccacttgca gtcactgccg cctgatgttg 120
ttactcttcc actccaaaag gatgcccgtg gccgaggccc cccaggtggc tggcgggcag 180
ggggacggag gtgatggcga ggaagcggag ccggagggga tgttcaaggc ctgtgaggac 240
tccaagagaa aagcccgggg ctacctccgc ctggtgcccc tgtttgtgct gctggccctg 300
ctcgtgctgg cttcggcggg ggtgctactc tggtatttcc tagggtacaa ggcggaggtg 360
atggtcagcc aggtgtactc aggcagtctg cgtgtactca atcgccactt ctcccaggat 420
cttacccgcc gggaatctag tgccttccgc agtgaaaccg ccaaagccca gaagatgctc 480
aaggagctca tcaccagcac ccgcctggga acttactaca actccagctc cgtctattcc 540
tttggggagg gaccgcctcac ctgcttcttc tggttcattc tccaaatccc cgagcaccgc 600
cggctgatgc tgagccccga ggtggtgcag gcactgctgg tggaggagct gctgtccaca 660
gtcaacagct cggctgccgt cccctacagg gccgagtacg aagtggaccc cgagggccta 720
gtgatcctgg aagccagtgt gaaagacata gctgcattga attccacgct gggttgttac 780
cgctacagct acgtgggcca gggccaggtc ctccggctga aggggcctga ccacctggcc 840
tccagctgcc tgtggcacct gcagggcccc aaggacctca tgctcaaact ccggctggag 900
tggacgctgg cagagtgccg ggaccgactg gccatgtatg acgtggccgg gcccctggag 960
aagaggctca tcacctcggt gtacggctgc agccgccagg agcccgtggt ggaggttctg 1020
gcgtcggggg ccatcatggc ggtcgtctgg aagaagggcc tgcacagcta ctacgacccc 1080
ttcgtgctct ccgtgcagcc ggtggtcttc caggcctgtg aagtgaacct gacgctggac 1140
aacaggctcg actcccaggg cgtcctcagc accccgtact tccccagcta ctactcgccc 1200
caaacccact gctcctggca cctcacggtg ccctctctgg actacggctt ggccctctgg 1260
tttgatgcct atgcactgag gaggcagaag tatgatttgc cgtgcaccca gggccagtgg 1320
acgatccaga acaggaggct gtgtggcttg cgcatcctgc agccctacgc cgagaggatc 1380
cccgtggtgg ccacggccgg gatcaccatc aacttcacct cccagatctc cctcaccggg 1440
cccggtgtgc gggtgcacta tggcttgtac aaccagtcgg acccctgccc tggagagttc 1500
ctctgttctg tgaatggact ctgtgtccct gcctgtgatg gggtcaagga ctgccccaac 1560
ggcctggatg agagaaactg cgtttgcaga gccacattcc agtgcaaaga ggacagcaca 1620
tgcatctcac tgcccaaggt ctgtgatggg cagcctgatt gtctcaacgg cagcgacgaa 1680
gagcagtgcc aggaaggggt gccatgtggg acattcacct tccagtgtga ggaccggagc 1740
tgcgtgaaga agcccaaccc gcagtgtgat gggcggcccg actgcaggga cggctcggat 1800
gaggagcact gtgactgtgg cctccagggc ccctccagcc gcattgttgg tggagctgtg 1860
tcctccgagg gtgagtggcc atggcaggcc agcctccagg ttcggggtcg acacatctgt 1920
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agcatggcct ccacggtgct gtggaccgtg ttcctgggca aggtgtggca gaactcgcgc 2040
tggcctggag aggtgtcctt caaggtgagc cgcctgctcc tgcacccgta ccacgaagag 2100
gacagccatg actacgacgt ggcgctgctg cagctcgacc acccggtggt gcgctcggcc 2160
gccgtgcgcc ccgtctgcct gcccgcgcgc tcccacttct tcgagcccgg cctgcactgc 2220
tggattacgg gctggggcgc cttgcgcgag ggcggcccca tcagcaacgc tctgcagaaa 2280
gtggatgtgc agttgatccc acaggacctg tgcagcgagg tctatcgcta ccaggtgacg 2340
ccacgcatgc tgtgtgccgg ctaccgcaag ggcaagaagg atgcctgtca gggtgactca 2400
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tggggcctgg gctgtggccg gcctaactac ttcggcgtct acacccgcat cacaggtgtg 2520
atcagctgga tccagcaagt ggtgacctga ggaactgccc ccctgcaaag cagggcccac 2580
ctcctggact cagagagccc agggcaactg ccaagcaggg ggacaagtat tctggcgggg 2640
ggtgggggag agagcaggcc ctgtggtggc aggaggtggc atcttgtctc gtccctgatg 2700

tctgctccag tgatggcagg aggatggaga agtgccagca gctgggggtc aagacgtccc 2760
ctgaggaccc aggcccacac ccagcccttc tgcctcccaa ttctctctcc tccgtcccct 2820
tcctccactg ctgcctaatg caaggcagtg gctcagcagc aagaatgctg gttctacatc 2880
ccgaggagtg tctgaggtgc gccccactct gtacagaggc tgtttgggca gccttgcctc 2940
cagagagcag attccagctt cggaagcccc tggtctaact tgggatctgg gaatggaagg 3000
tgctcccatc ggaggggacc ctcagagccc tggagactgc caggtgggcc tgctgccact 3060
gtaagccaaa aggtggggaa gtcctgactc cagggtcctt gccccacccc tgcctgccac 3120
ctgggccctc acagcccaga ccctcactgg gaggtgagct cagctgccct ttggaataaa 3180
gctgcctgat caaaaaaaaa aaaaaaaaaa aa 3212

<210> 259
<211> 811
<212> PRT
<213> Homo sapiens

<220>
<223> Mername-AA035 peptidase

<400> 259
Met Leu Leu Leu Phe His Ser Lys Arg Met Pro Val Ala Glu Ala Pro
1 5 10 15
Gln Val Ala Gly Gly Gln Gly Asp Gly Gly Asp Gly Glu Glu Ala Glu
20 25 30
Pro Glu Gly Met Phe Lys Ala Cys Glu Asp Ser Lys Arg Lys Ala Arg
35 40 45
Gly Tyr Leu Arg Leu Val Pro Leu Phe Val Leu Leu Ala Leu Leu Val
50 55 60
Leu Ala Ser Ala Gly Val Leu Leu Trp Tyr Phe Leu Gly Tyr Lys Ala
65 70 75 80
Glu Val Met Val Ser Gln Val Tyr Ser Gly Ser Leu Arg Val Leu Asn
85 90 95
Arg His Phe Ser Gln Asp Leu Thr Arg Arg Glu Ser Ser Ala Phe Arg
100 105 110
Ser Glu Thr Ala Lys Ala Gln Lys Met Leu Lys Glu Leu Ile Thr Ser
115 120 125
Thr Arg Leu Gly Thr Tyr Tyr Asn Ser Ser Ser Val Tyr Ser Phe Gly
130 135 140
Glu Gly Pro Leu Thr Cys Phe Phe Trp Phe Ile Leu Gln Ile Pro Glu
145 150 155 160
His Arg Arg Leu Met Leu Ser Pro Glu Val Val Gln Ala Leu Leu Val
165 170 175
Glu Glu Leu Leu Ser Thr Val Asn Ser Ser Ala Ala Val Pro Tyr Arg
180 185 190
Ala Glu Tyr Glu Val Asp Pro Glu Gly Leu Val Ile Leu Glu Ala Ser
195 200 205
Val Lys Asp Ile Ala Ala Leu Asn Ser Thr Leu Gly Cys Tyr Arg Tyr
210 215 220
Ser Tyr Val Gly Gln Gly Gln Val Leu Arg Leu Lys Gly Pro Asp His
225 230 235 240
Leu Ala Ser Ser Cys Leu Trp His Leu Gln Gly Pro Lys Asp Leu Met
245 250 255
Leu Lys Leu Arg Leu Glu Trp Thr Leu Ala Glu Cys Arg Asp Arg Leu
260 265 270
Ala Met Tyr Asp Val Ala Gly Pro Leu Glu Lys Arg Leu Ile Thr Ser
275 280 285
Val Tyr Gly Cys Ser Arg Gln Glu Pro Val Val Glu Val Leu Ala Ser
290 295 300

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Gly Ala Ile Met Ala Val Val Trp Lys Lys Gly Leu His Ser Tyr Tyr
305                 310                 315                 320
Asp Pro Phe Val Leu Ser Val Gln Pro Val Val Phe Gln Ala Cys Glu
                325                 330                 335
Val Asn Leu Thr Leu Asp Asn Arg Leu Asp Ser Gln Gly Val Leu Ser
            340                 345                 350
Thr Pro Tyr Phe Pro Ser Tyr Tyr Ser Pro Gln Thr His Cys Ser Trp
        355                 360                 365
His Leu Thr Val Pro Ser Leu Asp Tyr Gly Leu Ala Leu Trp Phe Asp
    370                 375                 380
Ala Tyr Ala Leu Arg Arg Gln Lys Tyr Asp Leu Pro Cys Thr Gln Gly
385                 390                 395                 400
Gln Trp Thr Ile Gln Asn Arg Arg Leu Cys Gly Leu Arg Ile Leu Gln
                405                 410                 415
Pro Tyr Ala Glu Arg Ile Pro Val Val Ala Thr Ala Gly Ile Thr Ile
            420                 425                 430
Asn Phe Thr Ser Gln Ile Ser Leu Thr Gly Pro Gly Val Arg Val His
        435                 440                 445
Tyr Gly Leu Tyr Asn Gln Ser Asp Pro Cys Pro Gly Glu Phe Leu Cys
    450                 455                 460
Ser Val Asn Gly Leu Cys Val Pro Ala Cys Asp Gly Val Lys Asp Cys
465                 470                 475                 480
Pro Asn Gly Leu Asp Glu Arg Asn Cys Val Cys Arg Ala Thr Phe Gln
                485                 490                 495
Cys Lys Glu Asp Ser Thr Cys Ile Ser Leu Pro Lys Val Cys Asp Gly
            500                 505                 510
Gln Pro Asp Cys Leu Asn Gly Ser Asp Glu Glu Gln Cys Gln Glu Gly
        515                 520                 525
Val Pro Cys Gly Thr Phe Thr Phe Gln Cys Glu Asp Arg Ser Cys Val
    530                 535                 540
Lys Lys Pro Asn Pro Gln Cys Asp Gly Arg Pro Asp Cys Arg Asp Gly
545                 550                 555                 560
Ser Asp Glu Glu His Cys Asp Cys Gly Leu Gln Gly Pro Ser Ser Arg
                565                 570                 575
Ile Val Gly Gly Ala Val Ser Ser Glu Gly Glu Trp Pro Trp Gln Ala
            580                 585                 590
Ser Leu Gln Val Arg Gly Arg His Ile Cys Gly Gly Ala Leu Ile Ala
        595                 600                 605
Asp Arg Trp Val Ile Thr Ala Ala His Cys Phe Gln Glu Asp Ser Met
    610                 615                 620
Ala Ser Thr Val Leu Trp Thr Val Phe Leu Gly Lys Val Trp Gln Asn
625                 630                 635                 640
Ser Arg Trp Pro Gly Glu Val Ser Phe Lys Val Ser Arg Leu Leu Leu
                645                 650                 655
His Pro Tyr His Glu Glu Asp Ser His Asp Tyr Asp Val Ala Leu Leu
            660                 665                 670
Gln Leu Asp His Pro Val Val Arg Ser Ala Ala Val Arg Pro Val Cys
        675                 680                 685
Leu Pro Ala Arg Ser His Phe Phe Glu Pro Gly Leu His Cys Trp Ile
    690                 695                 700
Thr Gly Trp Gly Ala Leu Arg Glu Gly Gly Pro Ile Ser Asn Ala Leu
705                 710                 715                 720
Gln Lys Val Asp Val Gln Leu Ile Pro Gln Asp Leu Cys Ser Glu Val
                725                 730                 735
Tyr Arg Tyr Gln Val Thr Pro Arg Met Leu Cys Ala Gly Tyr Arg Lys
            740                 745                 750
Gly Lys Lys Asp Ala Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys
```

```
        755                 760                 765
Lys Ala Leu Ser Gly Arg Trp Phe Leu Ala Gly Leu Val Ser Trp Gly
    770                 775                 780
Leu Gly Cys Gly Arg Pro Asn Tyr Phe Gly Val Tyr Thr Arg Ile Thr
785                 790                 795                 800
Gly Val Ile Ser Trp Ile Gln Gln Val Val Thr
                805                 810
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<210> 260
<211> 3750
<212> DNA
<213> Homo sapiens

<220>
<223> umbilical vein proteinase

<400> 260
gcgctgctcg ccagcttgct cgcactcggc tgtgcggcgg ggcaggcatg ggagccgcgc 60
gctctctccc ggcgcccaca cctgtctgag cggcgcagcg agccgcggcc cgggcgggct 120
gctcggcgcg gaacagtgct cggcatggca gggattccag ggctcctctt ccttctcttc 180
tttctgctct gtgctgttgg gcaagtgagc ccttacagtg ccccctggaa acccacttgg 240
cctgcatacc gcctccctgt cgtcttgccc cagtctaccc tcaatttagc caagccagac 300
tttggagccg aagccaaatt agaagtatct tcttcatgtg gaccccagtg tcataaggga 360
actccactgc ccacttacga agaggccaag caatatctgt cttatgaaac gctctatgcc 420
aatggcagcc gcacagagac gcaggtgggc atctacatcc tcagcagtag tggagatggg 480
gcccaacacc gagactcagg gtcttcagga aagtctcgaa ggaagcggca gatttatggc 540
tatgacagca ggttcagcat ttttgggaag gacttcctgc tcaactaccc tttctcaaca 600
tcagtgaagt tatccacggg ctgcaccggc accctggtgg cagagaagca tgtcctcaca 660
gctgcccact gcatacacga tggaaaaacc tatgtgaaag gaacccagaa gcttcgagtg 720
ggcttcctaa agcccaagtt taaagatggt ggtcgagggg ccaacgactc cacttcagcc 780
atgcccgagc agatgaaatt tcagtggatc cgggtgaaac gcacccatgt gcccaagggt 840
tggatcaagg gcaatgccaa tgacatcggc atggattatg attatgccct cctggaactc 900
aaaaagcccc acaagagaaa atttatgaag attggggtga gccctcctgc taagcagctg 960
ccaggggca gaattcactt ctctggttat gacaatgacc gaccaggcaa tttggtgtat 1020
cgcttctgtg acgtcaaaga cgagacctat gacttgctct accagcaatg cgatgcccag 1080
ccaggggcca gcgggtctgg ggtctatgtg aggatgtgga agagacagca gcagaagtgg 1140
gagcgaaaaa ttattggcat tttttcaggg caccagtggg tggacatgaa tggttcccca 1200
caggatttca acgtggctgt cagaatcact cctctcaaat atgcccagat ttgctattgg 1260
attaaaggaa actacctgga ttgtagggag gggtgacaca gtgttccctc ctggcagcaa 1320
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acacgtgtgt gtgtgtgtgt gtgtgtgtgt aaggtgtctt ataatctttt acctatttct 1440
tacaattgca agatgactgg ctttactatt tgaaaactgg tttgtgtatc atatcatata 1500
tcatttaagc agtttgaagg catacttttg catagaaata aaaaaaatac tgatttgggg 1560
caatgaggaa tatttgacaa ttaagttaat cttcacgttt ttgcaaactt tgatttttat 1620
ttcatctgaa cttgtttcaa agatttatat taaatatttg gcatacaaga gatatgaatt 1680
cttatatgtg tgcatgtgtg ttttcttctg agattcatct tggtggtggg ttttttgtt 1740
tttttaattc agtgcctgat ctttaatgct tccataaggc agtgttccca tttaggaact 1800
ttgacagcat ttgttaggca gaatattttg gatttggagg catttgcatg gtagtctttg 1860
aacagtaaaa tgatgtgttg actatactga tacacatatt aaactatacc ttatagtaaa 1920
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actttgtagg aagtctttgc atatggccct cccaacttta aagtcatacc agagtggcca 2040
agagtgttta tcccaaccct tccatttaac aggatttcac tcacatttct ggaactagct 2100
atttttcaga agacaataat cagggcttaa ttagaacagg ctgtatttcc tcccagcaaa 2160
cagttgtggc cacactaaaa acaatcatag cattttaccc ctggattata gcacatctca 2220
tgttttatca tttggatgga gtaatttaaa atgaattaaa ttccagagaa caatggaagc 2280
attgcctggc agatgtcaca acagaataac cacttgtttg gagcctggca cagtcctcca 2340

```
gcctgatcaa aaattattct gcatagtttt cagtgtgctt tctgggagct atgtacttct 2400
tcaatttgga aacttttctc tctcatttat agtgaaaata cttggaagtt actttaagaa 2460
aaccagtgtg gccttttttcc ctctagcttt aaaagggccg cttttgctgg aatgctctag 2520
gttatagata aacaattagg tataatagca aaaatgaaaa ttggaagaat gcaaaatgga 2580
tcagaatcat gccttccaat aaaggccttt acacatgttt tatcaatatg attatcaaat 2640
cacagcatat acagaaaaga cttggactta ttgtatgttt ttatttttatg gctctcggcc 2700
taagcacttc tttctaaatg tatcggagaa aaaatcaaat ggactacaag cacgtgtttg 2760
ctgtgcttgc accccaggta aacctgcatt gtagcaattt gtaaggatat tcagatggag 2820
cactgtcact tagacattct ctgggggatt ttctgcttgt ctttcttgag ctttttggaa 2880
ggataattct gataaggcac tcaagaaacg tacaaccaca gtgctttctt caaatcatat 2940
gagaaatact atgcatagca aggagatgca gagccgccag gaaaattctg agttccagca 3000
caattttctt tggaatctaa caggaatcta gcctgaggaa gaagggaggt ctccatttct 3060
atgtctggta tttgggggtt ttgtttgttt ttgctttagc ttggtgaaaa aaagttcact 3120
gaacaccaag accagaatgg attttttttaa aaaaatagat gttccttttg tgaagcacct 3180
tgattccttg attttgattt tttgcaaagt tagacaatgg cacaaagtca aaatgaaatc 3240
aatgtttagt tcacaagtag atgtaattta ctaaagaatg atacacccat atgctatata 3300
cagcttaact cacagaactg taaaagaaaa ttataaaata attcaacatg tccatctttt 3360
tagtgataat aaaagaaagc atggtattaa actatcatag aagtagacag aaaaagaaaa 3420
aaggactcat ggcattatta atataattag tgctttacat gtgttagtta tacatattag 3480
aagcatattt gcctagtaag gctagtagaa ccacatttcc caaagtgtgc tccttaaaca 3540
ctcatgcctt atgattttct accaaaagta aaaagggttg tattaagtca gaggaagatg 3600
cctctccatt ttccctctct ttatcagagg ttcacatgcc tgtctgcaca ttaaaagctc 3660
tgggaagacc tgttgtaaag ggacaagttg aggttgtaaa atctgcattt aaataaacat 3720
ctttgatcac aaaaaaaaaa aaaaaaaaaa                                  3750
```

<210> 261
<211> 383
<212> PRT
<213> Homo sapiens

<220>
<223> umbilical vein proteinase

<400> 261

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Met Ala Gly Ile Pro Gly Leu Leu Phe Leu Leu Phe Phe Leu Leu Cys
 1               5                  10                  15
Ala Val Gly Gln Val Ser Pro Tyr Ser Ala Pro Trp Lys Pro Thr Trp
            20                  25                  30
Pro Ala Tyr Arg Leu Pro Val Val Leu Pro Gln Ser Thr Leu Asn Leu
        35                  40                  45
Ala Lys Pro Asp Phe Gly Ala Glu Ala Lys Leu Glu Val Ser Ser Ser
    50                  55                  60
Cys Gly Pro Gln Cys His Lys Gly Thr Pro Leu Pro Thr Tyr Glu Glu
65                  70                  75                  80
Ala Lys Gln Tyr Leu Ser Tyr Glu Thr Leu Tyr Ala Asn Gly Ser Arg
                85                  90                  95
Thr Glu Thr Gln Val Gly Ile Tyr Ile Leu Ser Ser Ser Gly Asp Gly
            100                 105                 110
Ala Gln His Arg Asp Ser Gly Ser Ser Gly Lys Ser Arg Arg Lys Arg
        115                 120                 125
Gln Ile Tyr Gly Tyr Asp Ser Arg Phe Ser Ile Phe Gly Lys Asp Phe
    130                 135                 140
Leu Leu Asn Tyr Pro Phe Ser Thr Ser Val Lys Leu Ser Thr Gly Cys
145                 150                 155                 160
Thr Gly Thr Leu Val Ala Glu Lys His Val Leu Thr Ala Ala His Cys
                165                 170                 175
Ile His Asp Gly Lys Thr Tyr Val Lys Gly Thr Gln Lys Leu Arg Val
```

```
            180                 185                 190
Gly Phe Leu Lys Pro Lys Phe Lys Asp Gly Gly Arg Gly Ala Asn Asp
        195                 200                 205
Ser Thr Ser Ala Met Pro Glu Gln Met Lys Phe Gln Trp Ile Arg Val
    210                 215                 220
Lys Arg Thr His Val Pro Lys Gly Trp Ile Lys Gly Asn Ala Asn Asp
225                 230                 235                 240
Ile Gly Met Asp Tyr Asp Tyr Ala Leu Leu Glu Leu Lys Lys Pro His
                245                 250                 255
Lys Arg Lys Phe Met Lys Ile Gly Val Ser Pro Pro Ala Lys Gln Leu
            260                 265                 270
Pro Gly Gly Arg Ile His Phe Ser Gly Tyr Asp Asn Asp Arg Pro Gly
        275                 280                 285
Asn Leu Val Tyr Arg Phe Cys Asp Val Lys Asp Glu Thr Tyr Asp Leu
    290                 295                 300
Leu Tyr Gln Gln Cys Asp Ala Gln Pro Gly Ala Ser Gly Ser Gly Val
305                 310                 315                 320
Tyr Val Arg Met Trp Lys Arg Gln Gln Gln Lys Trp Glu Arg Lys Ile
                325                 330                 335
Ile Gly Ile Phe Ser Gly His Gln Trp Val Asp Met Asn Gly Ser Pro
            340                 345                 350
Gln Asp Phe Asn Val Ala Val Arg Ile Thr Pro Leu Lys Tyr Ala Gln
        355                 360                 365
Ile Cys Tyr Trp Ile Lys Gly Asn Tyr Leu Asp Cys Arg Glu Gly
    370                 375                 380
```

<210> 262
<211> 26
<212> PRT
<213> Homo sapiens

<220>
<223> LCLP proteinase (LCLP (N-terminus))

<400> 262
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Ile Ile Gly Gly Thr Glu Ser Lys Pro Asp Ser Arg Pro Tyr Met Ala
 1               5                  10                  15
Leu Leu Gln Ile Val Glu Pro Ala Val His
            20                  25
```

<210> 263
<211> 2265
<212> DNA
<213> Homo sapiens

<220>
<223> Spinesin

<400> 263
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acgcgggata cagggagggg ccatgtgcga accagggaga cctcatcttc caaccaagct 60
tgctgggctt gcatttaatc aatgcatggc cagagaacag gagcggaaca ttgcctagta 120
gaccctgagg ctttacaaca gtgctactga cccctatgag cctgatgctg gatgaccaac 180
cccctatgga ggcccagtat gcagaggagg gcccaggacc tgggatcttc agagcagagc 240
ctggagacca gcagcatccc atttctcagg cggtgtgctg gcgttccatg cgacgtggct 300
gtgcagtgct gggagccctg gggctgctgg ccggtgcagg tgttggctca tggctcctag 360
```

```
tgctgtatct gtgtcctgct gcctctcagc ccatttccgg gaccttgcag gatgaggaga 420
taactttgag ctgctcagag gccagcgctg aggaagctct gctccctgca ctccccaaaa 480
cagtatcttt cagaataaac agcgaagact tcttgctgga agcgcaagtg agggatcagc 540
cacgctggct cctggtctgc catgagggct ggagccccgc cctggggctg cagatctgct 600
ggagccttgg gcatctcaga ctcactcacc acaagggagt aaacctcact gacatcaaac 660
tcaacagttc ccaggagttt gctcagctct ctcctagact gggaggcttc ctggaggagg 720
cgtggcagcc caggaacaac tgcacttctg gtcaagttgt ttccctcaga tgctctgagt 780
gtggagcgag gcccctggct tcccggatag ttggtgggca gtctgtggct cctgggcgct 840
ggccgtggca ggccagcgtg gccctgggct tccggcacac gtgtgggggc tctgtgctag 900
cgccacgctg ggtggtgact gctgcacatt gtatgcacag tttcaggctg gcccgcctgt 960
ccagctggcg ggttcatgcg gggctggtca gccacagtgc cgtcaggccc caccaagggg 1020
ctctggtgga gaggattatc ccacaccccc tctacagtgc ccagaatcat gactacgacg 1080
tcgccctcct gaggctccag accgctctca acttctcaga cactgtgggc gctgtgtgcc 1140
tgccggccaa ggaacagcat tttccgaagg gctcgcggtg ctgggtgtct ggctggggcc 1200
acacccaccc tagccatact tacagctcgg atatgctcca ggacacggtg gtgcccttgt 1260
tcagcactca gctctgcaac agctcttgcg tgtacagcgg agccctcacc ccccgcatgc 1320
tttgcgctgg ctacctggac ggaagggctg atgcatgcca gggagatagc gggggccccc 1380
tagtgtgccc agatggggac acatggcgcc tagtgggggt ggtcagctgg gggcgtgcgt 1440
gcgcagagcc caatcaccca ggtgtctacg ccaaggtagc tgagtttctg gactggatcc 1500
atgacactgc tcaggactcc ctcctctgag tcctgctgtt tcctccagtc tcactgcaca 1560
ccactgcctc atgcttcctg gggcctccag cagctccact aatggaggag aggcagtagc 1620
ctccgacaca gaacgcatgg acctcctact actgtgtgtg aggaacagtc actacccact 1680
ggccagccac ccagccaaca ggtctctcct cttgggccct gatttcagag tcctctttct 1740
cactagagac tcaatgacag aagagaggct gggacttggt tgggcatgct gtggttgctg 1800
agggatgagg gggaggagag aggtaggagc tggagatgaa gagactgcta gaagcagcag 1860
gaagcctgcc cttctgccct ctcccctccc tgcccctgtg tgagtctttt agggagggtg 1920
actgggaggt gccccccgtc ccacctttt cctgtgctct aggtgggcta agtgcctccc 1980
tagaggactc catggctgag aggctcctgg gcagatgggg tcaaggctgg gccagtccca 2040
gatgaagcct atgggagtca ggaccctctc cactctccct ctccactccc cttcctgttc 2100
tcacctggct gtggctggcc ctgtgtgggg tgggtacact ggaaaacaag aaggttggag 2160
ttggtctagg acattggttt taaatgacag ttctgtgaac tggtccaagg aggttctgtt 2220
attaaagtga tatatggtct tgaaaaaaaa aaaaaaaaaa aaaaa                  2265

<210> 264
<211> 457
<212> PRT
<213> Homo sapiens

<220>
<223> Spinesin

<400> 264
Met Ser Leu Met Leu Asp Asp Gln Pro Pro Met Glu Ala Gln Tyr Ala
 1               5                  10                  15
Glu Glu Gly Pro Gly Pro Gly Ile Phe Arg Ala Glu Pro Gly Asp Gln
            20                  25                  30
Gln His Pro Ile Ser Gln Ala Val Cys Trp Arg Ser Met Arg Arg Gly
        35                  40                  45
Cys Ala Val Leu Gly Ala Leu Gly Leu Leu Ala Gly Ala Gly Val Gly
    50                  55                  60
Ser Trp Leu Leu Val Leu Tyr Leu Cys Pro Ala Ala Ser Gln Pro Ile
65                  70                  75                  80
Ser Gly Thr Leu Gln Asp Glu Glu Ile Thr Leu Ser Cys Ser Glu Ala
                85                  90                  95
Ser Ala Glu Glu Ala Leu Leu Pro Ala Leu Pro Lys Thr Val Ser Phe
            100                 105                 110
Arg Ile Asn Ser Glu Asp Phe Leu Leu Glu Ala Gln Val Arg Asp Gln
```

```
        115                 120                 125
Pro Arg Trp Leu Leu Val Cys His Glu Gly Trp Ser Pro Ala Leu Gly
    130                 135                 140
Leu Gln Ile Cys Trp Ser Leu Gly His Leu Arg Leu Thr His His Lys
145                 150                 155                 160
Gly Val Asn Leu Thr Asp Ile Lys Leu Asn Ser Ser Gln Glu Phe Ala
                165                 170                 175
Gln Leu Ser Pro Arg Leu Gly Gly Phe Leu Glu Glu Ala Trp Gln Pro
            180                 185                 190
Arg Asn Asn Cys Thr Ser Gly Gln Val Val Ser Leu Arg Cys Ser Glu
        195                 200                 205
Cys Gly Ala Arg Pro Leu Ala Ser Arg Ile Val Gly Gly Gln Ser Val
    210                 215                 220
Ala Pro Gly Arg Trp Pro Trp Gln Ala Ser Val Ala Leu Gly Phe Arg
225                 230                 235                 240
His Thr Cys Gly Gly Ser Val Leu Ala Pro Arg Trp Val Val Thr Ala
                245                 250                 255
Ala His Cys Met His Ser Phe Arg Leu Ala Arg Leu Ser Ser Trp Arg
            260                 265                 270
Val His Ala Gly Leu Val Ser His Ser Ala Val Arg Pro His Gln Gly
        275                 280                 285
Ala Leu Val Glu Arg Ile Ile Pro His Pro Leu Tyr Ser Ala Gln Asn
    290                 295                 300
His Asp Tyr Asp Val Ala Leu Leu Arg Leu Gln Thr Ala Leu Asn Phe
305                 310                 315                 320
Ser Asp Thr Val Gly Ala Val Cys Leu Pro Ala Lys Glu Gln His Phe
                325                 330                 335
Pro Lys Gly Ser Arg Cys Trp Val Ser Gly Trp Gly His Thr His Pro
            340                 345                 350
Ser His Thr Tyr Ser Ser Asp Met Leu Gln Asp Thr Val Val Pro Leu
        355                 360                 365
Phe Ser Thr Gln Leu Cys Asn Ser Ser Cys Val Tyr Ser Gly Ala Leu
    370                 375                 380
Thr Pro Arg Met Leu Cys Ala Gly Tyr Leu Asp Gly Arg Ala Asp Ala
385                 390                 395                 400
Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Pro Asp Gly Asp Thr
                405                 410                 415
Trp Arg Leu Val Gly Val Val Ser Trp Gly Arg Ala Cys Ala Glu Pro
            420                 425                 430
Asn His Pro Gly Val Tyr Ala Lys Val Ala Glu Phe Leu Asp Trp Ile
        435                 440                 445
His Asp Thr Ala Gln Asp Ser Leu Leu
    450                 455
```

<210> 265
<211> 1243
<212> DNA
<213> Homo sapiens

<220>
<223> Mername-AA178 peptidase

<400> 265
atggctgccc ctgcttccgt catgggccca ctcgggccct ctgccctggg ccttctgctg 60
ctgctcctgg tggtggcccc tccccgggtc gcagcattgg tccacagaca gccagagaac 120
cagggaatct ccctaactgg cagcgtggcc tgtggtcggc ccagcatgga ggggaaaatc 180

ctgggcggcg tccctgcgcc cgagaggaag tggccgtggc aggtcagcgt gcactacgca 240
ggcctccacg tctgcggcgg ctccatcctc aatgagtact gggtgctgtc agctgcgcac 300
tgctttcaca gggacaagaa tatcaaaatc tatgacatgt acgtaggcct cgtaaacctc 360
agggtggccg gcaaccacac ccagtggtat gaggtgaaca gggtgatcct gcaccccaca 420
tatgagatgt accaccccat cggaggtgac gtggccctgg tgcagctgaa gacccgcatt 480
gtgttttctg agtccgtgct cccggtttgc cttgcaactc cagaagtgaa ccttaccagt 540
gccaattgct gggctacggg atggggacta gtctcaaaac aaggtgagac ctcagacgag 600
ctgcaggaga tgcagctccc gctgatcctg gagccctggt gccacctgct ctacggacac 660
atgtcctaca tcatgcccga catgctgtgt gctggggaca tcctgaatgc taagaccgtg 720
tgtgagggcg actccggggg cccacttgtc tgtgaattca accgcagctg gttgcagatt 780
ggaattgtga gctggggccg aggctgctcc aaccctctgt accctggagt gtatgccagt 840
gtttcctatt tctcaaaatg gatatgtgat aacatagaaa tcacgcccac tcctgctcag 900
ccagcccctg ctctctctcc agctctgggg cccactctca gcgtcctaat ggccatgctg 960
gctggctggt cagtgctgtg aggtcaggat acccactcta ggattctcat ggctgcacac 1020
cctgccccag cccagctgcc tccagacccc taagcatctc ctgtcctggc ctctctgaag 1080
cagacaaggg ccacctatcc cgggggtgga tgctgagtcc aggaggtgat gagcaagtgt 1140
acaaaagaaa aaagggaagg gggagagggg ctggtcaggg agaacccagc ttgggcagag 1200
tgcacctgag atttgataag atcattaaat atttacaaag caa 1243

<210> 266
<211> 326
<212> PRT
<213> Homo sapiens

<220>
<223> Mername-AA178 peptidase

<400> 266
Met Ala Ala Pro Ala Ser Val Met Gly Pro Leu Gly Pro Ser Ala Leu
 1   5   10   15
Gly Leu Leu Leu Leu Leu Leu Val Val Ala Pro Pro Arg Val Ala Ala
            20   25   30
Leu Val His Arg Gln Pro Glu Asn Gln Gly Ile Ser Leu Thr Gly Ser
        35   40   45
Val Ala Cys Gly Arg Pro Ser Met Glu Gly Lys Ile Leu Gly Gly Val
    50   55   60
Pro Ala Pro Glu Arg Lys Trp Pro Trp Gln Val Ser Val His Tyr Ala
65   70   75   80
Gly Leu His Val Cys Gly Gly Ser Ile Leu Asn Glu Tyr Trp Val Leu
                85   90   95
Ser Ala Ala His Cys Phe His Arg Asp Lys Asn Ile Lys Ile Tyr Asp
            100   105   110
Met Tyr Val Gly Leu Val Asn Leu Arg Val Ala Gly Asn His Thr Gln
        115   120   125
Trp Tyr Glu Val Asn Arg Val Ile Leu His Pro Thr Tyr Glu Met Tyr
    130   135   140
His Pro Ile Gly Gly Asp Val Ala Leu Val Gln Leu Lys Thr Arg Ile
145   150   155   160
Val Phe Ser Glu Ser Val Leu Pro Val Cys Leu Ala Thr Pro Glu Val
                165   170   175
Asn Leu Thr Ser Ala Asn Cys Trp Ala Thr Gly Trp Gly Leu Val Ser
            180   185   190
Lys Gln Gly Glu Thr Ser Asp Glu Leu Gln Glu Met Gln Leu Pro Leu
        195   200   205
Ile Leu Glu Pro Trp Cys His Leu Leu Tyr Gly His Met Ser Tyr Ile
    210   215   220
Met Pro Asp Met Leu Cys Ala Gly Asp Ile Leu Asn Ala Lys Thr Val

```
225                 230                 235                 240
Cys Glu Gly Asp Ser Gly Gly Pro Leu Val Cys Glu Phe Asn Arg Ser
                245                 250                 255
Trp Leu Gln Ile Gly Ile Val Ser Trp Gly Arg Gly Cys Ser Asn Pro
            260                 265                 270
Leu Tyr Pro Gly Val Tyr Ala Ser Val Ser Tyr Phe Ser Lys Trp Ile
        275                 280                 285
Cys Asp Asn Ile Glu Ile Thr Pro Thr Pro Ala Gln Pro Ala Pro Ala
    290                 295                 300
Leu Ser Pro Ala Leu Gly Pro Thr Leu Ser Val Leu Met Ala Met Leu
305                 310                 315                 320
Ala Gly Trp Ser Val Leu
                325
```

<210> 267
<211> 1695
<212> DNA
<213> Homo sapiens

<220>
<223> Mername-AA180 peptidase

<400> 267
atgcttataa gcaggaacaa gctgatttta ctactaggaa tagtcttttt tgaacgaggt 60
aaatctgcaa ctctttcgct ccccaaagct cccagttgtg ggcagagtct ggttaaggta 120
cagccttgga attattttaa cattttcagt cgcattcttg gaggaagcca agtggagaag 180
ggttcctatc cctggcaggt atctctgaaa caaaggcaga agcatatttg tggaggaagc 240
atcgtctcac cacagtgggt gatcacggcg gctcactgca ttgcaaacag aaacattgtg 300
tctactttga atgttactgc tggagagtat gacttaagcc agacagaccc aggagagcaa 360
actctcacta ttgaaactgt catcatacat ccacatttct ccaccaagaa accaatggac 420
tatgatattg ccctttttgaa gatggctgga gccttccaat ttggccactt tgtggggccc 480
atatgtcttc cagagctgcg ggagcaattt gaggctggtt ttatttgtac aactgcaggc 540
tggggccgct taactgaagg tggcgtcctc tcacaagtct tgcaggaagt gaatctgcct 600
attttgacct gggaagagtg tgtggcagct ctgttaacac taaagaggcc catcagtggg 660
aagacctttc tttgcacagg ttttcctgat ggagggagag acgcatgtca gggagattca 720
ggaggttcac tcatgtgccg gaataagaaa ggggcctgga ctctggctgg tgtgacttcc 780
tggggtttgg gctgtggtcg aggctggaga aacaatgtga ggaaaagtga tcaaggatcc 840
cctgggatct tcacagacat tagtaaagtg cttccctgga tccacgaaca catccaaact 900
ggtaatcgga gaaagagctc cagagcctgg tgcagtgagc aggatgtcat agtcagcggg 960
gctgagggga agctgcactt cccagaaagc ctccacctat attatgagag caagcaacgg 1020
tgtgtctgga ccctgctggt accagaggaa atgcatgtgt tgctcagttt ttcccaccta 1080
gatgttgagt cttgtcacca cagttacctg tcaatgtatt ctttagaaga cagacccatt 1140
ggaaaatttt gtggagaaag cctcccttca tccattctta ttggctctaa ttctctaagg 1200
ctgaaattcg tctctgatgc cacagattat gcagctgggt ttaatcttac ctataaagct 1260
cttaaaccaa actacattcc tgattcaggt tgcagttact taactgtcct ttttgaagaa 1320
ggtctcatac agagtctaaa ctatcctgaa aactacagtg acaaggctaa ctgtgactgg 1380
atttttcaag cctccaaaca tcacctaatt aagctttcat ttcagagtct ggaaatagaa 1440
gaaagtggag actgcacttc cgactatgtg acagtgcaca gcgatgtaga aaggaagaag 1500
gaaatagctc ggctgtgtgg ctatgatgtc cccacccctg tgctgagccc ctccagcatc 1560
atgctcatca gcttccaatc agatgaaaac gggacctgca ggggctttca ggctacagtc 1620
tccttcattc ctaaagcagg taagaagata gagttaccaa ctctttggtt cccagttcta 1680
atccttgtga tgtga   1695

<210> 268
<211> 564
<212> PRT

<213> Homo sapiens

<220>
<223> Mername-AA180 peptidase

<400> 268
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Phe Glu Arg Gly Lys Ser Ala Thr Leu Ser Leu Pro Lys Ala Pro Ser
            20   25   30
Cys Gly Gln Ser Leu Val Lys Val Gln Pro Trp Asn Tyr Phe Asn Ile
        35   40   45
Phe Ser Arg Ile Leu Gly Gly Ser Gln Val Glu Lys Gly Ser Tyr Pro
    50   55   60
Trp Gln Val Ser Leu Lys Gln Arg Gln Lys His Ile Cys Gly Gly Ser
65   70   75   80
Ile Val Ser Pro Gln Trp Val Ile Thr Ala Ala His Cys Ile Ala Asn
                85   90   95
Arg Asn Ile Val Ser Thr Leu Asn Val Thr Ala Gly Glu Tyr Asp Leu
            100   105   110
Ser Gln Thr Asp Pro Gly Glu Gln Thr Leu Thr Ile Glu Thr Val Ile
        115   120   125
Ile His Pro His Phe Ser Thr Lys Lys Pro Met Asp Tyr Asp Ile Ala
    130   135   140
Leu Leu Lys Met Ala Gly Ala Phe Gln Phe Gly His Phe Val Gly Pro
145   150   155   160
Ile Cys Leu Pro Glu Leu Arg Glu Gln Phe Glu Ala Gly Phe Ile Cys
                165   170   175
Thr Thr Ala Gly Trp Gly Arg Leu Thr Glu Gly Gly Val Leu Ser Gln
            180   185   190
Val Leu Gln Glu Val Asn Leu Pro Ile Leu Thr Trp Glu Glu Cys Val
        195   200   205
Ala Ala Leu Leu Thr Leu Lys Arg Pro Ile Ser Gly Lys Thr Phe Leu
    210   215   220
Cys Thr Gly Phe Pro Asp Gly Gly Arg Asp Ala Cys Gln Gly Asp Ser
225   230   235   240
Gly Gly Ser Leu Met Cys Arg Asn Lys Lys Gly Ala Trp Thr Leu Ala
                245   250   255
Gly Val Thr Ser Trp Gly Leu Gly Cys Gly Arg Gly Trp Arg Asn Asn
            260   265   270
Val Arg Lys Ser Asp Gln Gly Ser Pro Gly Ile Phe Thr Asp Ile Ser
        275   280   285
Lys Val Leu Pro Trp Ile His Glu His Ile Gln Thr Gly Asn Arg Arg
    290   295   300
Lys Ser Ser Arg Ala Trp Cys Ser Glu Gln Asp Val Ile Val Ser Gly
305   310   315   320
Ala Glu Gly Lys Leu His Phe Pro Glu Ser Leu His Leu Tyr Tyr Glu
                325   330   335
Ser Lys Gln Arg Cys Val Trp Thr Leu Leu Val Pro Glu Glu Met His
            340   345   350
Val Leu Leu Ser Phe Ser His Leu Asp Val Glu Ser Cys His His Ser
        355   360   365
Tyr Leu Ser Met Tyr Ser Leu Glu Asp Arg Pro Ile Gly Lys Phe Cys
    370   375   380
Gly Glu Ser Leu Pro Ser Ser Ile Leu Ile Gly Ser Asn Ser Leu Arg
385   390   395   400
Leu Lys Phe Val Ser Asp Ala Thr Asp Tyr Ala Ala Gly Phe Asn Leu

```
                405                 410                 415
Thr Tyr Lys Ala Leu Lys Pro Asn Tyr Ile Pro Asp Ser Gly Cys Ser
            420                 425                 430
Tyr Leu Thr Val Leu Phe Glu Glu Gly Leu Ile Gln Ser Leu Asn Tyr
        435                 440                 445
Pro Glu Asn Tyr Ser Asp Lys Ala Asn Cys Asp Trp Ile Phe Gln Ala
    450                 455                 460
Ser Lys His His Leu Ile Lys Leu Ser Phe Gln Ser Leu Glu Ile Glu
465                 470                 475                 480
Glu Ser Gly Asp Cys Thr Ser Asp Tyr Val Thr Val His Ser Asp Val
                485                 490                 495
Glu Arg Lys Lys Glu Ile Ala Arg Leu Cys Gly Tyr Asp Val Pro Thr
            500                 505                 510
Pro Val Leu Ser Pro Ser Ser Ile Met Leu Ile Ser Phe Gln Ser Asp
        515                 520                 525
Glu Asn Gly Thr Cys Arg Gly Phe Gln Ala Thr Val Ser Phe Ile Pro
    530                 535                 540
Lys Ala Gly Lys Lys Ile Glu Leu Pro Thr Leu Trp Phe Pro Val Leu
545                 550                 555                 560
Ile Leu Val Met
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<210> 269
<211> 3420
<212> DNA
<213> Homo sapiens

<220>
<223> Mername-AA182 peptidase

<400> 269
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atgggcctgc tggccagtgc tggtttgttg ctgttgctgg tcatcggcca ccccagaagc 60
ctaggactga agtgtggaat tcgcatggtc aacatgaaaa gtaaggaacc tgccgtggga 120
tctagattct tctctagaat tagtagttgg agaaattcaa cagtgactgg acatccatgg 180
caggtctccc taaaatcaga tgagcaccac ttctgtggag gaagcttgat tcaagaagat 240
cgggttgtta cagcagcaca ctgcctggac agcctcagtg agaagcagct gaagaatata 300
actgtgactt ctggggagta cagcctcttt cagaaggata agcaagaaca gaatattcct 360
gtctcaaaaa ttattaccca tcctgaatac aacagccgtg aatatatgag tcctgatatt 420
gcactgctgt atctaaaaca caaagtcaag tttggaaatg ctgttcagcc aatctgtctt 480
cctgacagcg atgataaagt tgaaccagga attctttgct tatccagtgg atggggcaag 540
atttccaaaa catcagaata ttcaaatgtc ctacaagaaa tggaacttcc catcatggat 600
gacagagcgt gtaatactgt gctcaagagc atgaacctcc ctcccctggg aaggaccatg 660
ctgtgtgctg gcttccctga ttggggaatg gacgcctgcc agggggactc tggaggacca 720
ctggtttgta gaagaggtgg tggaatctgg attcttgctg ggataacttc ctgggtagct 780
ggttgtgctg gaggttcagt tcccgtaaga aacaaccatg tgaaggcatc acttggcatt 840
ttctccaaag tgtctgagtt gatggatttt atcactcaaa acctgttcac aggtttggat 900
cggggccaac ccctctcaaa agtgggctca aggtatataa caaaggccct gagttctgtc 960
caagaagtga atggaagcca gagaggaaag ggtattttag acatggaaaa gcaagttgga 1020
tgtgatcatg actatgtatc tttacgatca agcagtggag tgctttttaa tcagagatct 1080
ctcatggaag acgatggaaa acaaaacaaa cgtgtctgtg gaaaaatatt gccttcacca 1140
ttgctggcag agaccagtga ggccatggtt ccatttgttt ctgatacaga agacagtggc 1200
agtggctttg agcttaccgt tactgctgta cagaagtcag aagcagggtc aggttgtggg 1260
agtctggcta tattggtaga agaagggaca aatcactctg ccaagtatcc tgatttgtat 1320
cccagtaaca caaggtgtca ttggttcatt tgtgctccag agaagcacat tataaagttg 1380
acatttgagg actttgctgt caaatttagt ccaaactgta tttatgatgc tgttgtgatt 1440
tacggtgatt ctgaagaaaa gcacaagtta gctaaacttt gtggaatgtt gaccatcact 1500
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tcaatattca gttctagtaa catgacggtg atatacttta aaagtgatgg taaaaatcgt 1560
ttacaaggct tcaaggccag atttaccatt ttgccctcag agtctttaaa caaatttgaa 1620
ccaaagttac ctccccaaaa caatcctgta tctaccgtaa aagctattct gcatgatgtc 1680
tgtggcatcc ctccatttag tccccagtgg ctttccagaa gaatcgcagg aggggaagaa 1740
gcctgccccc actgttggcc atggcaggtg ggtctgaggt ttctaggcga ttaccaatgt 1800
ggaggtgcca tcatcaaccc agtgtggatt ctgaccgcag cccactgtgt gcaattgaag 1860
aataatccac tctcctggac tattattgct ggggaccatg acagaaacct gaaggaatca 1920
acagagcagg tgagaagggc caaacacata atagtgcatg aagactttaa cacactaagt 1980
tatgactctg acattgccct aatacaacta agctctcctc tggagtacaa ctcggtggtg 2040
aggccagtat gtctcccaca cagcgcagag cctctatttt cctcggagat ctgtgctgtg 2100
accggatggg gaagcatcag tgcagatggt ggcctagcaa gtcgcctaca gcagattcaa 2160
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ggagactctg gtgggccact agtatgtaga catgaaaatg gtccctttgt cctctatggc 2340
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ggtccaaagg acagtaaaat aaccagactt tcccaaagtt caaacagaga gcacttggtc 2940
ccttgtgagg atgttcttct gaccaagcca gaagggatca tgcagatccc aagaaattct 3000
cacagaacta ctatggggtg ccaatggaga ttagtagccc ctttaaatca catcattcag 3060
cttaatatta ttaacttccc gatgaagcca acaacttttg tctgtcatgg tcatctgcgt 3120
gtttacgaag gatttggacc aggaaaaaaa ttaatagctt cattcgctgg aactctggca 3180
atgatactga caaaagacat attaaaaaga gaaaaactga attttattaa cacatatatc 3240
atgcatatat gggaaaattc agtgtatgat aatgtaagaa gtgttggaaa aagaaaacag 3300
aagaaatttg catcaaattt aagttatagt atggaggctg agaagtccag gatccaggtg 3360
ccagcagatt tggtgcctgc taagggctca ctttctggtt cttaggcaca gcccattctc 3420
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<210> 270
<211> 1134
<212> PRT
<213> Homo sapiens

<220>
<223> Mername-AA182 peptidase

<400> 270

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Met Gly Leu Leu Ala Ser Ala Gly Leu Leu Leu Leu Leu Val Ile Gly
 1               5                  10                  15
His Pro Arg Ser Leu Gly Leu Lys Cys Gly Ile Arg Met Val Asn Met
            20                  25                  30
Lys Ser Lys Glu Pro Ala Val Gly Ser Arg Phe Phe Ser Arg Ile Ser
        35                  40                  45
Ser Trp Arg Asn Ser Thr Val Thr Gly His Pro Trp Gln Val Ser Leu
    50                  55                  60
Lys Ser Asp Glu His His Phe Cys Gly Gly Ser Leu Ile Gln Glu Asp
65                  70                  75                  80
Arg Val Val Thr Ala Ala His Cys Leu Asp Ser Leu Ser Glu Lys Gln
                85                  90                  95
Leu Lys Asn Ile Thr Val Thr Ser Gly Glu Tyr Ser Leu Phe Gln Lys
            100                 105                 110
```

```
Asp Lys Gln Glu Gln Asn Ile Pro Val Ser Lys Ile Ile Thr His Pro
        115                 120                 125
Glu Tyr Asn Ser Arg Glu Tyr Met Ser Pro Asp Ile Ala Leu Leu Tyr
    130                 135                 140
Leu Lys His Lys Val Lys Phe Gly Asn Ala Val Gln Pro Ile Cys Leu
145                 150                 155                 160
Pro Asp Ser Asp Asp Lys Val Glu Pro Gly Ile Leu Cys Leu Ser Ser
                165                 170                 175
Gly Trp Gly Lys Ile Ser Lys Thr Ser Glu Tyr Ser Asn Val Leu Gln
            180                 185                 190
Glu Met Glu Leu Pro Ile Met Asp Asp Arg Ala Cys Asn Thr Val Leu
        195                 200                 205
Lys Ser Met Asn Leu Pro Pro Leu Gly Arg Thr Met Leu Cys Ala Gly
    210                 215                 220
Phe Pro Asp Trp Gly Met Asp Ala Cys Gln Gly Asp Ser Gly Gly Pro
225                 230                 235                 240
Leu Val Cys Arg Arg Gly Gly Gly Ile Trp Ile Leu Ala Gly Ile Thr
                245                 250                 255
Ser Trp Val Ala Gly Cys Ala Gly Gly Ser Val Pro Val Arg Asn Asn
            260                 265                 270
His Val Lys Ala Ser Leu Gly Ile Phe Ser Lys Val Ser Glu Leu Met
        275                 280                 285
Asp Phe Ile Thr Gln Asn Leu Phe Thr Gly Leu Asp Arg Gly Gln Pro
    290                 295                 300
Leu Ser Lys Val Gly Ser Arg Tyr Ile Thr Lys Ala Leu Ser Ser Val
305                 310                 315                 320
Gln Glu Val Asn Gly Ser Gln Arg Gly Lys Gly Ile Leu Asp Met Glu
                325                 330                 335
Lys Gln Val Gly Cys Asp His Asp Tyr Val Ser Leu Arg Ser Ser Ser
            340                 345                 350
Gly Val Leu Phe Asn Gln Arg Ser Leu Met Glu Asp Asp Gly Lys Gln
        355                 360                 365
Asn Lys Arg Val Cys Gly Lys Ile Leu Pro Ser Pro Leu Leu Ala Glu
    370                 375                 380
Thr Ser Glu Ala Met Val Pro Phe Val Ser Asp Thr Glu Asp Ser Gly
385                 390                 395                 400
Ser Gly Phe Glu Leu Thr Val Thr Ala Val Gln Lys Ser Glu Ala Gly
                405                 410                 415
Ser Gly Cys Gly Ser Leu Ala Ile Leu Val Glu Glu Gly Thr Asn His
            420                 425                 430
Ser Ala Lys Tyr Pro Asp Leu Tyr Pro Ser Asn Thr Arg Cys His Trp
        435                 440                 445
Phe Ile Cys Ala Pro Glu Lys His Ile Ile Lys Leu Thr Phe Glu Asp
    450                 455                 460
Phe Ala Val Lys Phe Ser Pro Asn Cys Ile Tyr Asp Ala Val Val Ile
465                 470                 475                 480
Tyr Gly Asp Ser Glu Glu Lys His Lys Leu Ala Lys Leu Cys Gly Met
                485                 490                 495
Leu Thr Ile Thr Ser Ile Phe Ser Ser Ser Asn Met Thr Val Ile Tyr
            500                 505                 510
Phe Lys Ser Asp Gly Lys Asn Arg Leu Gln Gly Phe Lys Ala Arg Phe
        515                 520                 525
Thr Ile Leu Pro Ser Glu Ser Leu Asn Lys Phe Glu Pro Lys Leu Pro
    530                 535                 540
Pro Gln Asn Asn Pro Val Ser Thr Val Lys Ala Ile Leu His Asp Val
545                 550                 555                 560
Cys Gly Ile Pro Pro Phe Ser Pro Gln Trp Leu Ser Arg Arg Ile Ala
```

```
                565                 570                 575
Gly Gly Glu Glu Ala Cys Pro His Cys Trp Pro Trp Gln Val Gly Leu
            580                 585                 590
Arg Phe Leu Gly Asp Tyr Gln Cys Gly Gly Ala Ile Ile Asn Pro Val
        595                 600                 605
Trp Ile Leu Thr Ala Ala His Cys Val Gln Leu Lys Asn Asn Pro Leu
    610                 615                 620
Ser Trp Thr Ile Ile Ala Gly Asp His Asp Arg Asn Leu Lys Glu Ser
625                 630                 635                 640
Thr Glu Gln Val Arg Arg Ala Lys His Ile Ile Val His Glu Asp Phe
                645                 650                 655
Asn Thr Leu Ser Tyr Asp Ser Asp Ile Ala Leu Ile Gln Leu Ser Ser
            660                 665                 670
Pro Leu Glu Tyr Asn Ser Val Val Arg Pro Val Cys Leu Pro His Ser
        675                 680                 685
Ala Glu Pro Leu Phe Ser Ser Glu Ile Cys Ala Val Thr Gly Trp Gly
    690                 695                 700
Ser Ile Ser Ala Asp Gly Gly Leu Ala Ser Arg Leu Gln Gln Ile Gln
705                 710                 715                 720
Val His Val Leu Glu Arg Glu Val Cys Glu His Thr Tyr Tyr Ser Ala
                725                 730                 735
His Pro Gly Gly Ile Thr Glu Lys Met Ile Cys Ala Gly Phe Ala Ala
            740                 745                 750
Ser Gly Glu Lys Asp Phe Cys Gln Gly Asp Ser Gly Gly Pro Leu Val
        755                 760                 765
Cys Arg His Glu Asn Gly Pro Phe Val Leu Tyr Gly Ile Val Ser Trp
    770                 775                 780
Gly Ala Gly Cys Val Gln Pro Trp Lys Pro Gly Val Phe Ala Arg Val
785                 790                 795                 800
Met Ile Phe Leu Asp Trp Ile Gln Ser Lys Ile Asn Gly Pro Ala Ser
                805                 810                 815
Leu Gln Thr Asn Asn Lys Cys Lys Thr Leu Lys Gln Gln Leu Pro Pro
            820                 825                 830
Pro Thr Pro Ser Pro Asp Ser Ala Ser Trp Pro Gly Cys Cys Ser Glu
        835                 840                 845
Ala Glu Leu Glu Lys Pro Arg Gly Phe Phe Pro Thr Pro Arg Tyr Leu
    850                 855                 860
Leu Asp Tyr Arg Gly Arg Leu Glu Cys Ser Trp Val Leu Arg Val Ser
865                 870                 875                 880
Ala Ser Ser Met Ala Lys Phe Thr Ile Glu Tyr Leu Ser Leu Leu Gly
                885                 890                 895
Ser Pro Val Cys Gln Asp Ser Val Leu Ile Ile Tyr Glu Glu Arg His
            900                 905                 910
Ser Lys Arg Lys Thr Ala Gly Gly Leu His Gly Arg Arg Leu Tyr Ser
        915                 920                 925
Met Thr Phe Met Ser Pro Gly Pro Leu Val Arg Val Thr Phe His Ala
    930                 935                 940
Leu Val Arg Gly Ala Phe Gly Ile Ser Tyr Ile Asp Leu Lys Val Leu
945                 950                 955                 960
Gly Pro Lys Asp Ser Lys Ile Thr Arg Leu Ser Gln Ser Ser Asn Arg
                965                 970                 975
Glu His Leu Val Pro Cys Glu Asp Val Leu Leu Thr Lys Pro Glu Gly
            980                 985                 990
Ile Met Gln Ile Pro Arg Asn Ser His Arg Thr Thr Met Gly Cys Gln
        995                 1000                1005
Trp Arg Leu Val Ala Pro Leu Asn His Ile Ile Gln Leu Asn Ile Ile
    1010                1015                1020
```

```
Asn Phe Pro Met Lys Pro Thr Thr Phe Val Cys His Gly His Leu Arg
1025                1030                1035                1040
Val Tyr Glu Gly Phe Gly Pro Gly Lys Lys Leu Ile Ala Ser Phe Ala
                1045                1050                1055
Gly Thr Leu Ala Met Ile Leu Thr Lys Asp Ile Leu Lys Arg Glu Lys
            1060                1065                1070
Leu Asn Phe Ile Asn Thr Tyr Ile Met His Ile Trp Glu Asn Ser Val
        1075                1080                1085
Tyr Asp Asn Val Arg Ser Val Gly Lys Arg Lys Gln Lys Lys Phe Ala
    1090                1095                1100
Ser Asn Leu Ser Tyr Ser Met Glu Ala Glu Lys Ser Arg Ile Gln Val
1105                1110                1115                1120
Pro Ala Asp Leu Val Pro Ala Lys Gly Ser Leu Ser Gly Ser
                1125                1130
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<210> 271
<211> 2810
<212> DNA
<213> Homo sapiens

<220>
<223> Mername-AA122 peptidase

<400> 271
acttggctct gcctccgctg actctagcgc catggcccgg cacctgctcc tccccttgt 60
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ggaagaacct gaagatctgg actgcgggcg ccctgagccc tcggcccgca tcgtgggggg 180
gctcaaacgc gcagccgggc acctggcctt ggcaagtgag cctgcaccat ggaggtggcc 240
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tgacgaatgg gacgctggag cccgcggccg agtggtcggt actgctgggc gtgcactccc 360
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gcaccgcctg ctgggccacc ggctggggag acgtccagga ggcagatcct ctgcctctcc 600
cctgggtgct acaggaagtg gagctaaggc tgctgggcga ggccacctgt caatgtctct 660
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gctacccaga gggccgcagg gacacctgcc agggcgactc tgggggccc ctggtctgtg 780
aggaaggcgg ccgctggttc caggcaggaa tcaccagctt tggctttggc tgtggacgga 840
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tgatgggttc agagcctggg cctgctttc ccacccagcc ccagaagacc cagtcagatc 960
cccaggagcc cagggaggag aactgcacca ttgccctgcc tgagtgcggg aaggccccgc 1020
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gctccgacag cccaccccgc gacctcgacg cctggcgcgt gctgctgccc tcgcgcccgc 1200
gcgcggagcg ggtggcgcgc ctggtgcagc acgagaacgc ttcgtgggac aacgcctcgg 1260
acctggcgct gctgcagctg cgcacgcccg tgaacctgag tgcggcttcg cggcccgtgt 1320
gcctacccca cccggaacac tacttcctgc ccgggagccg ctgccgcctg gcccgctggg 1380
gccgcgggga acccgcgctt ggcccaggcg cgctgctgga ggcggagctg ttaggcggct 1440
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tgcggctgga ggctgctcca gtgggggtcc tgtggccctg gctggcagag gtgcatgtgg 1860
ctggtgatcg agtctgcact gggatcctcc tggccccagg ctgggtcctg gcagccactc 1920

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actgtgtcct caggccaggc tctacaacag tgccttacat tgaagtgtat ctgggccggg 1980
caggggccag ctccctccca cagggccacc aggtatcccg cttggtcatc agcatccggc 2040
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gctgctgggt gttgggctgg aaagaacccc aggaccgagt ccctgtggct gctgctgtct 2220
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gggagctgtt tgctgccatt ggtcctgaag aggcctggat ctcccagaca gtgggagagg 2460
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ctctcctgat ccagagctga ggggctaggg tcccagcacc acttcccccc tctccaccct 2640
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cccaccgaga ttgcagcggc tctggctaat tgggcctctg tgcccgggct attttgaacc 2760
caggaatcct tgggggtggt gggaggagcg gacaataaag gtgtaaacac             2810
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<210> 272
<211> 766
<212> PRT
<213> Homo sapiens

<220>
<223> Mername-AA122 peptidase

<400> 272

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Met Thr Asn Gly Thr Leu Glu Pro Ala Ala Glu Trp Ser Val Leu Leu
 1               5                  10                  15
Gly Val His Ser Gln Asp Gly Pro Leu Asp Gly Ala His Thr Arg Ala
            20                  25                  30
Val Ala Ala Ile Val Val Pro Ala Asn Tyr Ser Gln Val Glu Leu Gly
        35                  40                  45
Ala Asp Leu Ala Leu Leu Arg Leu Ala Ser Pro Ala Ser Leu Gly Pro
    50                  55                  60
Ala Val Trp Pro Val Cys Leu Pro Arg Ala Ser His Arg Phe Val His
65                  70                  75                  80
Gly Thr Ala Cys Trp Ala Thr Gly Trp Gly Asp Val Gln Glu Ala Asp
                85                  90                  95
Pro Leu Pro Leu Pro Trp Val Leu Gln Glu Val Glu Leu Arg Leu Leu
            100                 105                 110
Gly Glu Ala Thr Cys Gln Cys Leu Tyr Ser Gln Pro Gly Pro Phe Asn
        115                 120                 125
Leu Thr Leu Gln Ile Leu Pro Gly Met Leu Cys Ala Gly Tyr Pro Glu
    130                 135                 140
Gly Arg Arg Asp Thr Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys
145                 150                 155                 160
Glu Glu Gly Gly Arg Trp Phe Gln Ala Gly Ile Thr Ser Phe Gly Phe
                165                 170                 175
Gly Cys Gly Arg Arg Asn Arg Pro Gly Val Phe Thr Ala Val Ala Thr
            180                 185                 190
Tyr Glu Ala Trp Ile Arg Glu Gln Val Met Gly Ser Glu Pro Gly Pro
        195                 200                 205
Ala Phe Pro Thr Gln Pro Gln Lys Thr Gln Ser Asp Pro Gln Glu Pro
    210                 215                 220
Arg Glu Glu Asn Cys Thr Ile Ala Leu Pro Glu Cys Gly Lys Ala Pro
225                 230                 235                 240
Arg Pro Gly Ala Trp Pro Trp Glu Ala Gln Val Met Val Pro Gly Ser
                245                 250                 255
```

```
Arg Pro Cys His Gly Ala Leu Val Ser Glu Ser Trp Val Leu Ala Pro
            260                 265                 270
Ala Ser Cys Phe Leu Asp Pro Asn Ser Ser Asp Ser Pro Pro Arg Asp
        275                 280                 285
Leu Asp Ala Trp Arg Val Leu Leu Pro Ser Arg Pro Arg Ala Glu Arg
    290                 295                 300
Val Ala Arg Leu Val Gln His Glu Asn Ala Ser Trp Asp Asn Ala Ser
305                 310                 315                 320
Asp Leu Ala Leu Leu Gln Leu Arg Thr Pro Val Asn Leu Ser Ala Ala
                325                 330                 335
Ser Arg Pro Val Cys Leu Pro His Pro Glu His Tyr Phe Leu Pro Gly
            340                 345                 350
Ser Arg Cys Arg Leu Ala Arg Trp Gly Arg Gly Glu Pro Ala Leu Gly
        355                 360                 365
Pro Gly Ala Leu Leu Glu Ala Glu Leu Leu Gly Gly Trp Trp Cys His
    370                 375                 380
Cys Leu Tyr Gly Arg Gln Gly Ala Ala Val Pro Leu Pro Gly Asp Pro
385                 390                 395                 400
Pro His Ala Leu Cys Pro Ala Tyr Gln Glu Lys Glu Glu Val Gly Ser
                405                 410                 415
Cys Trp Asn Asp Ser Arg Trp Ser Leu Leu Cys Gln Glu Glu Gly Thr
            420                 425                 430
Trp Phe Leu Ala Gly Ile Arg Asp Phe Pro Ser Gly Cys Leu Arg Pro
        435                 440                 445
Arg Ala Phe Phe Pro Leu Gln Thr His Gly Pro Trp Ile Ser His Val
    450                 455                 460
Thr Arg Gly Ala Tyr Leu Glu Asp Gln Leu Ala Trp Asp Trp Gly Pro
465                 470                 475                 480
Asp Gly Glu Glu Thr Glu Thr Gln Thr Cys Pro Pro His Thr Glu His
                485                 490                 495
Gly Ala Cys Gly Leu Arg Leu Glu Ala Ala Pro Val Gly Val Leu Trp
            500                 505                 510
Pro Trp Leu Ala Glu Val His Val Ala Gly Asp Arg Val Cys Thr Gly
        515                 520                 525
Ile Leu Leu Ala Pro Gly Trp Val Leu Ala Ala Thr His Cys Val Leu
    530                 535                 540
Arg Pro Gly Ser Thr Thr Val Pro Tyr Ile Glu Val Tyr Leu Gly Arg
545                 550                 555                 560
Ala Gly Ala Ser Ser Leu Pro Gln Gly His Gln Val Ser Arg Leu Val
                565                 570                 575
Ile Ser Ile Arg Leu Pro Gln His Leu Gly Leu Arg Pro Pro Leu Ala
            580                 585                 590
Leu Leu Glu Leu Ser Ser Arg Val Glu Pro Ser Pro Ser Ala Leu Pro
        595                 600                 605
Ile Cys Leu His Pro Ala Gly Ile Pro Pro Gly Ala Ser Cys Trp Val
    610                 615                 620
Leu Gly Trp Lys Glu Pro Gln Asp Arg Val Pro Val Ala Ala Ala Val
625                 630                 635                 640
Ser Ile Leu Thr Gln Arg Ile Cys Asp Cys Leu Tyr Gln Gly Ile Leu
                645                 650                 655
Pro Pro Gly Thr Leu Cys Val Leu Tyr Ala Glu Gly Gln Glu Asn Arg
            660                 665                 670
Cys Glu Met Thr Ser Ala Pro Pro Leu Leu Cys Gln Met Thr Glu Gly
        675                 680                 685
Ser Trp Ile Leu Val Gly Met Ala Val Gln Gly Ser Arg Glu Leu Phe
    690                 695                 700
Ala Ala Ile Gly Pro Glu Glu Ala Trp Ile Ser Gln Thr Val Gly Glu
```

```
705                 710                 715                 720
Ala Asn Leu Leu Pro Pro Ser Gly Ser Pro His Trp Pro Thr Gly Gly
                725                 730                 735
Ser Asn Leu Cys Pro Pro Glu Leu Ala Lys Ala Ser Gly Ser Pro His
            740                 745                 750
Ala Val Tyr Phe Leu Leu Leu Leu Thr Leu Leu Ile Gln Ser
        755                 760                 765
```

<210> 273
<211> 1575
<212> DNA
<213> Homo sapiens

<220>
<223> Cathepsin L

<400> 273
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agaaccgcga cctccgcaac cttgagcggc atccgtggag tgcgcctgca gctacgaccg 60
cagcaggaaa gcgccgccgg ccaggcccag ctgtggccgg acagggactg gaagagagga 120
cgcggtcgag taggtgtgca ccagccctgg caacgagagc gtctaccccg aactctgctg 180
gccttgaggt ggggaagccg gggagggcag ttgaggaccc cgcggaggcg cgtgactggt 240
tgagcgggca ggccagcctc cgagccgggt ggacacaggt tttaaaacat gaatcctaca 300
ctcatccttg ctgccttttg cctgggaatt gcctcagcta ctctaacatt tgatcacagt 360
ttagaggcac agtggaccaa gtggaaggcg atgcacaaca gattatacgg catgaatgaa 420
gaaggatgga ggagagcagt gtgggagaag aacatgaaga tgattgaact gcacaatcag 480
gaatacaggg aagggaaaca cagcttcaca atggccatga acgcctttgg agacatgacc 540
agtgaagaat tcaggcaggt gatgaatggc tttcaaaacc gtaagcccag gaaggggaaa 600
gtgttccagg aacctctgtt ttatgaggcc cccagatctg tggattggag agagaaaggc 660
tacgtgactc ctgtgaagaa tcagggtcag tgtggttctt gttgggcttt tagtgctact 720
ggtgctcttg aaggacagat gttccggaaa actgggaggc ttatctcact gagtgagcag 780
aatctggtag actgctctgg gcctcaaggc aatgaaggct gcaatggtgg cctaatggat 840
tatgctttcc agtatgttca ggataatgga ggcctggact ctgaggaatc ctatccatat 900
gaggcaacag aagaatcctg taagtacaat cccaagtatt ctgttgctaa tgacaccggc 960
tttgtggaca tccctaagca ggagaaggcc ctgatgaagg cagttgcaac tgtggggccc 1020
atttctgttg ctattgatgc aggtcatgag tccttcctgt tctataaaga aggcatttat 1080
tttgagccag actgtagcag tgaagacatg gatcatggtg tgctggtggt tggctacgga 1140
tttgaaagca cagaatcaga taacaataaa tattggctgg tgaagaacag ctggggtgaa 1200
gaatggggca tgggtggcta cgtaaagatg gccaaagacc ggagaaacca ttgtggaatt 1260
gcctcagcag ccagctaccc cactgtgtga gctggtggac ggtgatgagg aaggacttga 1320
ctggggatgg cgcatgcatg ggaggaattc atcttcagtc taccagcccc cgctgtgtcg 1380
gatacacact cgaatcattg aagatccgag tgtgatttga attctgtgat attttcacac 1440
tggtaaatgt tacctctatt ttaattactg ctataaatag gtttatatta ttgattcact 1500
tactgacttt gcattttcgt ttttaaaagg atgtataaat ttttacctgt ttaaataaaa 1560
tttaatttca aatgt                                                  1575
```

<210> 274
<211> 333
<212> PRT
<213> Homo sapiens

<220>
<223> Cathepsin L

<400> 274
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Met Asn Pro Thr Leu Ile Leu Ala Ala Phe Cys Leu Gly Ile Ala Ser
 1               5                  10                  15
```

```
Ala Thr Leu Thr Phe Asp His Ser Leu Glu Ala Gln Trp Thr Lys Trp
            20                  25                  30
Lys Ala Met His Asn Arg Leu Tyr Gly Met Asn Glu Glu Gly Trp Arg
        35                  40                  45
Arg Ala Val Trp Glu Lys Asn Met Lys Met Ile Glu Leu His Asn Gln
    50                  55                  60
Glu Tyr Arg Glu Gly Lys His Ser Phe Thr Met Ala Met Asn Ala Phe
65                  70                  75                  80
Gly Asp Met Thr Ser Glu Glu Phe Arg Gln Val Met Asn Gly Phe Gln
                85                  90                  95
Asn Arg Lys Pro Arg Lys Gly Lys Val Phe Gln Glu Pro Leu Phe Tyr
            100                 105                 110
Glu Ala Pro Arg Ser Val Asp Trp Arg Glu Lys Gly Tyr Val Thr Pro
        115                 120                 125
Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr
    130                 135                 140
Gly Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Arg Leu Ile Ser
145                 150                 155                 160
Leu Ser Glu Gln Asn Leu Val Asp Cys Ser Gly Pro Gln Gly Asn Glu
                165                 170                 175
Gly Cys Asn Gly Gly Leu Met Asp Tyr Ala Phe Gln Tyr Val Gln Asp
            180                 185                 190
Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Glu Ala Thr Glu
        195                 200                 205
Glu Ser Cys Lys Tyr Asn Pro Lys Tyr Ser Val Ala Asn Asp Thr Gly
    210                 215                 220
Phe Val Asp Ile Pro Lys Gln Glu Lys Ala Leu Met Lys Ala Val Ala
225                 230                 235                 240
Thr Val Gly Pro Ile Ser Val Ala Ile Asp Ala Gly His Glu Ser Phe
                245                 250                 255
Leu Phe Tyr Lys Glu Gly Ile Tyr Phe Glu Pro Asp Cys Ser Ser Glu
            260                 265                 270
Asp Met Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Ser Thr
        275                 280                 285
Glu Ser Asp Asn Asn Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Glu
    290                 295                 300
Glu Trp Gly Met Gly Gly Tyr Val Lys Met Ala Lys Asp Arg Arg Asn
305                 310                 315                 320
His Cys Gly Ile Ala Ser Ala Ala Ser Tyr Pro Thr Val
                325                 330
```

<210> 275
<211> 1342
<212> DNA
<213> Homo sapiens

<220>
<223> Cathepsin V

<400> 275
cggctgtaat ctcagaggct tgtttgctga gggtgcctgc gcacgtgcga cggctgctgg 60
ttttgaaaca tgaatctttc gctcgtcctg gctgcctttt gcttgggaat agcctccgct 120
gttccaaaat ttgaccaaaa tttggataca aagtggtacc agtggaaggc aacacacaga 180
agattatatg gcgcgaatga agaaggatgg aggagagcag tgtgggaaaa gaatatgaaa 240
atgattgaac tgcacaatgg ggaatacagc caagggaaac atggcttcac aatggccatg 300
aatgcttttc ctgacatgac caatgaagaa ttcaggcaga tgatgggttg ctttcgaaac 360

```
cagaaattca ggaaggggaa agtgttccgt gagcctctgt ttcttgatct tcccaaatct 420
gtggattgga gaaagaaagg ctacgtgacg ccagtgaaga atcagaaaca gtgtggttct 480
tgttgggctt ttagtgcgac tggtgctctt gaaggacaga tgttccggaa aactgggaaa 540
cttgtctcac tgagcgagca gaatctggtg gactgttcgc gtcctcaagg caatcagggc 600
tgcaatggtg gcttcatggc tagggccttc cagtatgtca aggagaacgg aggcctggac 660
tctgaggaat cctatccata tgtagcagtg gatgaaatct gtaagtacag acctgagaat 720
tctgttgcta atgacactgg cttcacagtg gtcgcacctg gaaaggagaa ggccctgatg 780
aaagcagtcg caactgtggg gcccatctcc gttgctatgg atgcaggcca ttcgtccttc 840
cagttctaca aatcaggcat ttattttgaa ccagactgca gcagcaaaaa cctggatcat 900
ggtgttctgg tggttggcta cggctttgaa ggagcaaatt cgaataacag caagtattgg 960
ctcgtcaaaa acagctgggg tccagaatgg ggctcgaatg gctatgtaaa aatagccaaa 1020
gacaagaaca accactgtgg aatcgccaca gcagccagct accccaatgt gtgagctgat 1080
ggatggtgag gaggaaggac ttaaggacag catgtctggg gaaattttat cttgaaactg 1140
accaaacgct tattgtgtaa gataaaccag ttgaatcatt gaggatccaa gttgagattt 1200
taattctgtg acatttttac aagggtaaaa tgttaccact actttaatta ttgttataca 1260
cagctttatg atatcaaaga ctcattgctt aattctaaga cttttgaatt ttcatttttt 1320
aaaaagatgt acaaaacagt tt                                          1342

<210> 276
<211> 334
<212> PRT
<213> Homo sapiens

<220>
<223> Cathepsin V

<400> 276
Met Asn Leu Ser Leu Val Leu Ala Ala Phe Cys Leu Gly Ile Ala Ser
 1               5                  10                  15
Ala Val Pro Lys Phe Asp Gln Asn Leu Asp Thr Lys Trp Tyr Gln Trp
            20                  25                  30
Lys Ala Thr His Arg Arg Leu Tyr Gly Ala Asn Glu Glu Gly Trp Arg
        35                  40                  45
Arg Ala Val Trp Glu Lys Asn Met Lys Met Ile Glu Leu His Asn Gly
    50                  55                  60
Glu Tyr Ser Gln Gly Lys His Gly Phe Thr Met Ala Met Asn Ala Phe
65                  70                  75                  80
Gly Asp Met Thr Asn Glu Glu Phe Arg Gln Met Met Gly Cys Phe Arg
                85                  90                  95
Asn Gln Lys Phe Arg Lys Gly Lys Val Phe Arg Glu Pro Leu Phe Leu
            100                 105                 110
Asp Leu Pro Lys Ser Val Asp Trp Arg Lys Lys Gly Tyr Val Thr Pro
        115                 120                 125
Val Lys Asn Gln Lys Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr
    130                 135                 140
Gly Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Lys Leu Val Ser
145                 150                 155                 160
Leu Ser Glu Gln Asn Leu Val Asp Cys Ser Arg Pro Gln Gly Asn Gln
                165                 170                 175
Gly Cys Asn Gly Gly Phe Met Ala Arg Ala Phe Gln Tyr Val Lys Glu
            180                 185                 190
Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Val Ala Val Asp
        195                 200                 205
Glu Ile Cys Lys Tyr Arg Pro Glu Asn Ser Val Ala Asn Asp Thr Gly
    210                 215                 220
Phe Thr Val Val Ala Pro Gly Lys Glu Lys Ala Leu Met Lys Ala Val
225                 230                 235                 240
```

```
Ala Thr Val Gly Pro Ile Ser Val Ala Met Asp Ala Gly His Ser Ser
                245                 250                 255
Phe Gln Phe Tyr Lys Ser Gly Ile Tyr Phe Glu Pro Asp Cys Ser Ser
            260                 265                 270
Lys Asn Leu Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Gly
        275                 280                 285
Ala Asn Ser Asn Asn Ser Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly
    290                 295                 300
Pro Glu Trp Gly Ser Asn Gly Tyr Val Lys Ile Ala Lys Asp Lys Asn
305                 310                 315                 320
Asn His Cys Gly Ile Ala Thr Ala Ala Ser Tyr Pro Asn Val
                325                 330
```

<210> 277
<211> 1661
<212> DNA
<213> Homo sapiens

<220>
<223> Cathepsin K

<400> 277
attcggcacg agccgcaatc ccgatggaat aaatctagca cccctgatgg tgtgcccaca 60
ctttgctgcc gaaacgaagc cagacaacag atttccatca gcaggatgtg ggggctcaag 120
gttctgctgc tacctgtggt gagctttgct ctgtaccctg aggagatact ggacacccac 180
tgggagctat ggaagaagac ccacaggaag caatataaca acaaggtgga tgaaatctct 240
cggcgtttaa tttgggaaaa aaacctgaag tatatttcca tccataacct tgaggcttct 300
cttggtgtcc atacatatga actggctatg aaccacctgg gggacatgac cagtgaagag 360
gtggttcaga agatgactgg actcaaagta cccctgtctc attcccgcag taatgacacc 420
ctttatatcc cagaatggga aggtagagcc ccagactctg tcgactatcg aaagaaagga 480
tatgttactc ctgtcaaaaa tcagggtcag tgtggttcct gttgggcttt tagctctgtg 540
ggtgccctgg agggccaact caagaagaaa actggcaaac tcttaaatct gagtccccag 600
aacctagtgg attgtgtgtc tgagaatgat ggctgtggag ggggctacat gaccaatgcc 660
ttccaatatg tgcagaagaa ccggggtatt gactctgaag atgcctaccc atatgtggga 720
caggaagaga gttgtatgta caacccaaca ggcaaggcag ctaaatgcag agggtacaga 780
gagatccccg aggggaatga gaaagccctg aagagggcag tggcccgagt gggacctgtc 840
tctgtggcca ttgatgcaag cctgacctcc ttccagtttt acagcaaagg tgtgtattat 900
gatgaaagct gcaatagcga taatctgaac catgcggttt tggcagtggg atatggaatc 960
cagaagggaa acaagcactg gataattaaa aacagctggg gagaaaactg gggaaacaaa 1020
ggatatatcc tcatggctcg aaataagaac aacgcctgtg gcattgccaa cctggccagc 1080
ttccccaaga tgtgactcca gccagccaaa tccatcctgc tcttccattt cttccacgat 1140
ggtgcagtgt aacgatgcac tttggaaggg agttggtgtg ctatttttga agcagatgtg 1200
gtgatactga gattgtctgt tcagtttccc catttgtttg tgcttcaaat gatccttcct 1260
actttggttc tctcctccca tgacctttt cactgtggcc atcaggactt tccctgacag 1320
ctgtgtactc ttaggctaag agatgtgact acagcctgcc cctgactgtg ttgtcccagg 1380
gctgatgctg tacaggtaca ggctggagat tttcacatag gttagattct cattcacggg 1440
actagttagc tttaagcacc ctagaggact agggtaatct gacttctcac ttcctaagtt 1500
cccttcaata tcctcaaggt agaaatgtct atgttttcta ctccaattca taaatctatt 1560
cataagtctt tggtacaagt ttacatgata aaaagaaatg tgatttgtct tcccttcttt 1620
gcacttttga aataaagtat ttatctcctg tctacagttt a 1661

<210> 278
<211> 329
<212> PRT
<213> Homo sapiens

<220>
<223> Cathepsin K

<400> 278
Met Trp Gly Leu Lys Val Leu Leu Leu Pro Val Val Ser Phe Ala Leu
1 5 10 15
Tyr Pro Glu Glu Ile Leu Asp Thr His Trp Glu Leu Trp Lys Lys Thr
20 25 30
His Arg Lys Gln Tyr Asn Asn Lys Val Asp Glu Ile Ser Arg Arg Leu
35 40 45
Ile Trp Glu Lys Asn Leu Lys Tyr Ile Ser Ile His Asn Leu Glu Ala
50 55 60
Ser Leu Gly Val His Thr Tyr Glu Leu Ala Met Asn His Leu Gly Asp
65 70 75 80
Met Thr Ser Glu Glu Val Val Gln Lys Met Thr Gly Leu Lys Val Pro
85 90 95
Leu Ser His Ser Arg Ser Asn Asp Thr Leu Tyr Ile Pro Glu Trp Glu
100 105 110
Gly Arg Ala Pro Asp Ser Val Asp Tyr Arg Lys Lys Gly Tyr Val Thr
115 120 125
Pro Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ser
130 135 140
Val Gly Ala Leu Glu Gly Gln Leu Lys Lys Lys Thr Gly Lys Leu Leu
145 150 155 160
Asn Leu Ser Pro Gln Asn Leu Val Asp Cys Val Ser Glu Asn Asp Gly
165 170 175
Cys Gly Gly Gly Tyr Met Thr Asn Ala Phe Gln Tyr Val Gln Lys Asn
180 185 190
Arg Gly Ile Asp Ser Glu Asp Ala Tyr Pro Tyr Val Gly Gln Glu Glu
195 200 205
Ser Cys Met Tyr Asn Pro Thr Gly Lys Ala Ala Lys Cys Arg Gly Tyr
210 215 220
Arg Glu Ile Pro Glu Gly Asn Glu Lys Ala Leu Lys Arg Ala Val Ala
225 230 235 240
Arg Val Gly Pro Val Ser Val Ala Ile Asp Ala Ser Leu Thr Ser Phe
245 250 255
Gln Phe Tyr Ser Lys Gly Val Tyr Tyr Asp Glu Ser Cys Asn Ser Asp
260 265 270
Asn Leu Asn His Ala Val Leu Ala Val Gly Tyr Gly Ile Gln Lys Gly
275 280 285
Asn Lys His Trp Ile Ile Lys Asn Ser Trp Gly Glu Asn Trp Gly Asn
290 295 300
Lys Gly Tyr Ile Leu Met Ala Arg Asn Lys Asn Asn Ala Cys Gly Ile
305 310 315 320
Ala Asn Leu Ala Ser Phe Pro Lys Met
325

<210> 279
<211> 1255
<212> DNA
<213> Homo sapiens

<220>
<223> Cathepsin S

<400> 279

ctaaagatga aacggctggt ttgtgtgctc ttggtgtgct cctctgcagt ggcacagttg 60
cataaagatc ctaccctgga tcaccactgg catctctgga agaaaaccta tggcaaacaa 120
tacaaggaaa agaatgaaga agcagtacga cgtctcatct gggaaaagaa tctaaagttt 180
gtgatgcttc acaacctgga gcattcaatg ggaatgcact catacgatct gggcatgaac 240
cacctgggag acatgaccag tgaagaagtg atgtctttga cgagttccct gagagttccc 300
agccagtggc agagaaatat cacatataag tcaaacccta atcggatatt gcctgattct 360
gtggactgga gagagaaagg gtgtgttact gaagtgaaat atcaaggttc ttgtggtgct 420
tgctgggctt tcagtgctgt gggggccctg gaagcacagc tgaagctgaa aacaggaaag 480
ctggtgactc tcagtgccca gaacctggtg gattgctcaa ctgaaaaata tggaaacaaa 540
ggctgcaatg gtggcttcat gacaacggct ttccagtaca tcattgataa caagggcatc 600
gactcagacg cttcctatcc ctacaaagcc atggatcaga aatgtcaata tgactcaaaa 660
tatcgtgctg ccacatgttc aaagtacact gaacttcctt atgggagaga agatgtcctg 720
aaagaagctg tggccaataa aggcccagtg tctgttggtg tagatgcgcg tcatccttct 780
ttcttcctct acagaagtgg tgtctactat gaaccatcct gtactcagaa tgtgaatcat 840
ggtgtacttg tggttggcta tggtgatctt aatgggaaag aatactggct tgtgaaaaac 900
agctggggcc acaactttgg tgaagaagga tatattcgga tggcaagaaa taaaggaaat 960
cattgtggga ttgctagctt tccctcttac ccagaaatct agaggatctc tccttttttat 1020
aacaaatcaa gaaatatgaa gcactttctc ttaacttaat ttttcctgct gtatccagaa 1080
gaaataattg tgtcatgatt aatgtgtatt tactgtacta atagaaaata tagtttgagg 1140
ccgggcactg tctggctcac gcctgtaatc ccagtacttg ggaggccaag gaggcatatc 1200
aacttgaggc caggagttaa agagcagcct ggctaactgt gaaaccctct ctact 1255

<210> 280
<211> 331
<212> PRT
<213> Homo sapiens

<220>
<223> Cathepsin S

<400> 280
Met Lys Arg Leu Val Cys Val Leu Leu Val Cys Ser Ser Ala Val Ala
 1   5   10   15
Gln Leu His Lys Asp Pro Thr Leu Asp His His Trp His Leu Trp Lys
            20   25   30

Lys Thr Tyr Gly Lys Gln Tyr Lys Glu Lys Asn Glu Glu Ala Val Arg
        35   40   45
Arg Leu Ile Trp Glu Lys Asn Leu Lys Phe Val Met Leu His Asn Leu
    50   55   60
Glu His Ser Met Gly Met His Ser Tyr Asp Leu Gly Met Asn His Leu
65   70   75   80
Gly Asp Met Thr Ser Glu Glu Val Met Ser Leu Met Ser Ser Leu Arg
                85   90   95
Val Pro Ser Gln Trp Gln Arg Asn Ile Thr Tyr Lys Ser Asn Pro Asn
            100   105   110
Arg Ile Leu Pro Asp Ser Val Asp Trp Arg Glu Lys Gly Cys Val Thr
        115   120   125
Glu Val Lys Tyr Gln Gly Ser Cys Gly Ala Cys Trp Ala Phe Ser Ala
    130   135   140
Val Gly Ala Leu Glu Ala Gln Leu Lys Leu Lys Thr Gly Lys Leu Val
145   150   155   160
Thr Leu Ser Ala Gln Asn Leu Val Asp Cys Ser Thr Glu Lys Tyr Gly
                165   170   175
Asn Lys Gly Cys Asn Gly Gly Phe Met Thr Thr Ala Phe Gln Tyr Ile
            180   185   190
Ile Asp Asn Lys Gly Ile Asp Ser Asp Ala Ser Tyr Pro Tyr Lys Ala

```
        195                 200                 205
Met Asp Gln Lys Cys Gln Tyr Asp Ser Lys Tyr Arg Ala Ala Thr Cys
    210                 215                 220
Ser Lys Tyr Thr Glu Leu Pro Tyr Gly Arg Glu Asp Val Leu Lys Glu
225                 230                 235                 240
Ala Val Ala Asn Lys Gly Pro Val Ser Val Gly Val Asp Ala Arg His
                245                 250                 255
Pro Ser Phe Phe Leu Tyr Arg Ser Gly Val Tyr Tyr Glu Pro Ser Cys
            260                 265                 270
Thr Gln Asn Val Asn His Gly Val Leu Val Val Gly Tyr Gly Asp Leu
        275                 280                 285
Asn Gly Lys Glu Tyr Trp Leu Val Lys Asn Ser Trp Gly His Asn Phe
    290                 295                 300
Gly Glu Glu Gly Tyr Ile Arg Met Ala Arg Asn Lys Gly Asn His Cys
305                 310                 315                 320
Gly Ile Ala Ser Phe Pro Ser Tyr Pro Glu Ile
                325                 330
```

<210> 281
<211> 1517
<212> DNA
<213> Homo sapiens

<220>
<223> Cathepsin F

<400> 281
gaattccggg tctgttgggt ccgggccgcc ggcttcgccc tcgccatggc gccctggctg 60
cagctcctgt cgctgctggg gctgctcccg ggcgcagtgg ccgcccccgc ccagccccga 120
gccgccagct ttcaggcctg ggggccgccg tccccggagc tgctggcgcc cacccgcttc 180
gcgctggaga tgttcaaccg cggccgggct gcggggacgc gggccgtgct gggccttgtg 240
cgcggccgcg tccgccgggc gggtcagggg tcgctgtact ccctggaggc caccctggag 300
gagccaccct gcaacgaccc catggtgtgc cggctccccg tgtccaagaa aaccctgctc 360
tgcagcttcc aagtcctgga tgagctcgga agacacgtgc tgctgcggaa ggactgtggc 420
ccagtggaca ccaaggttcc aggtgctggg gagcccaagt cagccttcac tcagggctca 480
gccatgattt cttctctgtc ccaaaaccat ccagacaaca gaaacgagac tttcagctca 540
gtcatttccc tgttgaatga ggatcccctg tcccaggact tgcctgtgaa gatggcttca 600
atcttcaaga actttgtcat tacctataac cggacatatg agtcaaagga agaagcccgg 660

tggcgcctgt ccgtctttgt caataacatg gtgcgagcac agaagatcca ggccctggac 720
cgtgggacag ctcagtatgg agtcaccaag ttcagtgatc tcacagagga ggagttccgc 780
actatctacc tgaatactct cctgaggaaa gagcctggca acaagatgaa gcaagccaag 840
tctgtgggtg acctcgcccc acctgaatgg gactggagga gtaaggggc tgtcacaaaa 900
gtcaaagacc agggcatgtg tggctcctgc tgggccttct cagtcacagg caatgtggag 960
ggccagtggt ttctcaacca ggggaccctg ctctccctct ctgaacagga gctcttggac 1020
tgtgacaaga tggacaaggc ctgcatgggc ggcttgccct ccaatgccta ctcggccata 1080
aagaatttgg gagggctgga gacagaggat gactacagct accagggtca catgcagtcc 1140
tgcaacttct cagcagagaa ggccaaggtc tacatcaatg actccgtgga gctgagccag 1200
aacgagcaga agctggcagc ctggctggcc aagagaggcc caatctccgt ggccatcaat 1260
gcctttggca tgcagtttta ccgccacggg atctcccgcc ctctccggcc cctctgcagc 1320
ccttggctca ttgaccatgc ggtgttgctt gtgggctacg gcaaccgctc tgacgttccc 1380
ttttgggcca tcaagaacag ctggggcact gactggggtg agaagggtta ctactacttg 1440
catcgtgggt ccggggcctg tggcgtgaac accatggcca gctcggcggt ggtggactga 1500
agaggggccc cgaattc   1517

<210> 282

<211> 484
<212> PRT
<213> Homo sapiens

<220>
<223> Cathepsin F

<400> 282
Met Ala Pro Trp Leu Gln Leu Leu Ser Leu Leu Gly Leu Leu Pro Gly
 1   5   10   15
Ala Val Ala Ala Pro Ala Gln Pro Arg Ala Ala Ser Phe Gln Ala Trp
            20   25   30
Gly Pro Pro Ser Pro Glu Leu Leu Ala Pro Thr Arg Phe Ala Leu Glu
        35   40   45
Met Phe Asn Arg Gly Arg Ala Ala Gly Thr Arg Ala Val Leu Gly Leu
    50   55   60
Val Arg Gly Arg Val Arg Arg Ala Gly Gln Gly Ser Leu Tyr Ser Leu
65   70   75   80
Glu Ala Thr Leu Glu Glu Pro Pro Cys Asn Asp Pro Met Val Cys Arg
                85   90   95
Leu Pro Val Ser Lys Lys Thr Leu Leu Cys Ser Phe Gln Val Leu Asp
            100   105   110
Glu Leu Gly Arg His Val Leu Leu Arg Lys Asp Cys Gly Pro Val Asp
        115   120   125
Thr Lys Val Pro Gly Ala Gly Glu Pro Lys Ser Ala Phe Thr Gln Gly
    130   135   140
Ser Ala Met Ile Ser Ser Leu Ser Gln Asn His Pro Asp Asn Arg Asn
145   150   155   160
Glu Thr Phe Ser Ser Val Ile Ser Leu Leu Asn Glu Asp Pro Leu Ser
                165   170   175
Gln Asp Leu Pro Val Lys Met Ala Ser Ile Phe Lys Asn Phe Val Ile
            180   185   190
Thr Tyr Asn Arg Thr Tyr Glu Ser Lys Glu Glu Ala Arg Trp Arg Leu
        195   200   205
Ser Val Phe Val Asn Asn Met Val Arg Ala Gln Lys Ile Gln Ala Leu
    210   215   220
Asp Arg Gly Thr Ala Gln Tyr Gly Val Thr Lys Phe Ser Asp Leu Thr
225   230   235   240
Glu Glu Glu Phe Arg Thr Ile Tyr Leu Asn Thr Leu Leu Arg Lys Glu
                245   250   255
Pro Gly Asn Lys Met Lys Gln Ala Lys Ser Val Gly Asp Leu Ala Pro
            260   265   270
Pro Glu Trp Asp Trp Arg Ser Lys Gly Ala Val Thr Lys Val Lys Asp
        275   280   285
Gln Gly Met Cys Gly Ser Cys Trp Ala Phe Ser Val Thr Gly Asn Val
    290   295   300
Glu Gly Gln Trp Phe Leu Asn Gln Gly Thr Leu Leu Ser Leu Ser Glu
305   310   315   320
Gln Glu Leu Leu Asp Cys Asp Lys Met Asp Lys Ala Cys Met Gly Gly
                325   330   335
Leu Pro Ser Asn Ala Tyr Ser Ala Ile Lys Asn Leu Gly Gly Leu Glu
            340   345   350
Thr Glu Asp Asp Tyr Ser Tyr Gln Gly His Met Gln Ser Cys Asn Phe
        355   360   365
Ser Ala Glu Lys Ala Lys Val Tyr Ile Asn Asp Ser Val Glu Leu Ser
    370   375   380
Gln Asn Glu Gln Lys Leu Ala Ala Trp Leu Ala Lys Arg Gly Pro Ile

```
385                 390                 395                 400
Ser Val Ala Ile Asn Ala Phe Gly Met Gln Phe Tyr Arg His Gly Ile
                405                 410                 415
Ser Arg Pro Leu Arg Pro Leu Cys Ser Pro Trp Leu Ile Asp His Ala
            420                 425                 430
Val Leu Leu Val Gly Tyr Gly Asn Arg Ser Asp Val Pro Phe Trp Ala
        435                 440                 445
Ile Lys Asn Ser Trp Gly Thr Asp Trp Gly Glu Lys Gly Tyr Tyr Tyr
    450                 455                 460
Leu His Arg Gly Ser Gly Ala Cys Gly Val Asn Thr Met Ala Ser Ser
465                 470                 475                 480
Ala Val Val Asp
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<210> 283
<211> 2002
<212> DNA
<213> Homo sapiens

<220>
<223> Cathepsin B

<400> 283

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ggctctcggc tgcagcgctg ggctggtgtg cagtggtgcg accacggctc acggcagcct 120

cagccaccca gatgtaagcg atctggttcc cacctcagcc ttccgagtag tggatctagg 180
atctggcttc caacatgtgg cagctctggg cctccctctg ctgcctgctg gtgttggcca 240
atgcccggag caggccctct ttccatcccg tgtcggatga gctggtcaac tatgtcaaca 300
aacggaatac cacgtggcag gccgggcaca acttctacaa cgtggacatg agctacttga 360
agaggctatg tggtaccttc ctgggtgggc ccaagccacc ccagagagtt atgtttaccg 420
aggacctgaa gctgcctgca agcttcgatg cacgggaaca atggccacag tgtcccacca 480
tcaaagagat cagagaccag ggctcctgtg gctcctgctg ggccttcggg gctgtggaag 540
ccatctctga ccgcatctgc atccacacca atgcgcacgt cagcgtggag gtgtcggcgg 600
aggacctgct cacctgctgt ggcagcatgt gtggggacgg ctgtaatggt ggctatcctg 660
ctgaagcttg gaacttctgg acaagaaaag gcctggtttc tggtggcctc tatgaatccc 720
atgtagggtg cagaccgtac tccatccctc cctgtgagca ccacgtcaac ggctcccggc 780
ccccatgcac gggggaggga gataccccca agtgtagcaa gatctgtgag cctggctaca 840
gcccgaccta caaacaggac aagcactacg gatacaattc ctacagcgtc tccaatagcg 900
agaaggacat catggccgag atctacaaaa acggccccgt ggagggagct ttctctgtgt 960
attcggactt cctgctctac aagtcaggag tgtaccaaca cgtcaccgga gagatgatgg 1020
gtggccatgc catccgcatc ctgggctggg gagtggagaa tggcacaccc tactggctgg 1080
ttgccaactc ctggaacact gactggggtg acaatggctt ctttaaaata ctcagaggac 1140
aggatcactg cggaatcgaa tcagaagtgg tggctggaat tccacgcacc gatcagtact 1200
gggaaaagat ctaatctgcc gtgggcctgt cgtgccagtc ctgggggcga gatcggggta 1260
gaaagtcatt ttattcttta agttcacgta agatacaagt ttcaggcagg gtctgaagga 1320
ctggattggc caaagtcctc caaggagacc aagtcctggc tacatcccag cctgtggtta 1380
cagtgcagac aggccatgtg agccaccgct gccagcacag agcgtccttc cccctgtaga 1440
ctagtgccgt gggagtacct gctgcccagc tgctgtggcc ccctccgtga tccatccatc 1500
tccagggagc aagacagaga cgcaggatgg aaagcggagt tcctaacagg atgaaagttc 1560
ccccatcagt tcccccagta cctccaagca agtagctttc cacatttgtc acagaaatca 1620
gaggagagat ggtgttggga gccctttgga gaacgccagt ctccaggtcc ccctgcatct 1680
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gttttatttt tcgtgcactc tgctaatcat gtgggtgagc cagtggaaca gcgggagcct 1800
gtgctggttt gcagattgcc tcctaatgac gcggctcaaa aggaaaccaa gtggtcagga 1860
gttgtttctg acccactgat ctctactacc acaaggaaaa tagtttagga gaaaccagct 1920
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tttactgttt ttgaaaaatt acagcttcac cctgtcaagt taacaaggaa tgcctgtgcc 1980
aataaaaggt ttctccaact tg 2002

<210> 284
<211> 339
<212> PRT
<213> Homo sapiens

<220>
<223> Cathepsin B

<400> 284
Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn
 1   5   10   15
Ala Arg Ser Arg Pro Ser Phe His Pro Leu Ser Asp Glu Leu Val Asn
            20   25   30
Tyr Val Asn Lys Arg Asn Thr Thr Trp Gln Ala Gly His Asn Phe Tyr
        35   40   45
Asn Val Asp Met Ser Tyr Leu Lys Arg Leu Cys Gly Thr Phe Leu Gly
    50   55   60
Gly Pro Lys Pro Pro Gln Arg Val Met Phe Thr Glu Asp Leu Lys Leu
65   70   75   80
Pro Ala Ser Phe Asp Ala Arg Glu Gln Trp Pro Gln Cys Pro Thr Ile
                85   90   95
Lys Glu Ile Arg Asp Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Gly
            100   105   110
Ala Val Glu Ala Ile Ser Asp Arg Ile Cys Ile His Thr Asn Ala His
        115   120   125
Val Ser Val Glu Val Ser Ala Glu Asp Leu Leu Thr Cys Cys Gly Ser
    130   135   140
Met Cys Gly Asp Gly Cys Asn Gly Gly Tyr Pro Ala Glu Ala Trp Asn
145   150   155   160
Phe Trp Thr Arg Lys Gly Leu Val Ser Gly Gly Leu Tyr Glu Ser His
                165   170   175
Val Gly Cys Arg Pro Tyr Ser Ile Pro Pro Cys Glu His His Val Asn
            180   185   190
Gly Ser Arg Pro Pro Cys Thr Gly Glu Gly Asp Thr Pro Lys Cys Ser
        195   200   205
Lys Ile Cys Glu Pro Gly Tyr Ser Pro Thr Tyr Lys Gln Asp Lys His
    210   215   220
Tyr Gly Tyr Asn Ser Tyr Ser Val Ser Asn Ser Glu Lys Asp Ile Met
225   230   235   240
Ala Glu Ile Tyr Lys Asn Gly Pro Val Glu Gly Ala Phe Ser Val Tyr
                245   250   255
Ser Asp Phe Leu Leu Tyr Lys Ser Gly Val Tyr Gln His Val Thr Gly
            260   265   270
Glu Met Met Gly Gly His Ala Ile Arg Ile Leu Gly Trp Gly Val Glu
        275   280   285
Asn Gly Thr Pro Tyr Trp Leu Val Ala Asn Ser Trp Asn Thr Asp Trp
    290   295   300
Gly Asp Asn Gly Phe Phe Lys Ile Leu Arg Gly Gln Asp His Cys Gly
305   310   315   320
Ile Glu Ser Glu Val Val Ala Gly Ile Pro Arg Thr Asp Gln Tyr Trp
                325   330   335
Glu Lys Ile

<210> 285
<211> 1292
<212> DNA
<213> Carica papaya

<220>
<223> Papain

<400> 285
atccattccc acttaagaag taaaaagata tagctagtgt cacaatggct atgatacctt 60
caatttcaaa gttgcttttt gttgcaatat gtctttttgt ttatatgggt ttgtcatttg 120
gtgatttttc tattgtgggt tattctcaaa atgacttgac atccactgaa agacttattc 180
agctatttga atcgtggatg ttgaagcaca ataagattta taagaatatt gatgaaaaaa 240
tctacagatt tgaaattttt aaagataatc ttaaatatat tgatgagaca aataagaaaa 300
ataacagtta ttggcttgga ttaaatgtgt ttgctgatat gagcaatgat gaattcaaag 360
aaaagtatac tggttctatt gctggaaatt atacaacaac cgaactatca tacgaagaag 420
tgcttaatga tggtgatgta aatatcccgg agtatgtcga ttggagacaa aaaggagctg 480
tcactcctgt aaaaaatcag ggttcttgtg gtagttgttg ggcattctca gctgttgtaa 540
ctatagaggg aataattaag attagaactg ggaacttaaa tgaatactca gagcaagaac 600
tgcttgactg cgacagacgt agctacgggt gcaatggagg ttacccttgg agtgcacttc 660
aattagtggc tcaatatggt attcactaca gaaatactta cccatatgag ggagtgcaac 720
gttattgtcg ctcaagggag aaaggtcctt atgcagccaa aaccgatggg gttcgacaag 780
tgcaaccata taatgaaggg gctctcttat attcaattgc aaaccaacct gtgagcgttg 840
tccttgaagc tgctggaaaa gatttccaat tatatagagg gggaatattt gtggggccat 900
gcggaaacaa agtagatcat gcagtcgcag cagttgggta tggaccaaat tacatactca 960
taaagaattc atggggtaca ggatggggtg aaaatggata tataagaatc aaaagaggca 1020
ctggaaactc ctatggagta tgtggacttt atacaagctc attctatcct gttaaaaact 1080
gatgagatca cggctttcat aaaatccctt atatatatat atatatatag aacttgtata 1140
ctcatcgtgt gttgaaataa taaatgagag gattaataat ttgtgtaatc ctatatatca 1200
cagtttgttg tgacaaactt ttgcatcgct tgttatatta tttgtaataa tgtttgtttt 1260
gattgaataa actttacat atacttttat gc 1292

<210> 286
<211> 345
<212> PRT
<213> Carica papaya

<220>
<223> Papain

<400> 286
Met Ala Met Ile Pro Ser Ile Ser Lys Leu Leu Phe Val Ala Ile Cys
 1   5   10   15
Leu Phe Val Tyr Met Gly Leu Ser Phe Gly Asp Phe Ser Ile Val Gly
            20   25   30
Tyr Ser Gln Asn Asp Leu Thr Ser Thr Glu Arg Leu Ile Gln Leu Phe
        35   40   45
Glu Ser Trp Met Leu Lys His Asn Lys Ile Tyr Lys Asn Ile Asp Glu
    50   55   60
Lys Ile Tyr Arg Phe Glu Ile Phe Lys Asp Asn Leu Lys Tyr Ile Asp
65   70   75   80
Glu Thr Asn Lys Lys Asn Asn Ser Tyr Trp Leu Gly Leu Asn Val Phe
                85   90   95
Ala Asp Met Ser Asn Asp Glu Phe Lys Glu Lys Tyr Thr Gly Ser Ile
            100   105   110
Ala Gly Asn Tyr Thr Thr Thr Glu Leu Ser Tyr Glu Glu Val Leu Asn

```
        115                 120                 125
Asp Gly Asp Val Asn Ile Pro Glu Tyr Val Asp Trp Arg Gln Lys Gly
    130                 135                 140
Ala Val Thr Pro Val Lys Asn Gln Gly Ser Cys Gly Ser Cys Trp Ala
145                 150                 155                 160
Phe Ser Ala Val Val Thr Ile Glu Gly Ile Ile Lys Ile Arg Thr Gly
                165                 170                 175
Asn Leu Asn Glu Tyr Ser Glu Gln Glu Leu Leu Asp Cys Asp Arg Arg
            180                 185                 190
Ser Tyr Gly Cys Asn Gly Gly Tyr Pro Trp Ser Ala Leu Gln Leu Val
        195                 200                 205
Ala Gln Tyr Gly Ile His Tyr Arg Asn Thr Tyr Pro Tyr Glu Gly Val
    210                 215                 220
Gln Arg Tyr Cys Arg Ser Arg Glu Lys Gly Pro Tyr Ala Ala Lys Thr
225                 230                 235                 240
Asp Gly Val Arg Gln Val Gln Pro Tyr Asn Glu Gly Ala Leu Leu Tyr
                245                 250                 255
Ser Ile Ala Asn Gln Pro Val Ser Val Val Leu Glu Ala Ala Gly Lys
            260                 265                 270
Asp Phe Gln Leu Tyr Arg Gly Gly Ile Phe Val Gly Pro Cys Gly Asn
        275                 280                 285
Lys Val Asp His Ala Val Ala Ala Val Gly Tyr Gly Pro Asn Tyr Ile
    290                 295                 300
Leu Ile Lys Asn Ser Trp Gly Thr Gly Trp Gly Glu Asn Gly Tyr Ile

305                 310                 315                 320
Arg Ile Lys Arg Gly Thr Gly Asn Ser Tyr Gly Val Cys Gly Leu Tyr
                325                 330                 335
Thr Ser Ser Phe Tyr Pro Val Lys Asn
            340                 345
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<210> 287
<211> 1845
<212> DNA
<213> Trypanosoma cruzi

<220>
<223> Cruzain (Cruzapain)

<400> 287
atgtctggct gggcgcgtgc gctgttgctc gcggccgtcc tggtcgtcat ggcgtgcctc 60
gtccccgcgg cgacggcgag cctgcatgcg gaggagacgc tgacgtcgca attcgcagaa 120
ttcaagcaga agcatggcag ggtgtacgag agcgccgcgg aggaggcgtt ccgcctgagc 180
gtgttcaggg agaacctgtt tcttgcgagg ctgcacgccg cggcaaaccc acacgcgacc 240
ttcggcgtca cgcccttctc ggacctcacg cgcgaggaat tccggtcccg ctaccacaac 300
ggcgcggcgc actttgcggc ggcgcaggag cgcgcgagag tgccggtgaa ggtggaggta 360
gttggcgcgc ccgcggcagt ggattggcgt gcgagaggcg ccgtgacagc cgtcaaggac 420
cagggccaat gcggttcgtg ctgggccttc tccgccattg gcaacgttga gtgccagtgg 480
tttcttgccg gccacccgct gacgaacctg tcggagcaga tgctcgtgtc gtgcgacaaa 540
acggactctg gctgcagtgg tggcctgatg aacaacgcct ttgagtggat tgtgcaggag 600
aataacggcg ccgtgtacac ggaggacagc tacccttatg cgtcgggcga ggggatatcg 660
ccgccgtgca cgacgtcagg ccacacggtg ggtgccacga ttaccggtca cgttgaatta 720
cctcaggacg aggcccaaat agccgcatgg cttgcagtca atggcccggt tgccgttgcc 780
gtcgacgcca gcagctggat gacctacacg ggcggcgtta tgacgagctg cgtctccgag 840
cagctggatc acggcgttct tctcgtcggc tacaatgaca gcgccgcagt gccgtactgg 900
atcatcaaga actcgtggac cacgcagtgg ggcgaggaag gctacatccg cattgcaaag 960

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ggctcgaacc agtgccttgt caaggaggag gcgagctccg cggtggtcgg tggtcccgga 1020
cccactcccg agccaaccac cacgacaacc acaagtgccc caggaccgtc cccatcgtac 1080
tttgtgcaga tgtcctgcac tgacgctgcg tgcattgtcg ggtgcgagaa cgtgacgtta 1140
ccgaccggtc agtgtctcct gaccaccagc ggcgtctctg ccattgtcac gtgcggtgct 1200
gagactctca cagaagaagt cttccttacg agtacgcact gcagcggccc atcggtgagg 1260
tcctctgttc ctctcaacaa atgcaaccgg cttttaagag gctccgttga gttcttctgc 1320
ggctccagct ccagtggccg actggccgac gtggacaggc agcgtcgcca tcagccatac 1380
cacagccgtc atcgccgcct ctgagggcac tctttgtttc tgatgctgcc ttttctctca 1440
ttttactttt ttattattat tgagcgagcg tcggtgctgc ggcacactgg gcaaataagt 1500
cccagtggag tggattgttt attgatttgc tccatgtatg tgttttcttt tttgtgcaca 1560
actgcaaata tgtgtccgcg atcgacgtct cagccacgcg tgtgtttttt ctattatatg 1620
cttctgttga gcgcccgagc attccccact gtggctgaac ccaccgccgt ccccgactgt 1680
cacccgacca tgcggggcgg ggtggcgtgg caacgctcct ttgccgcggc gtgcacatac 1740
acgcgcgcat gcttcttctc tccacgtcaa cgccgacacc accacagtct gaaggtgacg 1800
ctgttgaagg cacacaagga aggaaacaca cccacacaag cagta                 1845
```

<210> 288
<211> 467
<212> PRT
<213> Trypanosoma cruzi

<220>
<223> Cruzain (Cruzapain)

<400> 288

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Met Ser Gly Trp Ala Arg Ala Leu Leu Leu Ala Ala Val Leu Val Val
 1               5                  10                  15
Met Ala Cys Leu Val Pro Ala Ala Thr Ala Ser Leu His Ala Glu Glu
            20                  25                  30
Thr Leu Thr Ser Gln Phe Ala Glu Phe Lys Gln Lys His Gly Arg Val
        35                  40                  45
Tyr Glu Ser Ala Ala Glu Glu Ala Phe Arg Leu Ser Val Phe Arg Glu
    50                  55                  60
Asn Leu Phe Leu Ala Arg Leu His Ala Ala Ala Asn Pro His Ala Thr
65                  70                  75                  80
Phe Gly Val Thr Pro Phe Ser Asp Leu Thr Arg Glu Glu Phe Arg Ser
                85                  90                  95
Arg Tyr His Asn Gly Ala Ala His Phe Ala Ala Ala Gln Glu Arg Ala
            100                 105                 110
Arg Val Pro Val Lys Val Glu Val Val Gly Ala Pro Ala Ala Val Asp
        115                 120                 125
Trp Arg Ala Arg Gly Ala Val Thr Ala Val Lys Asp Gln Gly Gln Cys
    130                 135                 140
Gly Ser Cys Trp Ala Phe Ser Ala Ile Gly Asn Val Glu Cys Gln Trp
145                 150                 155                 160
Phe Leu Ala Gly His Pro Leu Thr Asn Leu Ser Glu Gln Met Leu Val
                165                 170                 175
Ser Cys Asp Lys Thr Asp Ser Gly Cys Ser Gly Gly Leu Met Asn Asn
            180                 185                 190
Ala Phe Glu Trp Ile Val Gln Glu Asn Asn Gly Ala Val Tyr Thr Glu
        195                 200                 205
Asp Ser Tyr Pro Tyr Ala Ser Gly Glu Gly Ile Ser Pro Pro Cys Thr
    210                 215                 220
Thr Ser Gly His Thr Val Gly Ala Thr Ile Thr Gly His Val Glu Leu
225                 230                 235                 240
Pro Gln Asp Glu Ala Gln Ile Ala Ala Trp Leu Ala Val Asn Gly Pro
```

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                245                 250                 255
Val Ala Val Ala Val Asp Ala Ser Ser Trp Met Thr Tyr Thr Gly Gly
            260                 265                 270
Val Met Thr Ser Cys Val Ser Glu Gln Leu Asp His Gly Val Leu Leu
        275                 280                 285
Val Gly Tyr Asn Asp Ser Ala Ala Val Pro Tyr Trp Ile Ile Lys Asn
    290                 295                 300
Ser Trp Thr Thr Gln Trp Gly Glu Glu Gly Tyr Ile Arg Ile Ala Lys
305                 310                 315                 320
Gly Ser Asn Gln Cys Leu Val Lys Glu Glu Ala Ser Ser Ala Val Val
                325                 330                 335
Gly Gly Pro Gly Pro Thr Pro Glu Pro Thr Thr Thr Thr Thr Thr Ser
            340                 345                 350
Ala Pro Gly Pro Ser Pro Ser Tyr Phe Val Gln Met Ser Cys Thr Asp
        355                 360                 365
Ala Ala Cys Ile Val Gly Cys Glu Asn Val Thr Leu Pro Thr Gly Gln
    370                 375                 380
Cys Leu Leu Thr Thr Ser Gly Val Ser Ala Ile Val Thr Cys Gly Ala
385                 390                 395                 400
Glu Thr Leu Thr Glu Glu Val Phe Leu Thr Ser Thr His Cys Ser Gly
                405                 410                 415
Pro Ser Val Arg Ser Ser Val Pro Leu Asn Lys Cys Asn Arg Leu Leu
            420                 425                 430
Arg Gly Ser Val Glu Phe Phe Cys Gly Ser Ser Ser Ser Gly Arg Leu
        435                 440                 445
Ala Asp Val Asp Arg Gln Arg Arg His Gln Pro Tyr His Ser Arg His
    450                 455                 460
Arg Arg Leu
465
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<210> 289
<211> 379
<212> PRT
<213> Bacillus licheniformis

<220>
<223> Subtilisin Carlsberg precursor S08.001

<400> 289

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Met Met Arg Lys Lys Ser Phe Trp Leu Gly Met Leu Thr Ala Phe Met
 1               5                  10                  15
Leu Val Phe Thr Met Ala Phe Ser Asp Ser Ala Ser Ala Ala Gln Pro
            20                  25                  30
Ala Lys Asn Val Glu Lys Asp Tyr Ile Val Gly Phe Lys Ser Gly Val
        35                  40                  45
Lys Thr Ala Ser Val Lys Lys Asp Ile Ile Lys Glu Ser Gly Gly Lys
    50                  55                  60
Val Asp Lys Gln Phe Arg Ile Ile Asn Ala Ala Lys Ala Lys Leu Asp
65                  70                  75                  80
Lys Glu Ala Leu Lys Glu Val Lys Asn Asp Pro Asp Val Ala Tyr Val
                85                  90                  95
Glu Glu Asp His Val Ala His Ala Leu Ala Gln Thr Val Pro Tyr Gly
            100                 105                 110
Ile Pro Leu Ile Lys Ala Asp Lys Val Gln Ala Gln Gly Phe Lys Gly
        115                 120                 125
Ala Asn Val Lys Val Ala Val Leu Asp Thr Gly Ile Gln Ala Ser His
```

```
    130                 135                 140
Pro Asp Leu Asn Val Val Gly Gly Ala Ser Phe Val Ala Gly Glu Ala
145                 150                 155                 160
Tyr Asn Thr Asp Gly Asn Gly His Gly Thr His Val Ala Gly Thr Val
                165                 170                 175
Ala Ala Leu Asp Asn Thr Thr Gly Val Leu Gly Val Ala Pro Ser Val
            180                 185                 190
Ser Leu Tyr Ala Val Lys Val Leu Asn Ser Ser Gly Ser Gly Thr Tyr
        195                 200                 205
Ser Gly Ile Val Ser Gly Ile Glu Trp Ala Thr Thr Asn Gly Met Asp
    210                 215                 220
Val Ile Asn Met Ser Leu Gly Gly Pro Ser Gly Ser Thr Ala Met Lys
225                 230                 235                 240
Gln Ala Val Asp Asn Ala Tyr Ala Arg Gly Val Val Val Val Ala Ala
                245                 250                 255
Ala Gly Asn Ser Gly Ser Ser Gly Asn Thr Asn Thr Ile Gly Tyr Pro
            260                 265                 270
Ala Lys Tyr Asp Ser Val Ile Ala Val Gly Ala Val Asp Ser Asn Ser
        275                 280                 285
Asn Arg Ala Ser Phe Ser Ser Val Gly Ala Glu Leu Glu Val Met Ala
    290                 295                 300
Pro Gly Ala Gly Val Tyr Ser Thr Tyr Pro Thr Ser Thr Tyr Ala Thr
305                 310                 315                 320
Leu Asn Gly Thr Ser Met Ala Ser Pro His Val Ala Gly Ala Ala Ala
                325                 330                 335
Leu Ile Leu Ser Lys His Pro Asn Leu Ser Ala Ser Gln Val Arg Asn
            340                 345                 350
Arg Leu Ser Ser Thr Ala Thr Tyr Leu Gly Ser Ser Phe Tyr Tyr Gly
        355                 360                 365
Lys Gly Leu Ile Asn Val Glu Ala Ala Ala Gln
    370                 375
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<210> 290
<211> 1588
<212> DNA
<213> Bacillus licheniformis

<220>
<223> Subtilisin Carlsberg precursor S08.001

<400> 290
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ttttcataaa atgaatcaga tggagcaatc tcctgtcatt cgcggccctc gggacctctt 120
tccctgccag gctgaagcgg tctattcata ctttcgaact gaacattttt ctaaaacagt 180
tattaataac caaaaaattt taaattggtc ctccaaaaaa ataggcctac catataattc 240
attttttttc tataataaat taacagaata attggaatag attatattat ccttctattt 300
aaattattct gaataaagag gaggagagtg agtaatgatg aggaaaaaga gtttttggct 360
tgggatgctg acggccttca tgctcgtgtt cacgatggca ttcagcgatt ccgcttctgc 420
tgctcaaccg gcgaaaaatg ttgaaaagga ttatattgtc ggatttaagt caggagtgaa 480
aaccgcatct gtcaaaaagg acatcatcaa agagagcggc ggaaaagtgg acaagcagtt 540
tagaatcatc aacgcggcaa aagcgaagct agacaaagaa gcgcttaagg aagtcaaaaa 600
tgatccggat gtcgcttatg tggaagagga tcatgtggcc catgccttgg cgcaaaccgt 660
tccttacggc attcctctca ttaaagcgga caaagtgcag gctcaaggct ttaagggagc 720
gaatgtaaaa gtagccgtcc tggatacagg aatccaagct tctcatccgg acttgaacgt 780
agtcggcgga gcaagctttg tggctggcga agcttataac accgacggca acggacacgg 840

cacacatgtt gccggtacag tagctgcgct tgacaataca acgggtgtat taggcgttgc 900
gccaagcgta tccttgtacg cggttaaagt actgaattca agcggaagcg gaacttacag 960
cggcattgta agcggaatcg agtgggcgac gacaaacggc atggatgtta tcaacatgag 1020
tcttggagga ccatcaggct caacagcgat gaaacaggcg gttgacaatg catatgcaag 1080
aggggttgtc gttgtggcgg ctgctgggaa cagcggatct tcaggaaaca cgaatacaat 1140
cggctatcct gcgaaatacg actctgtcat cgcagttggc gcggtagact ctaacagcaa 1200
cagagcttca ttttccagcg tcggagcaga gcttgaagtc atggctcctg gcgcaggcgt 1260
gtacagcact tacccaacca gcacttatgc aacattgaac ggaacgtcaa tggcttctcc 1320
tcatgtagcg ggagcagcag ctttgatctt gtcaaaacat ccgaaccttt cagcttcaca 1380
agtccgcaac cgtctctcca gtacggcgac ttatttggga agctccttct actatggaaa 1440
aggtctgatc aatgtcgaag ctgccgctca ataacatatt ctaacaaatg gcatatagaa 1500
aaagctagtg tttttagcac tagctttttc ttcattcagt tgaagactgt tcaatatttt 1560
gaatccgttc cattatggtc ggatggcc 1588

<210> 291
<211> 275
<212> PRT
<213> Bacillus pumilus

<220>
<223> Subtilisin (Alkaline mesentericopeptidase) S08.002

<400> 291
Ala Gln Ser Val Pro Tyr Gly Ile Ser Gln Ile Lys Ala Pro Ala Leu
1 5 10 15
His Ser Gln Gly Tyr Thr Gly Ser Asn Val Lys Val Ala Val Ile Asp
20 25 30
Ser Gly Ile Asp Ser Ser His Pro Asp Leu Asn Val Arg Gly Gly Ala
35 40 45
Ser Phe Val Pro Ser Glu Thr Asn Pro Tyr Gln Asp Gly Ser Ser His
50 55 60
Gly Thr His Val Ala Gly Thr Ile Ala Ala Leu Asn Asn Ser Ile Gly
65 70 75 80
Val Leu Gly Val Ala Pro Ser Ser Ala Leu Tyr Ala Val Lys Val Leu
85 90 95
Asp Ser Thr Gly Ser Gly Gln Tyr Ser Trp Ile Ile Asn Gly Ile Glu
100 105 110
Trp Ala Ile Ser Asn Asn Met Asp Val Ile Asn Met Ser Leu Gly Gly
115 120 125
Pro Thr Gly Ser Thr Ala Leu Lys Thr Val Val Asp Lys Ala Val Ser
130 135 140
Ser Gly Ile Val Val Ala Ala Ala Ala Gly Asn Glu Gly Ser Ser Gly
145 150 155 160
Ser Thr Ser Thr Val Gly Tyr Pro Ala Lys Tyr Pro Ser Thr Ile Ala
165 170 175
Val Gly Ala Val Asn Ser Ala Asn Gln Arg Ala Ser Phe Ser Ser Ala
180 185 190
Gly Ser Glu Leu Asp Val Met Ala Pro Gly Val Ser Ile Gln Ser Thr
195 200 205
Leu Pro Gly Gly Thr Tyr Gly Ala Tyr Asn Gly Thr Ser Met Ala Thr
210 215 220
Pro His Val Ala Gly Ala Ala Ala Leu Ile Leu Ser Lys His Pro Thr
225 230 235 240
Trp Thr Asn Ala Gln Val Arg Asp Arg Leu Glu Ser Thr Ala Thr Tyr
245 250 255
Leu Gly Ser Ser Phe Tyr Tyr Gly Lys Gly Leu Ile Asn Val Gln Ala

260 265 270
Ala Ala Gln
275

<210> 292
<211> 269
<212> PRT
<213> Bacillus lentus

<220>
<223> Subtilisin Savinase (Alkaline protease) S08.003

<400> 292
Ala Gln Ser Val Pro Trp Gly Ile Ser Arg Val Gln Ala Pro Ala Ala
1 5 10 15
His Asn Arg Gly Leu Thr Gly Ser Gly Val Lys Val Ala Val Leu Asp
20 25 30
Thr Gly Ile Ser Thr His Pro Asp Leu Asn Ile Arg Gly Gly Ala Ser
35 40 45
Phe Val Pro Gly Glu Pro Ser Thr Gln Asp Gly Asn Gly His Gly Thr
50 55 60
His Val Ala Gly Thr Ile Ala Ala Leu Asn Asn Ser Ile Gly Val Leu
65 70 75 80
Gly Val Ala Pro Ser Ala Glu Leu Tyr Ala Val Lys Val Leu Gly Ala
85 90 95
Ser Gly Ser Gly Ser Val Ser Ser Ile Ala Gln Gly Leu Glu Trp Ala
100 105 110
Gly Asn Asn Gly Met His Val Ala Asn Leu Ser Leu Gly Ser Pro Ser
115 120 125
Pro Ser Ala Thr Leu Glu Gln Ala Val Asn Ser Ala Thr Ser Arg Gly
130 135 140
Val Leu Val Val Ala Ala Ser Gly Asn Ser Gly Ala Gly Ser Ile Ser
145 150 155 160
Tyr Pro Ala Arg Tyr Ala Asn Ala Met Ala Val Gly Ala Thr Asp Gln
165 170 175
Asn Asn Asn Arg Ala Ser Phe Ser Gln Tyr Gly Ala Gly Leu Asp Ile
180 185 190
Val Ala Pro Gly Val Asn Val Gln Ser Thr Tyr Pro Gly Ser Thr Tyr
195 200 205
Ala Ser Leu Asn Gly Thr Ser Met Ala Thr Pro His Val Ala Gly Ala
210 215 220
Ala Ala Leu Val Lys Gln Lys Asn Pro Ser Trp Ser Asn Val Gln Ile
225 230 235 240
Arg Asn His Leu Lys Asn Thr Ala Thr Ser Leu Gly Ser Thr Asn Leu
245 250 255
Tyr Gly Ser Gly Leu Val Asn Ala Glu Ala Ala Thr Arg
260 265

<210> 293
<211> 279
<212> PRT
<213> Thermoactinomyces vulgaris

<220>
<223> Thermitase S08.007

<400> 293
Tyr Thr Pro Asn Asp Pro Tyr Phe Ser Ser Arg Gln Tyr Gly Pro Gln
1 5 10 15
Lys Ile Gln Ala Pro Gln Ala Trp Asp Ile Ala Glu Gly Ser Gly Ala
20 25 30
Lys Ile Ala Ile Val Asp Thr Gly Val Gln Ser Asn His Pro Asp Leu
35 40 45
Ala Gly Lys Val Val Gly Gly Trp Asp Phe Val Asp Asn Asp Ser Thr
50 55 60
Pro Gln Asn Gly Asn Gly His Gly Thr His Cys Ala Gly Ile Ala Ala
65 70 75 80
Ala Val Thr Asn Asn Ser Thr Gly Ile Ala Gly Thr Ala Pro Lys Ala
85 90 95
Ser Ile Leu Ala Val Arg Val Leu Asp Asn Ser Gly Ser Gly Thr Trp
100 105 110
Thr Ala Val Ala Asn Gly Ile Thr Tyr Ala Ala Asp Gln Gly Ala Lys
115 120 125
Val Ile Ser Leu Ser Leu Gly Gly Thr Val Gly Asn Ser Gly Leu Gln
130 135 140
Gln Ala Val Asn Tyr Ala Trp Asn Lys Gly Ser Val Val Val Ala Ala
145 150 155 160
Ala Gly Asn Ala Gly Asn Thr Ala Pro Asn Tyr Pro Ala Tyr Tyr Ser
165 170 175
Asn Ala Ile Ala Val Ala Ser Thr Asp Gln Asn Asp Asn Lys Ser Ser
180 185 190
Phe Ser Thr Tyr Gly Ser Val Val Asp Val Ala Ala Pro Gly Ser Trp
195 200 205
Ile Tyr Ser Thr Tyr Pro Thr Ser Thr Tyr Ala Ser Leu Ser Gly Thr
210 215 220
Ser Met Ala Thr Pro His Val Ala Gly Val Ala Gly Leu Leu Ala Ser
225 230 235 240
Gln Gly Arg Ser Ala Ser Asn Ile Arg Ala Ala Ile Glu Asn Thr Ala
245 250 255
Asp Lys Ile Ser Gly Thr Gly Thr Tyr Trp Ala Lys Gly Arg Val Asn
260 265 270
Ala Tyr Lys Ala Val Gln Tyr
275

<210> 294
<211> 401
<212> PRT
<213> Bacillus sp. AK1

<220>
<223> Thermophilic serine proteinase precursor (Ak.1 protease) S08.009

<400> 294
Met Lys Phe Lys Ala Ile Val Ser Leu Ser Leu Ala Val Ser Met Ser
1 5 10 15
Leu Phe Pro Phe Leu Val Glu Ala Ala Ser Asn Asp Gly Val Glu Ser
20 25 30
Pro Lys Thr Val Ser Glu Ile Asn Val Ser His Glu Lys Gly Ala Tyr
35 40 45
Val Gln Gly Glu Val Ile Val Gln Phe Lys Glu Gln Val Asn Ala Glu

```
    50                  55                  60
Glu Lys Ala Lys Ala Leu Lys Glu Val Gly Ala Thr Ala Val Pro Asp
65                  70                  75                  80
Asn Asp Arg Val Lys Ser Lys Phe Asn Val Leu Lys Val Gly Asn Val
                85                  90                  95
Glu Ala Val Val Lys Ala Leu Asn Asn Asn Pro Leu Val Glu Tyr Ala
            100                 105                 110
Glu Pro Asn Tyr Leu Phe Asn Ala Ala Trp Thr Pro Asn Asp Thr Tyr
        115                 120                 125
Tyr Gln Gly Tyr Gln Tyr Gly Pro Gln Asn Thr Tyr Thr Asp Tyr Ala
    130                 135                 140
Trp Asp Val Thr Lys Gly Ser Ser Gly Gln Glu Ile Ala Val Ile Asp
145                 150                 155                 160
Thr Gly Val Asp Tyr Thr His Pro Asp Leu Asp Gly Lys Val Ile Lys
                165                 170                 175
Gly Tyr Asp Phe Val Asp Asn Asp Tyr Asp Pro Met Asp Leu Asn Asn
            180                 185                 190
His Gly Thr His Val Ala Gly Ile Ala Ala Ala Glu Thr Asn Asn Ala
        195                 200                 205
Thr Gly Ile Ala Gly Met Ala Pro Asn Thr Arg Ile Leu Ala Val Arg
    210                 215                 220
Ala Leu Asp Arg Asn Gly Ser Gly Thr Leu Ser Asp Ile Ala Asp Ala
225                 230                 235                 240
Ile Ile Tyr Ala Ala Asp Ser Gly Ala Glu Val Ile Asn Leu Ser Leu
                245                 250                 255
Gly Cys Asp Cys His Thr Thr Thr Leu Glu Asn Ala Val Asn Tyr Ala
            260                 265                 270
Trp Asn Lys Gly Ser Val Val Val Ala Ala Ala Gly Asn Asn Gly Ser
        275                 280                 285
Ser Thr Thr Phe Glu Pro Ala Ser Tyr Glu Asn Val Ile Ala Val Gly
    290                 295                 300
Ala Val Asp Gln Tyr Asp Arg Leu Ala Ser Phe Ser Asn Tyr Gly Thr
305                 310                 315                 320
Trp Val Asp Val Val Ala Pro Gly Val Asp Ile Val Ser Thr Ile Thr
                325                 330                 335
Gly Asn Arg Tyr Ala Tyr Met Ser Gly Thr Ser Met Ala Ser Pro His
            340                 345                 350
Val Ala Gly Leu Ala Ala Leu Leu Ala Ser Gln Gly Arg Asn Asn Ile
        355                 360                 365
Glu Ile Arg Gln Ala Ile Glu Gln Thr Ala Asp Lys Ile Ser Gly Thr
    370                 375                 380
Gly Thr Tyr Phe Lys Tyr Gly Arg Ile Asn Ser Tyr Asn Ala Val Thr
385                 390                 395                 400
Tyr
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<210> 295
<211> 1591
<212> DNA
<213> Bacillus sp

<220>
<223> Thermophilic serine proteinase precursor (Ak.1 protease) S08.009

<400> 295

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attatattaa aataaatgtc gagatttttg agaaaaaatt tttcattcct ccccccttcct 120
caacgtaaaa ttaataccgc aattccattt aaaggggggaa tatttccatg aagtttaaag 180
cgattgtaag tttatccctc gctgtttcca tgtcactttt tccattcctt gtggaagcag 240
cctctaatga tggggtagaa tctccaaaaa ccgtttccga aattaacgtg tctcatgaaa 300
aaggagcata tgtccaggga gaagtcattg tccaattcaa agaacaagta aatgctgaag 360
aaaaggcaaa ggcattaaaa gaagttgggg caacggcggt tccagataat gatcgagtta 420
aatctaaatt taatgtacta aaagtaggaa atgtggaagc tgttgtgaaa gcattaaata 480
ataacccgtt agtagaatac gcagagccaa actatttatt taatgcagct tggactccaa 540
atgatacgta ctatcagggt tatcaatatg gtccacaaaa tacgtatacc gactatgctt 600
gggatgttac aaaaggcagt agcggtcaag agattgctgt tattgataca ggtgtagatt 660
atacacatcc tgatttagat ggaaaagtca tcaaaggata tgatttcgta gataatgatt 720
acgacccaat ggatttgaat aatcatggta cgcacgtagc tggaatagca gctgcggaaa 780
caaacaatgc tacaggtatt gccggcatgg ccccaaacac aagaattttg gctgtgcgcg 840
ctttagatcg aaatggcagt ggtactctaa gtgatattgc cgatgcgatc atttatgctg 900
ctgattcagg cgctgaagtc attaacctgt cacttggttg tgattgtcat acaaccacat 960
tggagaatgc tgtaaactat gcatggaata agggttctgt agtagttgcc gcagccggaa 1020

ataatggatc ctctacaaca tttgaaccgg cttcttatga aaatgtaatt gcagttggcg 1080
cagtagatca atatgatcgg ttagcatcat tctcgaacta tggaacatgg gtagatgtcg 1140
tagctccagg tgtagacatt gtctcaacta ttactggtaa ccgatatgcc tatatgtcgg 1200
gcacttccat ggcatccccct catgtagccg gtcttgcagc cttactagcg agtcaaggac 1260
ggaataacat agaaattcgt caagccatcg agcaaacagc agacaaaatc tccggaactg 1320
gaacatactt caaatatgga agaatcaatt cttataatgc tgtaacatat taaatagatt 1380
taaataacga caccgtgcca acgccaaggg cacggtgtct taattcaagc tttttggaaa 1440
atcacgacat acaaattatg taagaaagct tattctccca taggaattga agaggaaaac 1500
caatattatt cttttatctc agcaaaaata aaaaaactgc caaatggcag actctaacta 1560
actatttttt gcttccttct ttctgctgca g                                1591
```

<210> 296
<211> 1167
<212> PRT
<213> Streptococcus pyogenes

<220>
<223> C5a peptidase precursor (SCP) S08.020

<400> 296

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Met Arg Lys Lys Gln Lys Leu Pro Phe Asp Lys Leu Ala Ile Ala Leu
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Met Ser Thr Ser Ile Leu Leu Asn Ala Gln Ser Asp Ile Lys Ala Asn
            20                  25                  30
Thr Val Thr Glu Asp Thr Pro Val Thr Glu Gln Ala Val Glu Thr Pro
        35                  40                  45
Gln Pro Thr Ala Val Ser Glu Glu Val Pro Ser Ser Lys Glu Thr Lys
    50                  55                  60
Thr Pro Gln Thr Pro Asp Asp Ala Glu Glu Thr Ile Ala Asp Asp Ala
65                  70                  75                  80
Asn Asp Leu Ala Pro Gln Ala Pro Ala Lys Thr Ala Asp Thr Pro Ala
                85                  90                  95
Thr Ser Lys Ala Thr Ile Arg Asp Leu Asn Asp Pro Ser Gln Val Lys
            100                 105                 110
Thr Leu Gln Glu Lys Ala Gly Lys Gly Ala Gly Thr Val Val Ala Val
        115                 120                 125
Ile Asp Ala Gly Phe Asp Lys Asn His Glu Ala Trp Arg Leu Thr Asp
    130                 135                 140
Lys Thr Lys Ala Arg Tyr Gln Ser Lys Glu Asp Leu Glu Lys Ala Lys
```

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145                 150                 155                 160
Lys Glu His Gly Ile Thr Tyr Gly Glu Trp Val Asn Asp Lys Val Ala
                165                 170                 175
Tyr Tyr His Asp Tyr Ser Lys Asp Gly Lys Thr Ala Val Asp Gln Glu
            180                 185                 190
His Gly Thr His Val Ser Gly Ile Leu Ser Gly Asn Ala Pro Ser Glu
        195                 200                 205
Thr Lys Glu Pro Tyr Arg Leu Glu Gly Ala Met Pro Glu Ala Gln Leu
    210                 215                 220
Leu Leu Met Arg Val Glu Ile Val Asn Gly Leu Ala Asp Tyr Ala Arg
225                 230                 235                 240
Asn Tyr Ala Gln Ala Ile Arg Asp Ala Val Asn Leu Gly Ala Lys Val
                245                 250                 255
Ile Asn Met Ser Phe Gly Asn Ala Ala Leu Ala Tyr Ala Asn Leu Pro
            260                 265                 270
Asp Glu Thr Lys Lys Ala Phe Asp Tyr Ala Lys Ser Lys Gly Val Ser
        275                 280                 285
Ile Val Thr Ser Ala Gly Asn Asp Ser Ser Phe Gly Gly Lys Thr Arg
    290                 295                 300
Leu Pro Leu Ala Asp His Pro Asp Tyr Gly Val Val Gly Thr Pro Ala
305                 310                 315                 320
Ala Ala Asp Ser Thr Leu Thr Val Ala Ser Tyr Ser Pro Asp Lys Gln
                325                 330                 335
Leu Thr Glu Thr Ala Met Val Lys Thr Asp Asp Gln Gln Asp Lys Glu
            340                 345                 350
Met Pro Val Leu Ser Thr Asn Arg Phe Glu Pro Asn Lys Ala Tyr Asp
        355                 360                 365
Tyr Ala Tyr Ala Asn Arg Gly Met Lys Glu Asp Asp Phe Lys Asp Val
    370                 375                 380
Lys Gly Lys Ile Ala Leu Ile Glu Arg Gly Asp Ile Asp Phe Lys Asp
385                 390                 395                 400
Lys Val Ala Asn Ala Lys Lys Ala Gly Ala Val Gly Val Leu Ile Tyr
                405                 410                 415
Asp Asn Gln Asp Lys Gly Phe Pro Ile Glu Leu Pro Asn Val Asp Gln
            420                 425                 430
Met Pro Ala Ala Phe Ile Ser Arg Lys Asp Gly Leu Leu Leu Lys Asp
        435                 440                 445
Asn Pro Gln Lys Thr Ile Thr Phe Asn Ala Thr Pro Lys Val Leu Pro
    450                 455                 460
Thr Ala Ser Gly Thr Lys Leu Ser Arg Phe Ser Ser Trp Gly Leu Thr
465                 470                 475                 480
Ala Asp Gly Asn Ile Lys Pro Asp Ile Ala Ala Pro Gly Gln Asp Ile
                485                 490                 495
Leu Ser Ser Val Ala Asn Asn Lys Tyr Ala Lys Leu Ser Gly Thr Ser
            500                 505                 510
Met Ser Ala Pro Leu Val Ala Gly Ile Met Gly Leu Leu Gln Lys Gln
        515                 520                 525
Tyr Glu Thr Gln Tyr Pro Asp Met Thr Pro Ser Glu Arg Leu Asp Leu
    530                 535                 540
Ala Lys Lys Val Leu Met Ser Ser Ala Thr Ala Leu Tyr Asp Glu Asp
545                 550                 555                 560
Glu Lys Ala Tyr Phe Ser Pro Arg Gln Gln Gly Ala Gly Ala Val Asp
                565                 570                 575
Ala Lys Lys Ala Ser Ala Ala Thr Met Tyr Val Thr Asp Lys Asp Asn
            580                 585                 590
Thr Ser Ser Lys Val His Leu Asn Asn Val Ser Asp Lys Phe Glu Val
        595                 600                 605
```

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Thr Val Thr Val His Asn Lys Ser Asp Lys Pro Gln Glu Leu Tyr Tyr
    610                 615                 620
Gln Ala Thr Val Gln Thr Asp Lys Val Asp Gly Lys His Phe Ala Leu
625                 630                 635                 640
Ala Pro Lys Val Leu Tyr Glu Ala Ser Trp Gln Lys Ile Thr Ile Pro
                645                 650                 655
Ala Asn Ser Ser Lys Gln Val Thr Val Pro Ile Asp Ala Ser Arg Phe
            660                 665                 670
Ser Lys Asp Leu Leu Ala Gln Met Lys Asn Gly Tyr Phe Leu Glu Gly
        675                 680                 685
Phe Val Arg Phe Lys Gln Asp Pro Thr Lys Glu Glu Leu Met Ser Ile
    690                 695                 700
Pro Tyr Ile Gly Phe Arg Gly Asp Phe Gly Asn Leu Ser Ala Val Glu
705                 710                 715                 720
Lys Pro Ile Tyr Asp Ser Lys Asp Gly Ser Ser Tyr Tyr His Glu Ala
                725                 730                 735
Asn Ser Asp Ala Lys Asp Gln Leu Asp Gly Asp Gly Leu Gln Phe Tyr
            740                 745                 750
Ala Leu Lys Asn Asn Phe Thr Ala Leu Thr Thr Glu Ser Asn Pro Trp
        755                 760                 765
Thr Ile Ile Lys Ala Val Lys Glu Gly Val Glu Asn Ile Glu Asp Ile
    770                 775                 780
Glu Ser Ser Glu Ile Thr Glu Thr Ile Phe Ala Gly Thr Phe Ala Lys
785                 790                 795                 800
Gln Asp Asp Asp Ser His Tyr Tyr Ile His Arg His Ala Asn Gly Glu
                805                 810                 815
Pro Tyr Ala Ala Ile Ser Pro Asn Gly Asp Gly Asn Arg Asp Tyr Val
            820                 825                 830
Gln Phe Gln Gly Thr Phe Leu Arg Asn Ala Lys Asn Leu Val Ala Glu
        835                 840                 845
Val Leu Asp Lys Glu Gly Asn Val Val Trp Thr Ser Glu Val Thr Glu
    850                 855                 860
Gln Val Val Lys Asn Tyr Asn Asn Asp Leu Ala Ser Thr Leu Gly Ser
865                 870                 875                 880
Thr Arg Phe Glu Lys Thr Arg Trp Asp Gly Lys Asp Lys Asp Gly Lys
                885                 890                 895
Val Val Ala Asn Gly Thr Tyr Thr Tyr Arg Val Arg Tyr Thr Pro Ile
            900                 905                 910
Ser Ser Gly Ala Lys Glu Gln His Thr Asp Phe Asp Val Ile Val Asp
        915                 920                 925
Asn Thr Thr Pro Glu Val Ala Thr Ser Ala Thr Phe Ser Thr Glu Asp
    930                 935                 940
Arg Arg Leu Thr Leu Ala Ser Lys Pro Lys Thr Ser Gln Pro Val Tyr
945                 950                 955                 960
Arg Glu Arg Ile Ala Tyr Thr Tyr Met Asp Glu Asp Leu Pro Thr Thr
                965                 970                 975
Glu Tyr Ile Ser Pro Asn Glu Asp Gly Thr Phe Thr Leu Pro Glu Glu
            980                 985                 990
Ala Glu Thr Met Glu Gly Ala Thr Val Pro Leu Lys Met Ser Asp Phe
        995                 1000                1005
Thr Tyr Val Val Glu Asp Met Ala Gly Asn Ile Thr Tyr Thr Pro Val
    1010                1015                1020
Thr Lys Leu Leu Glu Gly His Ser Asn Lys Pro Glu Gln Asp Gly Ser
1025                1030                1035                1040
Gly Gln Thr Pro Asp Lys Lys Pro Glu Ala Lys Pro Glu Gln Asp Gly
                1045                1050                1055
Ser Asp Gln Ala Pro Asp Lys Lys Pro Glu Ala Lys Pro Glu Gln Asp
```

```
            1060                1065                1070
Gly Ser Gly Gln Thr Pro Asp Lys Lys Pro Glu Thr Lys Pro Glu Lys
        1075                1080                1085
Asp Ser Ser Gly Gln Thr Pro Gly Lys Thr Pro Gln Lys Gly Gln Pro
    1090                1095                1100
Ser Arg Thr Leu Glu Lys Arg Ser Ser Lys Arg Ala Leu Ala Thr Lys
1105                1110                1115                1120
Ala Ser Thr Arg Asp Gln Leu Pro Thr Thr Asn Asp Lys Asp Thr Asn
            1125                1130                1135
Arg Leu His Leu Leu Lys Leu Val Met Thr Thr Phe Phe Phe Gly Leu
            1140                1145                1150
Val Ala His Ile Phe Lys Thr Lys Arg Gln Lys Glu Thr Lys Lys
        1155                1160                1165
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<210> 297
<211> 4637
<212> DNA
<213> Streptococcus pyogenes

<220>
<223> C5a peptidase precursor (SCP) S08.020

<400> 297

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cctgtattga tacatagccc aagaatatgc gtaaaaatag actcaatcaa gccttttttct 60
tgaaagcgac gggaataatt tttgccatag gttgtgaaat gtggcacctt gtcatccaaa 120
gtcaaaccta aaaaccagcg ataggcagta ttcacttcaa tatccttgat ggtctgacgc 180
atggaacgaa tgccataaaa gcactgaatc agagggattt taaccaacat gacaggatca 240
aggctagggc gaccattatc agacgaatag gtgtcttcta ctaggtcata gatgaagtcg 300
aagtcaatca cagcttccac ttagcgcagg aaatgttcat caggcactaa ctggtcaagg 360
gtatagaaac cgtactgatt gcggttatag tcaggttttt ctttgtgtaa cataggagaa 420
cctcacaagt ccttttttctt atattatact cctaaatatc atgaaaagcc cctagaaaag 480
cgattctaag gactttgtct tcagtctgaa gagagaaccg atcggttctc tcttttatgt 540
ctaaaagaat gaggataagg aggtcacaaa ctaaacaact cttaaaaagc tgacctttac 600
taataatcgt ctttttttta taataaagat gttagtaata taattgataa atgagataca 660
tttaatcatt atggcaaaag caagaaaaat agctgtatca tatgcaaata acccctgttt 720
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gacacattgc gtaaaaaaca aaaattacca tttgataaac ttgccattgc gctcatgtct 900
acgagcatct tgctcaatgc acaatcagac attaaagcaa atactgtgac agaagacact 960
cctgttaccg aacaagccgt agaaacccca caaccaacag cggtttctga ggaagtacca 1020
tcatcaaagg aaaccaaaac cccacaaact cctgatgacg cagaagaaac aatagcagat 1080
gacgctaatg atctagcccc tcaagctcct gctaaaactg ctgatacacc agcaacctca 1140
aaagcgacta ttagggattt gaacgaccct tctcaggtca aaaccctgca ggaaaaagca 1200
ggcaagggag ctgggactgt tgttgcagtg attgatgctg gttttgataa aaatcatgaa 1260
gcgtggcgct taacagacaa aaccaaagca cgttaccaat caaaagaaga tcttgaaaaa 1320
gctaaaaaag agcacggtat tacctatggc gagtgggtca atgataaggt tgcttattac 1380
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cctgcagcgg cagactcaac attgacagtt gcttcttaca gcccagataa acagctcact 1860
gaaactgcta tggtcaaaac agacgatcag caagataaag aaatgcctgt tctttcaaca 1920
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gtagaaaaac caatctatga tagcaaagac ggtagcagct actatcatga agcaaatagt 3060
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atttctccaa atgaagatgg tacctttact cttcctgaag aggctgaaac aatggaaggc 3840
gctactgttc cattgaaaat gtcagacttt acttatgttg ttgaagatat ggctggtaat 3900
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gataaaaaac cagaaactaa accagaaaaa gatagttcag gtcaaacacc aggtaaaact 4140
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<210> 298
<211> 699
<212> PRT
<213> Fervidobacterium pennivorans

<220>
<223> fervidolysin S08.020

<400> 298

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Leu Phe Ser Cys Ala Asn Pro Ser Phe Glu Pro Arg Ser Lys Ala Lys
            20                  25                  30
Asp Leu Ala Ser Leu Pro Glu Ile Lys Ser Gln Gly Tyr His Ile Leu
        35                  40                  45
Phe Gly Glu Leu Arg Asp Gly Glu Tyr Thr Glu Gly Lys Ile Leu Val
    50                  55                  60
Gly Tyr Asn Asp Arg Ser Glu Val Asp Lys Ile Val Lys Ala Val Asn
65                  70                  75                  80
Gly Lys Val Val Leu Glu Leu Pro Gln Ile Lys Val Val Ser Ile Lys
                85                  90                  95
Leu Asn Gly Met Thr Val Lys Gln Ala Tyr Asp Lys Ile Lys Ala Leu
            100                 105                 110
Ala Leu Lys Gly Ile Arg Tyr Val Glu Pro Ser Tyr Lys Arg Glu Leu
        115                 120                 125
Ile Lys Pro Thr Val Val Lys Pro Asn Pro Asp Met Tyr Lys Ile Arg
    130                 135                 140
Lys Pro Gly Leu Asn Ser Thr Ala Arg Asp Tyr Gly Glu Glu Leu Ser
145                 150                 155                 160
Asn Glu Leu Trp Gly Leu Glu Ala Ile Gly Val Thr Gln Gln Leu Trp
                165                 170                 175
Glu Glu Ala Ser Gly Thr Asn Ile Ile Val Ala Val Val Asp Thr Gly
            180                 185                 190
Val Asp Gly Thr His Pro Asp Leu Glu Gly Gln Val Ile Ala Gly Tyr
        195                 200                 205
Arg Pro Ala Phe Asp Glu Glu Leu Pro Ala Gly Thr Asp Ser Ser Tyr
    210                 215                 220
Gly Gly Ser His Gly Thr His Val Ala Gly Thr Ile Ala Ala Lys Lys
225                 230                 235                 240
Asp Gly Lys Gly Ile Val Gly Val Ala Pro Gly Ala Lys Ile Met Pro
                245                 250                 255
Ile Val Ile Phe Asp Asp Pro Ala Leu Val Gly Gly Asn Gly Tyr Val
            260                 265                 270
Gly Asp Asp Tyr Val Ala Ala Gly Ile Ile Trp Ala Thr Asp His Gly
        275                 280                 285
Ala Lys Val Met Asn His Ser Trp Gly Gly Trp Gly Tyr Ser Tyr Thr
    290                 295                 300
Met Lys Glu Ala Phe Asp Tyr Ala Met Glu His Gly Val Val Met Val
305                 310                 315                 320
Val Ser Ala Gly Asn Asn Thr Ser Asp Ser His His Gln Tyr Pro Ala
                325                 330                 335
Gly Tyr Pro Gly Val Ile Gln Val Ala Ala Leu Asp Tyr Tyr Gly Gly
            340                 345                 350
Thr Phe Arg Val Ala Gly Phe Ser Ser Arg Ser Asp Gly Val Ser Val
        355                 360                 365
Gly Ala Pro Gly Val Thr Ile Leu Ser Thr Val Pro Gly Glu Asp Ser
    370                 375                 380
Ile Gly Tyr Glu Gly His Asn Glu Asn Val Pro Ala Thr Asn Gly Gly
385                 390                 395                 400
Thr Tyr Asp Tyr Tyr Gln Gly Thr Ser Met Ala Ala Pro His Val Thr
                405                 410                 415
Gly Val Val Ala Val Leu Leu Gln Lys Phe Pro Asn Ala Lys Pro Trp
            420                 425                 430
Gln Ile Arg Lys Leu Leu Glu Asn Thr Ala Phe Asp Phe Asn Gly Asn
        435                 440                 445
Gly Trp Asp His Asp Thr Gly Tyr Gly Leu Val Lys Leu Asp Ala Ala
```

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    450                 455                 460
Leu Gln Gly Pro Leu Pro Thr Gln Gly Gly Val Glu Glu Phe Gln Val
465                 470                 475                 480
Val Val Thr Asp Ala Lys Gly Asn Phe Gly Val Pro Thr Val Phe Val
                485                 490                 495
Ser Met Met Arg Asp Asn Gly Ser Cys Tyr Tyr Ala Lys Thr Gly Pro
            500                 505                 510
Asp Gly Ile Ala Arg Phe Pro His Ile Asp Ser Gly Thr Tyr Asp Ile
        515                 520                 525
Phe Val Gly Gly Pro Asp His Trp Asp Arg Ala Leu Ala Pro Tyr Asp
    530                 535                 540
Gly Glu Ser Ile Pro Gly Gly Tyr Ala Ile Ala Leu Arg Met Ala Glu
545                 550                 555                 560
Glu Arg Gln Ala Ser Phe Val Gly Phe Gly Val Ser Pro Asp Ala Thr
                565                 570                 575
Gln Leu Asn Val Asn Phe Asn Ser Thr Leu Gln Val Lys Phe Ser Thr
            580                 585                 590
Asn Leu Ser Thr Leu Lys Asp Pro Gln Phe Val Val Val Asp Pro Leu
        595                 600                 605
Leu Arg Gly Val Tyr Gly Arg Val Ala Tyr Ala Arg Asn Gln Thr Tyr
    610                 615                 620
Asp Leu Ser Leu Leu Ser Gly Gln Ile Ser Phe Gly Ile Gln Thr Leu
625                 630                 635                 640
Leu Pro Ala Ala Thr Asp Ile Thr Ile Gln Gly Thr Val Thr Leu Asn
                645                 650                 655
Gly Glu Asp Ile Pro Val Tyr Gly Val Leu Lys Ala Gly Thr Thr Trp
            660                 665                 670
Thr Ile Ile Asp Asp Phe Gly Gly Leu Asn Leu Gly Thr Asp Ser Gln
        675                 680                 685
Pro Ile Tyr Val Trp Trp Thr Ile Phe Gly Gln
    690                 695
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<210> 299
<211> 2227
<212> DNA
<213> Fervidobacterium pennivorans

<220>
<223> fervidolysin S08.020

<400> 299
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gagaaaagta ttgttgatag cttccattgt tgctcttatt ctcgcgctct tttcatgtgc 120
aaatccgagt tttgagccaa ggagcaaagc aaaagattta gcatcgttac cggagataaa 180
atctcagggt taccatatac tcttcggtga attgagggac ggggaatata ccgagggtaa 240
aatcctcgtt ggttacaacg ataggtcgga agtagataaa atagtcaaag cagttaacgg 300
taaagtagtg ctcgaattac cacagattaa agtggtctcc ataaaactca atggaatgac 360
ggttaaacaa gcatacgaca agataaaggc acttgcactt aaaggtatca ggtatgttga 420
accaagttac aagagggagc tcataaaacc aacagttgtg aagccaaatc ctgatatgta 480
caaaatcaga aaacctgggt tgaacagtac tgcaagagat tacggtgaag aactttccaa 540
cgaactctgg ggccttgagg caattggtgt aacacaacag ctttgggaag aagcatcggg 600
aacaaatatt atcgttgcgg ttgttgatac tggtgtcgac ggcacccatc cagatttgga 660
agggcaagtt atcgcaggat acagaccggc atttgatgaa gaactcccag caggaacaga 720
ttcatcctac ggtggttcac atggaacaca cgttgctgga acgattgcgg caaagaaaga 780
tggaaaaggt atcgttggtg ttgcacctgg tgcaaagata atgccgatag ttatattcga 840

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tgacccagca cttgttggtg gaaatggtta cgttggcgac gattatgtcg cagcaggtat 900
aatttgggca acagaccatg gtgcaaaggt aatgaaccac tcttggggtg gctggggtta 960
cagctacaca atgaaagaag catttgatta tgcgatggag catggagttg tcatggttgt 1020
ctcagctggt aacaatacat cagattcaca ccatcaatat ccagcaggtt atcctggtgt 1080
tatccaagtt gctgctcttg actactacgg tggaacattt agagtggcag gtttttcaag 1140
cagaagcgat ggagtctcag ttggcgcacc tggagttacg attctctcga cggttcctgg 1200
cgaagatagt atcggatacg aagggcacaa cgaaaacgtt cctgcaacaa atggcggtac 1260
ttatgattac tatcaaggaa cctcaatggc tgcaccgcat gtaacaggtg ttgttgctgt 1320
attgctacaa aaattcccga acgcaaaacc atggcagata agaaaattac tcgaaaacac 1380
agcattcgat tttaacggaa atggttggga tcacgatacc ggttatggtc tggtaaagct 1440
cgatgcagca ttgcaaggtc ctcttccgac acaaggtgga gtcgaagagt tccaagtagt 1500
tgttacggat gctaaaggaa atttcggagt cccaacggtc tttgtatcaa tgatgagaga 1560
caatggttca tgctattatg cgaaaacagg tcctgatggt atagcaaggt tcccacacat 1620
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ttttaattcg acactgcaag ttaaattcag cactaacctc tcaacactga aagacccaca 1860
atttgtggtt gttgatccgt tactaagagg agtttacggt cgtgtggcat acgcaagaaa 1920
tcaaacatac gatttgtcgt tactctcagg tcaaatttca tttggtatac aaacgctctt 1980
accagcagcg acagatatta caatccaagg aacagtaaca ttgaacggtg aagacatccc 2040
tgtttacgga gttctaaaag ctggaaccac atggactata attgatgact ttggtggatt 2100
gaatttgggc accgactcgc agccaatcta tgtctggtgg acaatcttcg gacagtgata 2160
gtttcatttt aacgtcaaag caaaccgatg gggtgttcag accccatcgg ttttttgttt 2220
tgccttt                                                          2227
```

<210> 300
<211> 381
<212> PRT
<213> Geobacillus stearothermophilus

<220>
<223> Subtilisin J precursor S08.035

<400> 300

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Met Arg Ser Lys Lys Leu Trp Ile Ser Leu Leu Phe Ala Leu Thr Leu
 1               5                  10                  15
Ile Phe Thr Met Ala Phe Ser Asn Met Ser Val Gln Ala Ala Gly Lys
            20                  25                  30
Ser Ser Thr Glu Lys Lys Tyr Ile Val Gly Phe Lys Gln Thr Met Ser
        35                  40                  45
Ala Met Ser Ser Ala Lys Lys Lys Asp Val Ile Ser Glu Lys Gly Gly
    50                  55                  60
Lys Val Gln Lys Gln Phe Lys Tyr Val Asn Ala Ala Ala Ala Thr Leu
65                  70                  75                  80
Asp Glu Lys Ala Val Lys Glu Leu Lys Lys Asp Pro Ser Val Ala Tyr
                85                  90                  95
Val Glu Glu Asp His Ile Ala His Glu Tyr Ala Gln Ser Val Pro Tyr
            100                 105                 110
Gly Ile Ser Gln Ile Lys Ala Pro Ala Leu His Ser Gln Gly Tyr Thr
        115                 120                 125
Gly Ser Asn Val Lys Val Ala Val Ile Asp Ser Gly Ile Asp Ser Ser
    130                 135                 140
His Pro Asp Leu Asn Val Arg Gly Gly Ala Ser Phe Val Pro Ser Glu
145                 150                 155                 160
Thr Asn Pro Tyr Gln Asp Gly Ser Ser His Gly Thr His Val Ala Gly
                165                 170                 175
Thr Ile Ala Ala Leu Asn Asn Ser Ile Gly Val Leu Gly Val Ser Pro
```

```
            180                 185                 190
Ser Ala Ser Leu Tyr Ala Val Lys Val Leu Asp Ser Thr Gly Ser Gly
        195                 200                 205
Gln Tyr Ser Trp Ile Ile Asn Gly Ile Glu Trp Ala Ile Ser Asn Asn
    210                 215                 220
Met Asp Val Ile Asn Met Ser Leu Gly Gly Pro Ser Gly Ser Thr Ala
225                 230                 235                 240
Leu Lys Thr Val Val Asp Lys Ala Val Ser Ser Gly Ile Val Val Ala
                245                 250                 255
Ala Ala Ala Gly Asn Glu Gly Ser Ser Gly Ser Ser Ser Thr Val Gly
            260                 265                 270
Tyr Pro Ala Lys Tyr Pro Ser Thr Ile Ala Val Gly Ala Val Asn Ser
        275                 280                 285
Ser Asn Gln Arg Ala Ser Phe Ser Ser Ala Gly Ser Glu Leu Asp Val
    290                 295                 300
Met Ala Pro Gly Val Ser Ile Gln Ser Thr Leu Pro Gly Gly Thr Tyr
305                 310                 315                 320
Gly Ala Tyr Asn Gly Thr Ser Met Ala Thr Pro His Val Ala Gly Ala
                325                 330                 335
Ala Ala Leu Ile Leu Ser Lys His Pro Thr Trp Thr Asn Ala Gln Val
            340                 345                 350
Arg Asp Arg Leu Glu Ser Thr Ala Thr Tyr Leu Gly Asn Ser Phe Tyr
        355                 360                 365
Tyr Gly Lys Gly Leu Ile Asn Val Gln Ala Ala Ala Gln
    370                 375                 380
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<210> 301
<211> 2494
<212> DNA
<213> Geobacillus stearothermophilus

<220>
<223> Subtilisin J precursor S08.035

<400> 301
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aaacaacggc gcaatggcgg ccgcatctga tgtctttgct tggcgaatgt tcatcttatt 180
tcttcctccc tctcaataat ttttttcattc tatccctttt ctgtaaagtt tatttttcag 240
aatactttta tcatcatgct ttgaaaaaat atcacgataa tatccattgt tctcacggaa 300
gcacacgcag gtcatttgaa cgaatttttt cgacagaaat ttgccgggac tcaggagcat 360
ttaacctaaa aaagcatgac atttcagcat aatgaacatt tactcatgtc tattttcgtt 420
cttttctgta tgaaaatagt tatttcgagt ctctacggaa atagcgagag atgatatacc 480
taaatagaga taaaatcatc tcaaaaaaat gggtctacta aaatattatt ccatctatta 540
caataaattc acagaatagt cttttaagta agtctactct gaatttttttt aaaaggagag 600
ggtaaagagt gagaagcaaa aaattgtgga tcagcttgtt gtttgcgtta acgttaatct 660
ttacgatggc gttcagcaac atgtctgtgc aggctgccgg aaaaagcagt acagaaaaga 720
aatacattgt cggatttaaa cagacaatga gtgccatgag ttccgccaag aaaaaggatg 780
ttatttctga aaaaggcgga aaggttcaaa agcaatttaa gtatgttaac gcggccgcag 840
caacattgga tgaaaaagct gtaaaagaat tgaaaaaaga tccgagcgtt gcatatgtgg 900
aagaagatca tattgcacat gaatatgcgc aatctgttcc ttatggcatt tctcaaatta 960
aagcgccggc tcttcactct caaggctaca caggctctaa cgtaaaagta gctgttatcg 1020
acagcggaat tgactcttct catcctgact taaacgtcag aggcggagca agcttcgtac 1080
cttctgaaac aaacccatac caggacggca gttctcacgg tacgcatgta gccggtacga 1140
ttgccgctct taataactca atcggtgttc tgggcgtcag cccaagcgca tcattatatg 1200

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cagtaaaagt gcttgattca acaggaagcg gccaatatag ctggattatt aacggcattg 1260
aatgggccat ttccaacaat atggatgtta ttaacatgag ccttggcgga ccttctggtt 1320
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caggttctga gcttgatgtg atggctcctg gcgtatccat ccaaagcaca cttcctggag 1560
gcacttacgg tgcttacaac ggcacgtcca tggcgactcc tcacgttgcc ggagcagcag 1620
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cagctgcaca ataatagtaa aaagaagcag gttcctccat acctgcttct ttttatttgt 1800
cagcatcctg atgttccggc gcattctctt ctttctccgt atgttgaatc cgttccatga 1860
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ccgtcacggc caaatcctga aacgttttaa cagcggcttc tctgttctct gtcaactcga 1980
tcccatactg gtcagcctta ttctcctgat aacgcgagac agcattagaa aaaggcgtca 2040
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gcccttctaa atgaaacatg ctgcgggtta ggcgaaccgt ccgcttgtaa agcttatcaa 2160
tgacataaaa tccggcgagc gacacgagca aataaccagc cagaccgatg taaacgtgct 2220
tcatgacata atggcccatt tcgtggccca taataaacag gatttctgaa tcgtcaagtt 2280
tgttcagcgt cgtatcccac aatacaatcc gtttattggc cccaattcct gtaacatagg 2340
cattcagcgc atttgttttt tctgacatgt tcacttcata tacatggtca gccggaatat 2400
tggcttcatc tgccagctct aaaatttttgc tttcaagctc tttgtttttc agcggataaa 2460
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```

<210> 302
<211> 381
<212> PRT
<213> Bacillus subtilis

<220>
<223> Subtilisin E precursor S08.036

<400> 302

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 1               5                  10                  15
Ile Phe Thr Met Ala Phe Ser Asn Met Ser Val Gln Ala Ala Gly Lys
            20                  25                  30
Ser Ser Thr Glu Lys Lys Tyr Ile Val Gly Phe Lys Gln Thr Met Ser
        35                  40                  45
Ala Met Ser Ser Ala Lys Lys Lys Asp Val Ile Ser Glu Lys Gly Gly
    50                  55                  60
Lys Val Gln Lys Gln Phe Lys Tyr Val Asn Ala Ala Ala Ala Thr Leu
65                  70                  75                  80
Asp Glu Lys Ala Val Lys Glu Leu Lys Lys Asp Pro Ser Val Ala Tyr
                85                  90                  95
Val Glu Glu Asp His Ile Ala His Glu Tyr Ala Gln Ser Val Pro Tyr
            100                 105                 110
Gly Ile Ser Gln Ile Lys Ala Pro Ala Leu His Ser Gln Gly Tyr Thr
        115                 120                 125
Gly Ser Asn Val Lys Val Ala Val Ile Asp Ser Gly Ile Asp Ser Ser
    130                 135                 140
His Pro Asp Leu Asn Val Arg Gly Gly Ala Ser Phe Val Pro Ser Glu
145                 150                 155                 160
Thr Asn Pro Tyr Gln Asp Gly Ser Ser His Gly Thr His Val Ala Gly
                165                 170                 175
Thr Ile Ala Ala Leu Asn Asn Ser Ile Gly Val Leu Gly Val Ser Pro
            180                 185                 190
Ser Ala Ser Leu Tyr Ala Val Lys Val Leu Asp Ser Thr Gly Ser Gly
```

```
        195                 200                 205
Gln Tyr Ser Trp Ile Ile Asn Gly Ile Glu Trp Ala Ile Ser Asn Asn
    210                 215                 220
Met Asp Val Ile Asn Met Ser Leu Gly Gly Pro Thr Gly Ser Thr Ala
225                 230                 235                 240
Leu Lys Thr Val Val Asp Lys Ala Val Ser Ser Gly Ile Val Val Ala
                245                 250                 255
Ala Ala Ala Gly Asn Glu Gly Ser Ser Gly Ser Thr Ser Thr Val Gly
            260                 265                 270
Tyr Pro Ala Lys Tyr Pro Ser Thr Ile Ala Val Gly Ala Val Asn Ser
        275                 280                 285
Ser Asn Gln Arg Ala Ser Phe Ser Ser Ala Gly Ser Glu Leu Asp Val
    290                 295                 300
Met Ala Pro Gly Val Ser Ile Gln Ser Thr Leu Pro Gly Gly Thr Tyr
305                 310                 315                 320
Gly Ala Tyr Asn Gly Thr Ser Met Ala Thr Pro His Val Ala Gly Ala
                325                 330                 335
Ala Ala Leu Ile Leu Ser Lys His Pro Thr Trp Thr Asn Ala Gln Val
            340                 345                 350
Arg Asp Arg Leu Glu Ser Thr Ala Thr Tyr Leu Gly Asn Ser Phe Tyr
        355                 360                 365
Tyr Gly Lys Gly Leu Ile Asn Val Gln Ala Ala Ala Gln
    370                 375                 380
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<210> 303
<211> 1500
<212> DNA
<213> Bacillus subtilis

<220>
<223> Subtilisin E precursor S08.036

<400> 303

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aaggagaggg taaagagtga gaagcaaaaa attgtggatc agcttgttgt ttgcgttaac 180
gttaatcttt acgatggcgt tcagcaacat gtctgcgcag gctgccggaa aaagcagtac 240
agaaaagaaa tacattgtcg gatttaaaca gacaatgagt gccatgagtt ccgccaagaa 300
aaaggatgtt atttctgaaa aaggcggaaa ggttcaaaag caatttaagt atgttaacgc 360
ggccgcagca acattggatg aaaaagctgt aaaagaattg aaaaaagatc cgagcgttgc 420
atatgtggaa gaagatcata ttgcacatga atatgcgcaa tctgttcctt atggcatttc 480
tcaaattaaa gcgccggctc ttcactctca aggctacaca ggctctaacg taaaagtagc 540
tgttatcgac agcggaattg actcttctca tcctgactta aacgtcagag gcggagcaag 600
cttcgtacct tctgaaacaa acccatacca ggacggcagt tctcacggta cgcatgtagc 660
cggtacgatt gccgctctta ataactcaat cggtgttctg ggcgttagcc caagcgcatc 720
attatatgca gtaaaagtgc ttgattcaac aggaagcggc caatatagct ggattattaa 780
cggcattgag tgggccattt ccaacaatat ggatgttatc aacatgagcc ttggcggacc 840
tactggttct acagcgctga aaacagtcgt tgacaaagcc gtttccagcg gtatcgtcgt 900
tgctgccgca gccggaaacg aaggttcatc cggaagcaca agcacagtcg gctaccctgc 960
aaaatatcct tctactattg cagtaggtgc ggtaaacagc agcaaccaaa gagcttcatt 1020
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tttagaaagc actgcaacat atcttggaaa ctctttctac tatggaaaag ggttaatcaa 1260
cgtacaagca gctgcacaat aatagtaaaa agaagcaggt tcctccatac ctgcttcttt 1320
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<210> 304
<211> 274
<212> PRT
<213> Bacillus licheniformis

<220>
<223> Subtilisin DY S08.037

<400> 304
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Gln Ala Gln Gly Tyr Lys Gly Ala Asn Val Lys Val Gly Ile Ile Asp
20 25 30
Thr Gly Ile Ala Ala Ser His Thr Asp Leu Lys Val Val Gly Gly Ala
35 40 45
Ser Phe Val Ser Gly Glu Ser Tyr Asn Thr Asp Gly Asn Gly His Gly
50 55 60
Thr His Val Ala Gly Thr Val Ala Ala Leu Asp Asn Thr Thr Gly Val
65 70 75 80
Leu Gly Val Ala Pro Asn Val Ser Leu Tyr Ala Ile Lys Val Leu Asn
85 90 95
Ser Ser Gly Ser Gly Thr Tyr Ser Ala Ile Val Ser Gly Ile Glu Trp
100 105 110
Ala Thr Gln Asn Gly Leu Asp Val Ile Asn Met Ser Leu Gly Gly Pro
115 120 125
Ser Gly Ser Thr Ala Leu Lys Gln Ala Val Asp Lys Ala Tyr Ala Ser
130 135 140
Gly Ile Val Val Val Ala Ala Ala Gly Asn Ser Gly Ser Ser Gly Ser
145 150 155 160
Gln Asn Thr Ile Gly Tyr Pro Ala Lys Tyr Asp Ser Val Ile Ala Val
165 170 175
Gly Ala Val Asp Ser Asn Lys Asn Arg Ala Ser Phe Ser Ser Val Gly
180 185 190
Ala Glu Leu Glu Val Met Ala Pro Gly Val Ser Val Tyr Ser Thr Tyr
195 200 205
Pro Ser Asn Thr Tyr Thr Ser Leu Asn Gly Thr Ser Met Ala Ser Pro
210 215 220
His Val Ala Gly Ala Ala Ala Leu Ile Leu Ser Lys Tyr Pro Thr Leu
225 230 235 240
Ser Ala Ser Gln Val Arg Asn Arg Leu Ser Ser Thr Ala Thr Asn Leu
245 250 255
Gly Asp Ser Phe Tyr Tyr Gly Lys Gly Leu Ile Asn Val Glu Ala Ala
260 265 270
Ala Gln

<210> 305
<211> 384
<212> PRT
<213> Engyodontium album

<220>
<223> Proteinase K precursor S08.054

<400> 305
Met Arg Leu Ser Val Leu Leu Ser Leu Leu Pro Leu Ala Leu Gly Ala
1 5 10 15
Pro Ala Val Glu Gln Arg Ser Glu Ala Ala Pro Leu Ile Glu Ala Arg
20 25 30
Gly Glu Met Val Ala Asn Lys Tyr Ile Val Lys Phe Lys Glu Gly Ser
35 40 45
Ala Leu Ser Ala Leu Asp Ala Ala Met Glu Lys Ile Ser Gly Lys Pro
50 55 60
Asp His Val Tyr Lys Asn Val Phe Ser Gly Phe Ala Ala Thr Leu Asp
65 70 75 80
Glu Asn Met Val Arg Val Leu Arg Ala His Pro Asp Val Glu Tyr Ile
85 90 95
Glu Gln Asp Ala Val Val Thr Ile Asn Ala Ala Gln Thr Asn Ala Pro
100 105 110
Trp Gly Leu Ala Arg Ile Ser Ser Thr Ser Pro Gly Thr Ser Thr Tyr
115 120 125
Tyr Tyr Asp Glu Ser Ala Gly Gln Gly Ser Cys Val Tyr Val Ile Asp
130 135 140
Thr Gly Ile Glu Ala Ser His Pro Glu Phe Glu Gly Arg Ala Gln Met
145 150 155 160
Val Lys Thr Tyr Tyr Tyr Ser Ser Arg Asp Gly Asn Gly His Gly Thr
165 170 175
His Cys Ala Gly Thr Val Gly Ser Arg Thr Tyr Gly Val Ala Lys Lys
180 185 190
Thr Gln Leu Phe Gly Val Lys Val Leu Asp Asp Asn Gly Ser Gly Gln
195 200 205
Tyr Ser Thr Ile Ile Ala Gly Met Asp Phe Val Ala Ser Asp Lys Asn
210 215 220
Asn Arg Asn Cys Pro Lys Gly Val Val Ala Ser Leu Ser Leu Gly Gly
225 230 235 240
Gly Tyr Ser Ser Ser Val Asn Ser Ala Ala Ala Arg Leu Gln Ser Ser
245 250 255
Gly Val Met Val Ala Val Ala Ala Gly Asn Asn Asn Ala Asp Ala Arg
260 265 270
Asn Tyr Ser Pro Ala Ser Glu Pro Ser Val Cys Thr Val Gly Ala Ser
275 280 285
Asp Arg Tyr Asp Arg Arg Ser Ser Phe Ser Asn Tyr Gly Ser Val Leu
290 295 300
Asp Ile Phe Gly Pro Gly Thr Ser Ile Leu Ser Thr Trp Ile Gly Gly
305 310 315 320
Ser Thr Arg Ser Ile Ser Gly Thr Ser Met Ala Thr Pro His Val Ala
325 330 335
Gly Leu Ala Ala Tyr Leu Met Thr Leu Gly Lys Thr Thr Ala Ala Ser
340 345 350
Ala Cys Arg Tyr Ile Ala Asp Thr Ala Asn Lys Gly Asp Leu Ser Asn
355 360 365
Ile Pro Phe Gly Thr Val Asn Leu Leu Ala Tyr Asn Asn Tyr Gln Ala
370 375 380

<210> 306
<211> 2347

<212> DNA
<213> Engyodontium album

<220>
<223> Proteinase K precursor S08.054

<400> 306
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atcattcccc caaagtggga acgccagtgg cgacaaatct gtatactgtt tcctgctttt 120
tctggtttgt caaggttctc attaccctct tggctttctc ctcttttcgc gacattgtgc 180
ttgtggtgtg cctatgtatg ttgtagtcaa tgctatatgt caatggtttt tgtcaaatgc 240
catggcctag tggctctatg ctggagctgc taattctggg cctttatcga ctcctccgac 300
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tgatccttcg caataacctt cacggctgct cgaatgactt gacgtcacga tgggcctact 420
atccaacttc cagaacagga aagtcgagat agttctacat agaccatgga cgagttcatg 480
agatgttgga ttcaaggata aatagctggc catgtcgccg cttcgataca gtttgtttca 540
tctccatcat cagcatcaat cgcagcaata caaagcatcc tctcaaactc aacaaacttt 600
cttgattaag caccgctttc tcattcatca acaacagcca aaatgcgttt gtctgttctt 660
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aacaacaacg ctgacgcccg caactactcc cctgcttctg agccctcggt ctgcactgtc 1560
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acttaat 2347

<210> 307
<211> 534
<212> PRT
<213> Vibrio alginolyticus

<220>
<223> Alkaline serine exoprotease A precursor S08.050

<400> 307
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His Ser Ser Leu Ala Phe Ser Gln Pro Asn Glu Ile Ala Asp Ser Ala
20 25 30
Glu Leu Gln Gln Ala Pro Asp Thr Leu Pro Ala Thr Leu Met Leu Ala
35 40 45
Pro Asp Asp Ile Ala Ile Ala Asp Arg Tyr Ile Val Val Phe Gln Gln
50 55 60
Pro Gln Met Met Ala Ser Ser Ser Pro Glu Phe Glu Gln Phe Thr Gln
65 70 75 80
Gln Ser Val Asp Arg Met Ser Gly Leu Tyr Ser Ile Gln Val Glu Ser
85 90 95
Val Phe Asp His Ser Ile Ser Gly Phe Val Ala Asn Leu Ser Pro Glu
100 105 110
Gln Leu Lys Asp Leu Arg Ser Asp Pro Arg Val Asp Tyr Ile Glu Gln
115 120 125
Asp Arg Ile Leu Ser Leu Asp Pro Ile Val Ser Ala Asp Ala Asn Gln
130 135 140
Thr Asn Ala Ile Trp Gly Leu Asp Arg Ile Asp Gln Arg Asn Leu Pro
145 150 155 160
Leu Asp Asn Asn Tyr Ser Ala Asn Phe Asp Gly Thr Gly Val Thr Ala
165 170 175
Tyr Val Ile Asp Thr Gly Val Asn Asn Ala His Val Glu Phe Gly Gly
180 185 190
Arg Ser Val Ser Gly Tyr Asp Phe Val Asp Asn Asp Ala Asp Ala Ser
195 200 205
Asp Cys Asn Gly His Gly Thr His Val Ala Gly Thr Ile Gly Gly Ser
210 215 220
Leu Tyr Gly Val Ala Lys Asn Val Asn Leu Val Gly Val Arg Val Leu
225 230 235 240
Ser Cys Ser Gly Ser Gly Ser Thr Ser Gly Val Ile Ala Gly Val Asp
245 250 255
Trp Val Ala Ala Asn Ala Ser Gly Pro Ser Val Ala Asn Met Ser Leu
260 265 270
Gly Gly Gly Gln Ser Val Ala Leu Asp Ser Ala Val Gln Ser Ala Val
275 280 285
Gln Ser Gly Val Ser Phe Met Leu Ala Ala Gly Asn Ser Asn Ala Asp
290 295 300
Ala Cys Asn Tyr Ser Pro Ala Arg Val Ala Thr Gly Val Thr Val Gly
305 310 315 320
Ser Thr Thr Ser Thr Asp Ala Arg Ser Ser Phe Ser Asn Trp Gly Ser
325 330 335
Cys Val Asp Val Phe Ala Pro Gly Ser Gln Ile Lys Ser Ala Trp Tyr
340 345 350
Asp Gly Gly Tyr Lys Thr Ile Ser Gly Thr Ser Met Ala Thr Pro His
355 360 365
Val Ala Gly Val Ala Ala Leu Tyr Leu Gln Glu Asn Ser Ser Val Ser
370 375 380
Pro Ser Gln Val Glu Ala Leu Ile Val Ser Arg Ala Ser Thr Gly Lys
385 390 395 400
Val Thr Asp Thr Arg Gly Ser Val Asn Lys Leu Leu Tyr Ser Leu Thr
405 410 415
Asp Ala Asp Cys Gly Gln Asp Cys Gly Gly Pro Asp Pro Thr Pro Asp
420 425 430
Pro Glu Gly Lys Leu Thr Ser Gly Val Pro Val Ser Gly Leu Ser Gly

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        435                 440                 445
Ser Ser Gly Gln Val Ala Tyr Tyr Tyr Val Asp Val Glu Ala Gly Gln
    450                 455                 460
Arg Leu Thr Val Gln Met Tyr Gly Gly Ser Gly Asp Ala Asp Leu Tyr
465                 470                 475                 480
Leu Arg Phe Gly Ala Lys Pro Thr Leu Asn Ala Trp Asp Cys Arg Pro
                485                 490                 495
Phe Lys Tyr Gly Asn Asn Glu Thr Cys Thr Val Ser Ala Thr Gln Ser
            500                 505                 510
Gly Arg Tyr His Val Met Ile Gln Gly Tyr Ser Asn Tyr Ser Gly Val
        515                 520                 525
Ser Ile Gln Ala Asn Tyr
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<210> 308
<211> 1856
<212> DNA
<213> Vibrio alginolyticus

<220>
<223> Alkaline serine exoprotease A precursor S08.050

<400> 308
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agttgttgta tcacctccgc gctctgtttt cattcttctc tcgcttttc gcaacccaat 180
gagattgcgg acagtgcaga gttacaacaa gctcccgaca cattgcctgc cactttgatg 240
cttgcaccgg acgacatcgc cattgcagat cgatatatag tggtatttca acaaccgcaa 300
atgatggcga gcagctcacc ggaattcgag caattcacgc aacagtctgt agaccgcatg 360
tccggtttat attcgataca agtggagtcg gtttttgacc actcgatcag tggatttgtc 420
gctaacttga gtcctgagca actaaaagat ctgcgttctg atcctcgtgt ggactacatt 480
gagcaagaca gaatcctatc gcttgaccca atagtctcgg cagacgcaaa tcaaaccaat 540
gccatttggg gactagatcg aatcgaccaa cgtaacttgc cactcgataa caactacagt 600
gccaactttg atgggactgg tgtaacggct tatgttatcg atactggtgt gaacaatgca 660
catgttgagt ttggtgggcg ctcggtttct gggtatgact ttgtcgataa tgatgcagat 720
gcaagtgact gtaatggaca cggcacacac gtggcgggca ccattggcgg cagcttgtat 780
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atcaaatctg cgtggtatga cggtggttac aaaaccatta gtggtacatc gatggcgacg 1200
ccacatgtag cgggtgtagc agcactgtat cttcaagaaa acagttccgt gtcgccaagc 1260
caagtagagg ccttgatcgt gagccgcgca agtaccggaa aggtgacgga cacaagaggc 1320
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ccagatccaa caccggaccc agaaggcaag ttaacctcgg gcgtgccagt gagcggttta 1440
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gtcagcgcga cacaaagtgg acgctaccac gtcatgattc aaggttactc aaactatagc 1680
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<210> 309
<211> 461
<212> PRT
<213> Staphylococcus epidermidis

<220>
<223> Epidermin leader peptide-processing serine protease epiP precursor S08.060

<400> 309
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20 25 30
Ser Tyr Tyr Ser Val Glu Tyr Asp Asn Ala Lys Thr Phe Lys Glu Ser
35 40 45
Ile Lys Gln Lys Asn Ile Glu Leu Thr Tyr Lys Ile Pro Glu Leu His
50 55 60
Thr Ala Gln Ile Lys Thr Ser Lys Ser Lys Leu Asn Ser Leu Ile Lys
65 70 75 80
Ser Asn Lys Asn Val Lys Phe Val Asn Pro Thr Cys Ser Thr Cys Val
85 90 95
Val Glu Lys Ser Val Lys Thr Gly Lys Asn Leu Asn Asn Lys Lys Asn
100 105 110
Gly Ser His Asp Leu Phe Asp Arg Gln Trp Asp Met Arg Lys Ile Thr
115 120 125
Asn Glu Gly Lys Ser Tyr Lys Leu Ser Pro Asp Arg Lys Lys Ala Lys
130 135 140
Val Ala Leu Val Asp Ser Gly Val Asn Ser Ser His Thr Asp Leu Lys
145 150 155 160
Ser Ile Asn Lys Ile Val Asn Glu Val Pro Lys Asn Gly Phe Arg Gly
165 170 175
Ser Glu Asn Asp Glu Ser Gly Asn Lys Asn Phe Glu Glu Asp Lys Leu
180 185 190
Asn His Gly Thr Leu Val Ala Gly Gln Ile Gly Ala Asn Gly Asn Leu
195 200 205
Lys Gly Val Asn Pro Gly Val Glu Met Asn Val Tyr Arg Val Phe Gly
210 215 220
Ser Lys Lys Ser Glu Met Leu Trp Val Ser Lys Gly Ile Ile Asp Ala
225 230 235 240
Ala Asn Asp Asp Asn Asp Val Ile Asn Val Ser Leu Gly Asn Tyr Leu
245 250 255
Ile Lys Asp Asn Gln Asn Lys Lys Lys Leu Arg Asp Asp Glu Lys Val
260 265 270
Asp Tyr Asp Ala Leu Gln Lys Ala Ile Asn Tyr Ala Gln Lys Lys Gly
275 280 285
Ser Ile Val Val Ala Ala Val Gly Asn Asp Gly Ile Asn Val Lys Lys
290 295 300
Val Lys Glu Ile Asn Lys Lys Arg Asn Leu Asn Ser Lys Thr Ser Lys
305 310 315 320
Lys Val Tyr Asp Ser Pro Ala Asn Leu Asn Asn Val Met Thr Val Gly
325 330 335
Ser Ile Asp Asp Asn Asp Tyr Ile Ser Glu Phe Ser Asn Tyr Gly Asn
340 345 350
Asn Phe Ile Asp Leu Met Thr Ile Gly Gly Ser Tyr Lys Leu Leu Asp
355 360 365

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Lys Tyr Gly Lys Asp Ala Trp Leu Glu Lys Gly Tyr Met Gln Lys Gln
    370                 375                 380
Ser Val Leu Ser Thr Ser Ser Asn Gly Arg Tyr Ile Tyr Gln Ser Gly
385                 390                 395                 400
Thr Ser Leu Ala Ala Pro Lys Val Ser Gly Ala Leu Ala Leu Glu Ile
                405                 410                 415
Asp Lys Tyr Gln Leu Lys Asp Gln Pro Glu Thr Ala Ile Glu Leu Phe
            420                 425                 430
Lys Lys Lys Gly Ile Glu Lys Glu Lys Tyr Met Asp Lys Lys His Tyr
        435                 440                 445
Gly Asn Gly Lys Leu Asp Val Tyr Lys Leu Leu Lys Glu
    450                 455                 460
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<210> 310
<211> 8700
<212> DNA
<213> Staphylococcus epidermidis

<220>
<223> Epidermin leader peptide-processing serine protease epiP precursor S08.060

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aataatgtac tttttccaca cccactttca cctataatat tgtagatata acctttatga 180
agatccaaac ttatagaatt tattatttgt ttattgtctt ttgtgaagtt caaatcattt 240
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atatctccgc ttttcatcat attatttcc attaagtaat aacccaaaaa taaaatacca 480
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gataatttag cagtagcttc ttgagattta cttgatactc ttttcattat atttcctata 720
ggtagtatta caattatcaa tataggtaat gtacacacta aatataatgt caaggttttg 780
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ctataatgac aacgacatat aatctttatc aaagtattgg caaaatagac tgggaaaagg 1800
ataataaaaa aaccagaaat gtaaaagaaa gtttattaaa atatctcata agaatgagta 1860
ctagaagtac accatatgga atgctaagcg gtgtagcttt aggggaattt agtgaaaata 1920

ataatattaa aattaaggac tcttcgtttc ataaaaaaga tgtaaaaata gatgggcaat 1980
ggttatataa attagtccat tatttagaaa gcgattacac atattataaa gacagttttg 2040
tcatatggaa tcaacaaaat tatatttata acaatcgttt atatttagat aataattcat 2100
caatcactga aaataaaaga aatgatgtat tatctgtcaa atacaattct atattagtgt 2160
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aatctttcat tatacctaaa aatagaaata agcacttcaa taatcttaaa gattggtttt 3780
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gtaatgacat aagagaatat aaaaatttat tagctaaact taccaatcct aaaaatgact 4320
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gaaaaagcta catatattat agaaaatcaa agtgagtatt gggatcctta tactctatct 4680

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<212> PRT
<213> Cricetulus griseus

<220>
<223> Site-1 protease (Subtilisin/kexin-isozyme 1)
S08.063

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Ser Thr Val Val Glu Tyr Glu Tyr Ile Val Ala Phe Asn Gly Tyr Phe
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Thr Ala Lys Ala Arg Asn Ser Phe Ile Ser Ser Ala Leu Lys Ser Ser
65 70 75 80

Glu Val Asp Asn Trp Arg Ile Ile Pro Arg Asn Asn Pro Ser Ser Asp
85 90 95
Tyr Pro Ser Asp Phe Glu Val Ile Gln Ile Lys Glu Lys Gln Lys Ala
100 105 110
Gly Leu Leu Thr Leu Glu Asp His Pro Asn Ile Lys Arg Val Thr Pro
115 120 125
Gln Arg Lys Val Phe Arg Ser Leu Lys Phe Ala Glu Ser Asp Pro Ile
130 135 140
Val Pro Cys Asn Glu Thr Arg Trp Ser Gln Lys Trp Gln Ser Ser Arg
145 150 155 160
Pro Leu Arg Arg Ala Ser Leu Ser Leu Gly Ser Gly Phe Trp His Ala
165 170 175
Thr Gly Arg His Ser Ser Arg Arg Leu Leu Arg Ala Ile Pro Arg Gln
180 185 190
Val Ala Gln Thr Leu Gln Ala Asp Val Leu Trp Gln Met Gly Tyr Thr
195 200 205
Gly Ala Asn Val Arg Val Ala Val Phe Asp Thr Gly Leu Ser Glu Lys
210 215 220
His Pro His Phe Lys Asn Val Lys Glu Arg Thr Asn Trp Thr Asn Glu
225 230 235 240
Arg Thr Leu Asp Asp Gly Leu Gly His Gly Thr Phe Val Ala Gly Val
245 250 255
Ile Ala Ser Met Arg Glu Cys Gln Gly Phe Ala Pro Asp Ala Glu Leu
260 265 270
His Ile Phe Arg Val Phe Thr Asn Asn Gln Val Ser Tyr Thr Ser Trp
275 280 285
Phe Leu Asp Ala Phe Asn Tyr Ala Ile Leu Lys Lys Ile Asp Val Leu
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Asn Leu Ser Ile Gly Gly Pro Asp Phe Met Asp His Pro Phe Val Asp
305 310 315 320
Lys Val Trp Glu Leu Thr Ala Asn Asn Val Ile Met Val Ser Ala Ile

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Arg Phe Ser Ser Arg Gly Met Thr Thr Trp Glu Leu Pro Gly Gly Tyr
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Gly Arg Val Lys Pro Asp Ile Val Thr Tyr Gly Ala Gly Val Arg Gly
385                 390                 395                 400
Ser Gly Val Lys Gly Gly Cys Arg Ala Leu Ser Gly Thr Ser Val Ala
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Ser Pro Val Val Ala Gly Ala Val Thr Leu Leu Val Ser Thr Val Gln

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Tyr Leu Ala Ile Ser Ile Ser Val Thr Lys Lys Ala Ala Ser Trp Glu
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Gly Ile Ala Gln Gly His Ile Met Ile Thr Val Ala Ser Pro Ala Glu
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Thr Glu Ala Lys Asn Gly Ala Glu His Thr Ser Thr Val Lys Leu Pro
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Trp Asp Gln Tyr His Asn Leu Arg Tyr Pro Pro Gly Tyr Phe Pro Arg
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Asp Asn Leu Arg Met Lys Asn Asp Pro Leu Asp Trp Asn Gly Asp His
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Val His Thr Asn Phe Arg Asp Met Tyr Gln His Leu Arg Ser Met Gly
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Tyr Phe Val Glu Val Leu Gly Ala Pro Phe Thr Cys Phe Asp Ala Thr
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Gln Tyr Gly Thr Leu Leu Met Val Asp Ser Glu Glu Glu Tyr Phe Pro
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Glu Glu Ile Ala Lys Leu Arg Arg Asp Val Asp Asn Gly Leu Ser Leu
705                 710                 715                 720
Val Ile Phe Ser Asp Trp Tyr Asn Thr Ser Val Met Arg Lys Val Lys
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Phe Tyr Asp Glu Asn Thr Arg Gln Trp Trp Met Pro Asp Thr Gly Gly
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Gln Glu Thr Ala Val Val Glu Asn Val Pro Ile Leu Gly Leu Tyr Gln
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His Leu Ser Trp Ala Lys Pro Gln Pro Leu Asn Glu Thr Ala Pro Ser
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Asn Leu Trp Lys His Gln Lys Leu Leu Ser Ile Asp Leu Asp Lys Val
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Val Leu Pro Asn Phe Arg Ser Asn Arg Pro Gln Val Arg Pro Leu Ser
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Pro Gly Glu Ser Gly Ala Trp Asp Ile Pro Gly Gly Ile Met Pro Gly
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Arg Tyr Asn Gln Glu Val Gly Gln Thr Ile Pro Val Phe Ala Phe Leu
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Gly Ala Met Val Ala Leu Ala Phe Phe Val Val Gln Ile Ser Lys Ala
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<213> Cricetulus griseus

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<223> Site-1 protease (Subtilisin/kexin-isozyme 1) S08.063

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<213> Hypocrea lixii

<220>
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Asp Ser His Leu Ala Trp Val Thr Asp Ile His Thr Arg Ser Leu Thr
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Lys Arg Ser Thr Ala Gly Val Glu Lys Thr Tyr Asn Ile His Thr Trp
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Asn Ala Tyr Ala Gly Glu Phe Asp Glu Glu Thr Ile Glu Gln Ile Lys
85 90 95
Ser Asn Pro Asp Val Ala Ser Val Glu Pro Asp Tyr Ile Met His Leu
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Ser Asp Ile Val Glu Asp Lys Arg Ala Leu Thr Thr Gln Ser Gly Ala
115 120 125
Pro Trp Gly Leu Gly Thr Val Ser His Arg Thr Ser Gly Ser Thr Ser
130 135 140
Tyr Ile Tyr Asp Ser Ser Ala Gly Ala Gly Thr Phe Ala Tyr Val Val
145 150 155 160
Asp Ser Gly Ile Asn Thr Ser His Gln Gln Phe Gly Gly Arg Ala Ser
165 170 175
Leu Gly Tyr Asn Ala Ala Gly Gly Gln His Val Asp Thr Leu Gly His
180 185 190
Gly Thr His Val Ser Gly Thr Ile Gly Gly Ser Thr Tyr Gly Val Ala
195 200 205
Lys Gln Ala Ser Leu Ile Ser Val Lys Val Phe Ala Gly Glu Ser Ala
210 215 220
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225 230 235 240
Val Ser Lys Ser Arg Ala Ser Lys Ser Ala Ile Asn Met Ser Leu Gly
245 250 255
Gly Pro Ala Ser Ser Thr Trp Thr Thr Ala Ile Asn Ala Ala Phe Asn
260 265 270
Gln Gly Val Leu Thr Ile Val Ala Ala Gly Asn Gly Asp Ser Leu Gly
275 280 285
Asn Pro Gln Pro Val Ser Gly Thr Ser Pro Ala Asn Val Pro Asn Ala
290 295 300
Ile Thr Val Ala Ala Leu Asp Ile Asn Trp Arg Thr Ala Ser Phe Thr
305 310 315 320
Asn Tyr Gly Ala Gly Val Asp Val Phe Ala Pro Gly Val Asn Ile Leu
325 330 335
Ser Ser Trp Ile Gly Ser Asn Thr Ala Thr Asn Thr Ile Ser Gly Thr

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gtaaccggaa gcctcaacgg cagccccaac gttatcatct tcaacggaaa cagttcttaa 1260
atcgttgatg gagcgaagga tgaagtgaaa tgttcatgga agggcagcac agctgttgct 1320
tggcttgctt agctcattta agaagctaat caccatgatg gagtgcgatg ggtatataag 1380
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atgacagata cctgtgct 1458

<210> 315
<211> 1045
<212> PRT
<213> Serratia marcescens

<220>
<223> Extracellular serine protease precursor S08.094

<400> 315
Met Ile Leu Asn Lys Arg Leu Lys Leu Ala Tyr Cys Val Phe Leu Gly

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 1               5                  10                  15
Cys Tyr Gly Leu Ser Ile His Ser Ser Leu Ala Ala Tyr Gln Asp Pro
            20                  25                  30
Gly Arg Leu Gly Ala Pro Asp Ser Trp Lys Thr Ala Glu Phe Asn Arg
        35                  40                  45
Gln Trp Gly Leu Glu Ala Ile Ser Ala Glu Phe Ala Tyr Ala Arg Gly
    50                  55                  60
Tyr Thr Gly Lys Gly Ile Thr Ile Gly Val Ile Asp Asn Ala Ile Leu
65                  70                  75                  80
Ser His Ser Glu Phe Ser Gly Lys Leu Thr Arg Leu Asp Asn Gly Ser
                85                  90                  95
Tyr Asn Phe Ser Tyr Asp Lys Gln Asp Asn Met Ser Phe Gly Asp His
            100                 105                 110
Gly Thr His Val Ala Gly Ile Ala Ala Ala Lys Arg Asp Gly Ala Gly
        115                 120                 125
Met His Gly Val Ala Phe Asp Ala Asp Ile Ile Gly Thr Lys Leu Asn
    130                 135                 140
Asp Tyr Gly Asn Arg Asn Gly Arg Glu Glu Leu Ile Gln Ser Ala Ala
145                 150                 155                 160
Arg Val Ile Asn Asn Ser Trp Gly Ile Ala Pro Asp Ile Arg Arg Asp
                165                 170                 175
Ala Lys Gly Asp Ile Ile Trp Leu Pro Asn Gly Arg Pro Asp Tyr Val
            180                 185                 190
Ala Phe Val Lys Ser Glu Val Ile Ala Glu Met Met Arg Ser Lys Ser
        195                 200                 205
Ser Val Glu Trp Gly Ser Glu Gln Pro Val Pro Thr Gly Gly His Ser
    210                 215                 220
Ala Met Ser Thr Leu Leu Arg Ala Ala Arg His Gly Lys Leu Ile Val
225                 230                 235                 240
Phe Ser Ala Gly Asn Tyr Asn Asn Tyr Asn Ile Pro Glu Ala Gln Lys
                245                 250                 255
Ser Leu Pro Tyr Ala Phe Pro Asp Val Leu Asn Asn Tyr Leu Ile Val
            260                 265                 270
Thr Asn Leu Ser Asp Glu Asn Gln Leu Ser Val Ser Ser Thr Ser Cys
        275                 280                 285
Gly Gln Thr Ala Ser Tyr Cys Val Ser Ala Pro Gly Ser Asp Ile Tyr
    290                 295                 300
Ser Thr Val Gly Arg Leu Glu Ser Asn Thr Gly Gly Ala Val Asn Arg
305                 310                 315                 320
Glu Ala Tyr Asn Lys Gly Glu Leu Ser Leu Asn Pro Gly Tyr Gly Asn
                325                 330                 335
Lys Ser Gly Thr Ser Met Ala Ala Pro His Val Thr Gly Val Ala Ala
            340                 345                 350
Val Leu Met Gln Arg Phe Pro Tyr Met Ser Ala Asp Gln Ile Ser Ala
        355                 360                 365
Val Ile Lys Thr Thr Ala Thr Asp Leu Gly Val Ala Gly Ile Asp Asn
    370                 375                 380
Leu Phe Gly Trp Gly Arg Val Asn Leu Arg Asp Ala Ile Asn Gly Pro
385                 390                 395                 400
Lys Met Phe Ile Thr Lys Glu Asp Ile Pro Gln Glu Tyr Tyr Val Pro
                405                 410                 415
Gly Ser Tyr Ser Glu Lys Gln Phe Val Val Asn Ile Pro Gly Leu Gly
            420                 425                 430
Asn Ile Val Glu Pro Gly Thr Pro Val Glu Arg Arg Cys Thr Ser Ser
        435                 440                 445
Glu Cys Ser Phe Asp Ser Trp Ser Asn Asp Ile Ser Gly His Gly Gly
    450                 455                 460
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Leu Thr Lys Thr Gly Ala Gly Thr Leu Ala Leu Leu Gly Asn Asn Thr
465                 470                 475                 480
Tyr Arg Gly Asp Thr Trp Val Lys Gln Gly Val Leu Ala Ile Asp Gly
                485                 490                 495
Ser Val Ala Ser Asn Val Tyr Ile Glu Asn Ser Gly Thr Leu Ser Gly
            500                 505                 510
Glu Gly Thr Val Gly Ala Phe Arg Ala Ala Arg Ser Gly Ser Val Ala
        515                 520                 525
Pro Gly Asn Gly Ile Gly Thr Leu His Val Leu His Asp Ala Ile Phe
    530                 535                 540
Asp Arg Gly Ser Gln Tyr Asn Val Glu Val Ala Asp Asn Gly Arg Ser
545                 550                 555                 560
Asp Lys Ile Ala Ala Arg Arg Ala Phe Leu Asn Gly Gly Ser Val Asn
                565                 570                 575
Val Ser Leu Glu Arg Ser Gln Asn Leu Leu Ser Gln Asn Glu Ala Gln
            580                 585                 590
Ser Leu Leu Gly Asn Lys Tyr Thr Ile Leu Thr Thr Thr Asp Gly Val
        595                 600                 605
Thr Gly Arg Phe Glu Asn Ala Asn Pro Ser Tyr Pro Phe Val Lys Val
    610                 615                 620
Ala Leu Asp Tyr Arg Gly Asn Asp Val Gly Leu Gly Ile Thr Arg Thr
625                 630                 635                 640
Asp Ala Ser Phe Asp Ser Leu Ala Ser Thr Glu Asn Glu Lys Ala Val
                645                 650                 655
Ala Arg Ala Val Glu Thr Leu Asn Ala Thr Glu Pro Val Thr Glu Thr
            660                 665                 670
Ala Lys Arg Ser Val Ala Ile Pro Ala Ala Glu Glu Ala Asn Leu Leu
        675                 680                 685
Gln Ser Asp Gly Gly Glu Ala Gln Ala Val Asn Glu Glu Ala Ser Ile
    690                 695                 700
Val Ala Gly His Pro Ile Tyr Glu Ser Phe Leu Gly Phe Thr Ser Ala
705                 710                 715                 720
Arg Glu Leu Gln Gln Ala Thr Arg Gln Leu Ser Gly Gln Ile His Ala
                725                 730                 735
Asp Met Ala Ser Ala Gln Ile Asn Glu Ser Arg Tyr Leu Arg Asp Thr
            740                 745                 750
Ala Thr Glu Arg Leu Arg Gln Ala Glu Gly Arg Arg Thr Ala Thr Asp
        755                 760                 765
Ile Lys Ala Asp Asp Asn Gly Ala Trp Ala Lys Leu Leu Gly Ser Trp
    770                 775                 780
Gly His Ala Ser Gly Asn Asp Asn Ala Thr Gly Tyr Gln Thr Ser Thr
785                 790                 795                 800
Tyr Gly Val Leu Leu Gly Leu Asp Ser Glu Leu Phe Gly Asp Gly Arg
                805                 810                 815
Leu Gly Met Met Thr Gly Tyr Thr Arg Thr Ser Leu Asp Gly Gly Tyr
            820                 825                 830
Gln Ser Asp Ala His Ser Asp Asn Tyr His Leu Gly Leu Tyr Gly Asp
        835                 840                 845
Lys Arg Phe Gly Ala Leu Ala Leu Arg Ala Gly Gly Thr Tyr Thr Trp
    850                 855                 860
His Arg Ile Asp Thr Ser Arg Ser Val Asn Tyr Gly Ala Gln Ser Asp
865                 870                 875                 880
Arg Glu Lys Ala Lys Tyr Asn Ala Arg Thr Gly Gln Leu Phe Ile Glu
                885                 890                 895
Ser Gly Tyr Asp Trp Thr Ser Asp Ala Val Asn Leu Glu Pro Phe Ala
            900                 905                 910
Asn Leu Ala Tyr Thr His Tyr Arg Asn Glu Glu Ile Asn Glu Gln Gly
```

```
        915                 920                 925
Gly Ala Ala Ala Leu Arg Gly Asp Lys Gln Ser Gln Ser Ala Thr Ala
    930                 935                 940
Ser Thr Leu Gly Leu Arg Ala Asp Thr Glu Trp Gln Thr Asp Ser Val
945                 950                 955                 960
Ala Ile Ala Leu Arg Gly Glu Leu Gly Trp Gln His Gln Tyr Gly Lys
                965                 970                 975
Leu Glu Arg Lys Thr Gln Leu Met Phe Lys Arg Thr Asp Ala Ala Phe
            980                 985                 990
Asp Val Asn Ser Val Pro Val Ser Arg Asp Gly Ala Ile Leu Lys Ala
        995                 1000                1005
Gly Val Asp Val Ser Ile Asn Lys Asn Ala Val Leu Ser Leu Gly Tyr
    1010                1015                1020
Gly Gly Gln Leu Ser Ser Asn His Gln Asp Asn Ser Val Asn Ala Gly
1025                1030                1035                1040
Leu Thr Trp Arg Phe
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<210> 316
<211> 3675
<212> DNA
<213> Serratia marcescens

<220>
<223> Extracellular serine protease precursor S08.094

<400> 316

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gcgcccattt gcatctctca gcatgtctgt tcgtgcggcc cgcgccgggt ccgcatgtgt 180
tatccgtcgt ttcacgatca taggaggttt cagcgcggtt aaaacgtaag ttttcttctg 240
ggtataaata aacatggagc gtaaaatgat acttaataaa agattgaagt tagcgtattg 300
cgtttttctg ggttgttatg gcttatccat tcattcttct cttgccgctt atcaggatcc 360
cggtcgattg ggcgcgcctg acagttggaa aaccgcggag tttaatcgcc aatgggggct 420
tgaagctatt tccgccgaat tcgcctatgc cagaggctat accggaaaag gtataaccat 480
cggcgttatc gataacgcta ttctttccca ttctgaattc tccggtaaac tgacgcgcct 540
ggataacggc agttataatt tctcgtatga taaacaagat aatatgtctt tcggcgatca 600
cggcacgcac gtagccggta tcgctgcggc taaaagagat ggcgcaggca tgcacggcgt 660
cgctttcgac gcggatatta tcggcaccaa attgaatgat tacggtaatc gcaacggccg 720
tgaagagctg attcagagcg cggctcgcgt catcaataac agctgggga tcgcgccgga 780
tatccggcga gacgccaaag gcgatatcat ctggttgccg aacggcaggc cggactacgt 840
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caataccggc ggcgccgtga atcgcgaagc ttataataag ggcgagctgt cgcttaatcc 1260
tggttacggc aacaaatccg gcacctcaat ggcggcgccg catgtgaccg gcgtcgccgc 1320
cgtattgatg cagcgcttcc catatatgag cgccgatcaa atatctgcag tcattaaaac 1380
caccgccacc gatttaggcg ttgccggcat tgataattta ttcggctggg ggcgcgtcaa 1440
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aaatatcgtc gaacccggca cgccggttga gcggcgctgc acgtcgagcg aatgcagttt 1620
cgattcgtgg agtaacgaca tcagcgggca cggcggcttg accaaaacgg gcgccggtac 1680
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gctggcgctg ttgggtaata acacctatcg cggtgatacc tgggtgaaac agggcgtgtt 1740
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cgagggcacc gtaggcgcct tcagagcggc tcggagcggc agcgtcgcgc cgggcaacgg 1860
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cggcagtgtg aatgtcagcc tggaacgcag ccaaaacctg ctgtcgcaga atgaggcgca 2040
gagtctgctg ggcaacaagt acaccatcct gaccacgacg gacggcgtta ccggtagatt 2100
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cgtcggcctt ggcatcacgc gcaccgacgc cagctttgac agcctggcca gcactgagaa 2220
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tcggcgctga ggcct                                                  3675
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<210> 317
<211> 1441
<212> PRT
<213> Drosophila melanogaster

<220>
<223> Tripeptidyl-peptidase II (TPP-II)
S08.090

<400> 317

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            20                  25                  30
Ile Ile Ser Leu Ser Arg Pro Tyr Met Ala Tyr Met Gly Thr Glu Arg
        35                  40                  45
Ser Val Val Met Ile Thr Ala Pro Ala Thr Lys Glu Phe Ala Glu Ser
    50                  55                  60
Ser Glu Arg Ser Asn Ser Ser Lys Lys Thr Thr Asn Lys Glu Gln Ser
65                  70                  75                  80
Asp Lys Ser Ala Glu Ser Arg Met Ala Thr Ser Gly Ile Val Glu Ser
                85                  90                  95
```

```
Phe Pro Thr Gly Ala Leu Val Pro Lys Ala Glu Thr Gly Val Leu Asn
            100                 105                 110
Phe Leu Gln Lys Tyr Pro Glu Tyr Asp Gly Arg Asp Val Thr Ile Ala
        115                 120                 125
Ile Phe Asp Ser Gly Val Asp Pro Arg Ala Thr Gly Leu Glu Thr Leu
    130                 135                 140
Cys Asp Gly Lys Thr Val Lys Val Ile Glu Arg Tyr Asp Cys Ser Gly
145                 150                 155                 160
Cys Gly Asp Val Asp Met Lys Lys Lys Val Thr Pro Asp Glu Asn Gly
                165                 170                 175
Asn Ile Lys Gly Leu Ser Gly Asn Ser Leu Lys Leu Ser Pro Glu Leu
            180                 185                 190
Met Ala Leu Asn Thr Asp Pro Glu Lys Ala Val Arg Val Gly Leu Lys
        195                 200                 205
Ser Phe Ser Asp Leu Leu Pro Ser Lys Val Arg Asn Asn Ile Val Ala
    210                 215                 220
Gln Ala Lys Leu Lys His Trp Asp Lys Pro His Lys Thr Ala Thr Ala
225                 230                 235                 240
Asn Ala Ser Arg Lys Ile Val Glu Phe Glu Ser Gln Asn Pro Gly Glu
                245                 250                 255
Ala Ser Lys Leu Pro Trp Asp Lys Lys Ile Leu Lys Glu Asn Leu Asp
            260                 265                 270
Phe Glu Leu Glu Met Leu Asn Ser Tyr Glu Lys Val Tyr Gly Asp Ile
        275                 280                 285
Lys Thr Ser Tyr Asp Cys Ile Leu Phe Pro Thr Ala Asp Gly Trp Leu
    290                 295                 300
Thr Ile Val Asp Thr Thr Glu Gln Gly Asp Leu Asp Gln Ala Leu Arg
305                 310                 315                 320
Ile Gly Glu Tyr Ser Arg Thr His Glu Thr Arg Asn Val Asp Asp Phe
                325                 330                 335
Leu Ser Ile Ser Val Asn Val His Asp Glu Gly Asn Val Leu Glu Val
            340                 345                 350
Val Gly Met Ser Ser Pro His Gly Thr His Val Ser Ser Ile Ala Ser
        355                 360                 365
Gly Asn His Ser Ser Arg Asp Val Asp Gly Val Ala Pro Asn Ala Lys
    370                 375                 380
Ile Val Ser Met Thr Ile Gly Asp Gly Arg Leu Gly Ser Met Glu Thr
385                 390                 395                 400
Gly Thr Ala Leu Val Arg Ala Met Thr Lys Val Met Glu Leu Cys Arg
                405                 410                 415
Asp Gly Arg Arg Ile Asp Val Ile Asn Met Ser Tyr Gly Glu His Ala
            420                 425                 430
Asn Trp Ser Asn Ser Gly Arg Ile Gly Glu Leu Met Asn Glu Val Val
        435                 440                 445
Asn Lys Tyr Gly Val Val Trp Val Ala Ser Ala Gly Asn His Gly Pro
    450                 455                 460
Ala Leu Cys Thr Val Gly Thr Pro Pro Asp Ile Ser Gln Pro Ser Leu
465                 470                 475                 480
Ile Gly Val Gly Ala Tyr Val Ser Pro Gln Met Met Glu Ala Glu Tyr
                485                 490                 495
Ala Met Arg Glu Lys Leu Pro Gly Asn Val Tyr Thr Trp Thr Ser Arg
            500                 505                 510
Asp Pro Cys Ile Asp Gly Gly Gln Gly Val Thr Val Cys Ala Pro Gly
        515                 520                 525
Gly Ala Ile Ala Ser Val Pro Gln Phe Thr Met Ser Lys Ser Gln Leu
    530                 535                 540
Met Asn Gly Thr Ser Met Ala Ala Pro His Val Ala Gly Ala Val Ala
```

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545                 550                 555                 560
Leu Leu Ile Ser Gly Leu Lys Gln Gln Asn Ile Glu Tyr Ser Pro Tyr
                565                 570                 575
Ser Ile Lys Arg Ala Ile Ser Val Thr Ala Thr Lys Leu Gly Tyr Val
            580                 585                 590
Asp Pro Phe Ala Gln Gly His Gly Leu Leu Asn Val Glu Lys Ala Phe
        595                 600                 605
Glu His Leu Thr Glu His Arg Gln Ser Lys Asp Asn Met Leu Arg Phe
    610                 615                 620
Ser Val Arg Val Gly Asn Asn Ala Asp Lys Gly Ile His Leu Arg Gln
625                 630                 635                 640
Gly Val Gln Arg Asn Ser Ile Asp Tyr Asn Val Tyr Ile Glu Pro Ile
                645                 650                 655
Phe Tyr Asn Asp Lys Glu Ala Asp Pro Lys Asp Lys Phe Asn Phe Asn
            660                 665                 670
Val Arg Leu Asn Leu Ile Ala Ser Gln Pro Trp Val Gln Cys Gly Ala
        675                 680                 685
Phe Leu Asp Leu Ser Tyr Gly Thr Arg Ser Ile Ala Val Arg Val Asp
    690                 695                 700
Pro Thr Gly Leu Gln Pro Gly Val His Ser Ala Val Ile Arg Ala Tyr
705                 710                 715                 720
Asp Thr Asp Cys Val Gln Lys Gly Ser Leu Phe Glu Ile Pro Val Thr
                725                 730                 735
Val Val Gln Pro His Val Leu Glu Ser Asp Gln Asn Thr Pro Val Phe
            740                 745                 750
Glu Pro Ala Ser Ser Lys Gly Asp Asn Ser Val Glu Phe Gln Pro Asn
        755                 760                 765
Thr Ile Gln Arg Asp Phe Ile Leu Val Pro Glu Arg Ala Thr Trp Ala
    770                 775                 780
Glu Leu Arg Met Arg Ile Thr Asp Pro Asn Arg Gly Glu Asp Ile Gly
785                 790                 795                 800
Lys Phe Phe Val His Thr Asn Gln Leu Leu Pro Lys Gln Ser Cys Arg
                805                 810                 815
Lys Leu Glu Thr Met Lys Ile Val Ser Val Gly Ser Glu Asn Glu Ser
            820                 825                 830
Ile Met Ala Phe Lys Val Lys Ser Gly Arg Ile Leu Glu Leu Cys Ile
        835                 840                 845
Ala Lys Tyr Trp Ser Asn Tyr Gly Gln Ser His Leu Lys Tyr Ser Leu
    850                 855                 860
Arg Phe Arg Gly Val Glu Ala His Asn Pro Asn Ala Tyr Val Met His
865                 870                 875                 880
Ala Gly Arg Gly Ile His Lys Leu Glu Ile Glu Ala Leu Val Ala Glu
                885                 890                 895
Asp Val Gln Pro Gln Leu Gln Leu Lys Asn Ala Glu Val Val Leu Lys
            900                 905                 910
Pro Thr Glu Ala Lys Ile Ser Pro Leu Ser Ala Thr Arg Asp Val Ile
        915                 920                 925
Pro Asp Gly Arg Gln Val Tyr Gln Asn Leu Leu Ala Phe Asn Leu Asn
    930                 935                 940
Val Ala Lys Ala Ala Asp Val Ser Ile Tyr Ala Pro Ile Phe Asn Asp
945                 950                 955                 960
Leu Leu Tyr Glu Ala Glu Phe Glu Ser Gln Met Trp Met Leu Phe Asp
                965                 970                 975
Ala Asn Lys Ala Leu Val Ala Thr Gly Asp Ala His Ser His Thr Ser
            980                 985                 990
Phe Thr Lys Leu Asp Lys Gly Glu Tyr Thr Ile Arg Leu Gln Val Arg
        995                 1000                1005
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His Glu Lys Arg Asp Leu Leu Glu Lys Ile Ser Glu Ala Asn Leu Val
    1010                1015                1020
Ala Ser Phe Lys Leu Thr Ser Pro Leu Thr Leu Asp Phe Tyr Glu Asn
1025                1030                1035                1040
Tyr Asn Gln Cys Ile Val Gly Gly Arg Lys Tyr Val Ser Ser Pro Leu
                1045                1050                1055
Arg Leu Ser Thr Arg Val Leu Tyr Ile Ala Pro Ile Thr Gln Glu Arg
            1060                1065                1070
Leu Thr Lys Ala Asn Leu Pro Ala Gln Cys Ala Trp Leu Ser Gly Asn
        1075                1080                1085
Leu Val Phe Pro Gln Asp Glu Val Gly Arg Arg Val Ala Gln His Pro
    1090                1095                1100
Phe Thr Tyr Ile Leu Asn Pro Ala Glu Lys Lys Ser His Thr Asn Gly
1105                1110                1115                1120
Ser Ser Asn Gly Ser Ser Ala Ala Gly Ser Thr Ala Thr Ala Ala Ala
                1125                1130                1135
Val Thr Thr Ala Asn Gly Ala Lys Pro Lys Ala Pro Ala Thr Pro Gln
            1140                1145                1150
Ala Ala Thr Ser Val Thr Asn Pro Ala Ala Gly Asp Gly Ile Ser Val
        1155                1160                1165
Gln Asn Asp Pro Pro Val Asp Ser Ser Gly Ser Pro Ala Ser Pro Lys
    1170                1175                1180
Lys Gly Lys Ala Asn Ala Asp Asp Tyr Ala Glu Ser Phe Arg Asp Phe
1185                1190                1195                1200
Gln Cys Ser Gln Ile Val Lys Cys Glu Leu Glu Met Ala Glu Lys Ile
                1205                1210                1215
Tyr Asn Asp Val Val Ala Ala His Pro Lys His Leu Gln Ala Asn Leu
            1220                1225                1230
Leu Leu Ile Gln Asn Ile Glu Ser Asn Gln Leu Lys Ser Gln Leu Pro
        1235                1240                1245
Leu Thr Phe Val Asn Ala Gln Lys Thr Ser Pro Pro Glu Ala Gly Glu
    1250                1255                1260
Ser Ala Asp Lys Gln Lys Glu Asp Gln Lys Lys Val Arg Ser Ala Leu
1265                1270                1275                1280
Glu Arg Ile Val Lys Leu Ala Asp Lys Val Ile Gln Glu Thr Asp Ser
                1285                1290                1295
Glu Ala Leu Leu Ser Tyr Tyr Gly Leu Lys Asn Asp Thr Arg Ala Asp
            1300                1305                1310
Ala Ala Lys Ile Lys Thr Asn Met Asp Lys Gln Lys Asn Thr Leu Ile
        1315                1320                1325
Glu Ala Leu Ser Lys Lys Gly Ile Ala Val Ala Lys Leu Ala Val Leu
    1330                1335                1340
Asp Asp Cys Ile Lys Asp Ser Leu Ala Glu Ile Asn Glu Leu Tyr Thr
1345                1350                1355                1360
Glu Ile Ile Lys Phe Val Asp Ala Asn Asp Ser Lys Ala Ile Gln Phe
                1365                1370                1375
Ala Leu Trp His Ala Tyr Ala His Gly His Tyr Gly Arg Met Tyr Lys
            1380                1385                1390
Tyr Val Val Lys Leu Ile Glu Glu Lys Arg Thr Arg Asp His Phe Val
        1395                1400                1405
Glu Leu Ala Ala Ile Asn Gly Ala Leu Gly His Glu His Ile Arg Thr
    1410                1415                1420
Val Ile Asn Arg Met Met Ile Thr Ala Phe Pro Ser Ser Phe Arg Leu
1425                1430                1435                1440
Phe
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<210> 318
<211> 4309
<212> DNA
<213> Drosophila melanogaster

<220>
<223> Tripeptidyl-peptidase II (TPP-II) S08.090

<400> 318
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agcaggatgg ccaccagcgg tattgtcgag tcatttccca cgggcgcact ggtgcccaag 180
gcggagacgg gagtcctgaa ctttctgcag aagtacccgg agtacgatgg acgcgacgtc 240
accatagcca tcttcgattc cggcgtcgat ccccgggcaa cgggactgga gacgctgtgc 300
gatggaaaga ccgttaaagt aatagagcgg tacgactgtt ccggatgcgg cgacgtggac 360
atgaagaaga aggtgacgcc ggacgagaac ggcaacatta agggcctgtc cggaaactcg 420
ctcaagctga gtccggagct gatggctctg aacacagatc cggagaaggc ggtgcgggta 480
ggcctcaaga gcttcagcga tttgttgccc tccaaggtgc ggaacaacat tgtggcccag 540
gccaagctga agcactggga caagccgcac aagacggcca ctgcaaacgc cagtcgcaag 600
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atattgaaag agaatctaga ctttgagcta gagatgttga atagctacga gaaggtgtac 720
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<210> 319
<211> 806
<212> PRT
<213> Bacillus subtilis

<220>
<223> Minor extracellular protease vpr precursor
S08.114

<400> 319

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            20                  25                  30
Ser Lys Thr Ser Ala Asp Leu Glu Lys Ala Glu Val Phe Gly Asp Ile
        35                  40                  45
Asp Met Thr Thr Ser Lys Lys Thr Thr Val Ile Val Glu Leu Lys Glu
    50                  55                  60
Lys Ser Leu Ala Glu Ala Lys Glu Ala Gly Glu Ser Gln Ser Lys Ser
65                  70                  75                  80
Lys Leu Lys Thr Ala Arg Thr Lys Ala Lys Asn Lys Ala Ile Lys Ala
                85                  90                  95
Val Lys Asn Gly Lys Val Asn Arg Glu Tyr Glu Gln Val Phe Ser Gly
            100                 105                 110
Phe Ser Met Lys Leu Pro Ala Asn Glu Ile Pro Lys Leu Leu Ala Val
        115                 120                 125
Lys Asp Val Lys Ala Val Tyr Pro Asn Val Thr Tyr Lys Thr Asp Asn
    130                 135                 140
Met Lys Asp Lys Asp Val Thr Ile Ser Glu Asp Ala Val Ser Pro Gln
```

```
145                 150                 155                 160
Met Asp Asp Ser Ala Pro Tyr Ile Gly Ala Asn Asp Ala Trp Asp Leu
                165                 170                 175
Gly Tyr Thr Gly Lys Gly Ile Lys Val Ala Ile Ile Asp Thr Gly Val
            180                 185                 190
Glu Tyr Asn His Pro Asp Leu Lys Lys Asn Phe Gly Gln Tyr Lys Gly
        195                 200                 205
Tyr Asp Phe Val Asp Asn Asp Tyr Asp Pro Lys Glu Thr Pro Thr Gly
    210                 215                 220
Asp Pro Arg Gly Glu Ala Thr Asp His Gly Thr His Val Ala Gly Thr
225                 230                 235                 240
Val Ala Ala Asn Gly Thr Ile Lys Gly Val Ala Pro Asp Ala Thr Leu
                245                 250                 255
Leu Ala Tyr Arg Val Leu Gly Pro Gly Gly Ser Gly Thr Thr Glu Asn
            260                 265                 270
Val Ile Ala Gly Val Glu Arg Ala Val Gln Asp Gly Ala Asp Val Met
        275                 280                 285
Asn Leu Ser Leu Gly Asn Ser Leu Asn Asn Pro Asp Trp Ala Thr Ser
    290                 295                 300
Thr Ala Leu Asp Trp Ala Met Ser Glu Gly Val Val Ala Val Thr Ser
305                 310                 315                 320
Asn Gly Asn Ser Gly Pro Asn Gly Trp Thr Val Gly Ser Pro Gly Thr
                325                 330                 335
Ser Arg Glu Ala Ile Ser Val Gly Ala Thr Gln Leu Pro Leu Asn Glu
            340                 345                 350
Tyr Ala Val Thr Phe Gly Ser Tyr Ser Ser Ala Lys Val Met Gly Tyr
        355                 360                 365
Asn Lys Glu Asp Asp Val Lys Ala Leu Asn Asn Lys Glu Val Glu Leu
    370                 375                 380
Val Glu Ala Gly Ile Gly Glu Ala Lys Asp Phe Glu Gly Lys Asp Leu
385                 390                 395                 400
Thr Gly Lys Val Ala Val Val Lys Arg Gly Ser Ile Ala Phe Val Asp
                405                 410                 415
Lys Ala Asp Asn Ala Lys Lys Ala Gly Ala Ile Gly Met Val Val Tyr
            420                 425                 430
Asn Asn Leu Ser Gly Glu Ile Glu Ala Asn Val Pro Gly Met Ser Val
        435                 440                 445
Pro Thr Ile Lys Leu Ser Leu Glu Asp Gly Glu Lys Leu Val Ser Ala
    450                 455                 460
Leu Lys Ala Gly Glu Thr Lys Thr Thr Phe Lys Leu Thr Val Ser Lys
465                 470                 475                 480
Ala Leu Gly Glu Gln Val Ala Asp Phe Ser Ser Arg Gly Pro Val Met
                485                 490                 495
Asp Thr Trp Met Ile Lys Pro Asp Ile Ser Ala Pro Gly Val Asn Ile
            500                 505                 510
Val Ser Thr Ile Pro Thr His Asp Pro Asp His Pro Tyr Gly Tyr Gly
        515                 520                 525
Ser Lys Gln Gly Thr Ser Met Ala Ser Pro His Ile Ala Gly Ala Val
    530                 535                 540
Ala Val Ile Lys Gln Ala Lys Pro Lys Trp Ser Val Glu Gln Ile Lys
545                 550                 555                 560
Ala Ala Ile Met Asn Thr Ala Val Thr Leu Lys Asp Ser Asp Gly Glu
                565                 570                 575
Val Tyr Pro His Asn Ala Gln Gly Ala Gly Ser Ala Arg Ile Met Asn
            580                 585                 590
Ala Ile Lys Ala Asp Ser Leu Val Ser Pro Gly Ser Tyr Ser Tyr Gly
        595                 600                 605
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Thr Phe Leu Lys Glu Asn Gly Asn Glu Thr Lys Asn Glu Thr Phe Thr
    610                 615                 620
Ile Glu Asn Gln Ser Ser Ile Arg Lys Ser Tyr Thr Leu Glu Tyr Ser
625                 630                 635                 640
Phe Asn Gly Ser Gly Ile Ser Thr Ser Gly Thr Ser Arg Val Val Ile
                645                 650                 655
Pro Ala His Gln Thr Gly Lys Ala Thr Ala Lys Val Lys Val Asn Thr
            660                 665                 670
Lys Lys Thr Lys Ala Gly Thr Tyr Glu Gly Thr Val Ile Val Arg Glu
        675                 680                 685
Gly Gly Lys Thr Val Ala Lys Val Pro Thr Leu Leu Ile Val Lys Glu
    690                 695                 700
Pro Asp Tyr Pro Arg Val Thr Ser Val Ser Val Ser Glu Gly Ser Val
705                 710                 715                 720
Gln Gly Thr Tyr Gln Ile Glu Thr Tyr Leu Pro Ala Gly Ala Glu Glu
                725                 730                 735
Leu Ala Phe Leu Val Tyr Asp Ser Asn Leu Asp Phe Ala Gly Gln Ala
            740                 745                 750
Gly Ile Tyr Lys Asn Gln Asp Lys Gly Tyr Gln Tyr Phe Asp Trp Asp
        755                 760                 765
Gly Thr Ile Asn Gly Gly Thr Lys Leu Pro Ala Gly Glu Tyr Tyr Leu
    770                 775                 780
Leu Ala Tyr Ala Ala Asn Lys Gly Lys Ser Ser Gln Val Leu Thr Glu
785                 790                 795                 800
Glu Pro Phe Thr Val Glu
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<210> 320
<211> 2931
<212> DNA
<213> Bacillus subtilis

<220>
<223> Minor extracellular protease vpr precursor S08.114

<400> 320
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acacaaacaa aatccaataa atggtccaaa tgacacaagg atttttttga attttcaaga 180
aatatatact agatctttca catttttttct aaatacaaag ggggaaacac attgaaaaag 240
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acgggcgttc aggcagctcc ggcttcttca aaaacgtcgg ctgatctgga aaaagccgag 360
gtattcggtg atatcgatat gacgacaagc aaaaaaacaa ccgttatagt ggaattaaaa 420
gaaaaatcct tggcagaagc gaaggaagcg ggagaaagcc aatcgaaaag caagctgaaa 480
accgctcgca ccaaagcaaa aaacaaagca atcaaagcag tgaaaaacgg aaaagtaaac 540
cgggaatatg agcaggtatt ctcaggcttc tctatgaagc ttccagctaa tgagattcca 600
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aatatgaagg ataaagacgt cacaatctcc gaagacgccg tatctccgca aatggatgac 720
agtgcgcctt atatcggagc aaacgatgca tgggatttag gctacacagg aaaaggcatc 780
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ccaggcatgt ctgtcccaac gattaagctt tcattagaag acggcgaaaa actcgtcagc 1620
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gttctttcgt accaacaatc attcgatttc gattatcagc aattcgtctc tgttcataag 2880
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<210> 321
<211> 1902
<212> PRT
<213> Lactococcus lactis subsp. cremoris

<220>
<223> PIII-type proteinase precursor (Lactocepin)
S08.116

<400> 321

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Ala Ala Ile Ser Gln Gln Thr Lys Gly Ser Ser Leu Ala Asn Thr Val
        35                  40                  45
Thr Ala Ala Thr Ala Lys Gln Ala Ala Thr Asp Thr Thr Ala Ala Thr
    50                  55                  60
Thr Asn Gln Ala Ile Ala Thr Gln Leu Ala Ala Lys Gly Ile Asp Tyr
65                  70                  75                  80
Asn Lys Leu Asn Lys Val Gln Gln Gln Asp Ile Tyr Val Asp Val Ile
                85                  90                  95
Val Gln Met Ser Ala Ala Pro Ala Ser Glu Asn Gly Ile Leu Arg Thr
            100                 105                 110
Asp Tyr Ser Ser Thr Ala Glu Ile Gln Gln Glu Thr Asn Lys Val Ile
        115                 120                 125
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Ala Ala Gln Ala Ser Val Lys Ala Ala Val Glu Gln Val Thr Gln Gln
    130                 135                 140
Thr Ala Gly Glu Ser Tyr Gly Tyr Val Val Asn Gly Phe Ser Thr Lys
145                 150                 155                 160
Val Arg Val Val Asp Ile Pro Lys Leu Lys Gln Ile Ala Gly Val Lys
                165                 170                 175
Thr Val Thr Leu Ala Lys Val Tyr Tyr Pro Thr Asp Ala Lys Ala Asn
            180                 185                 190
Ser Met Ala Asn Val Gln Ala Val Trp Ser Asn Tyr Lys Tyr Lys Gly
        195                 200                 205
Glu Gly Thr Val Val Ser Val Ile Asp Ser Gly Ile Asp Pro Thr His
    210                 215                 220
Lys Asp Met Arg Leu Ser Asp Asp Lys Asp Val Lys Leu Thr Lys Ser
225                 230                 235                 240
Asp Val Glu Lys Phe Thr Asp Thr Val Lys His Gly Arg Tyr Phe Asn
                245                 250                 255
Ser Lys Val Pro Tyr Gly Phe Asn Tyr Ala Asp Asn Asn Asp Thr Ile
            260                 265                 270
Thr Asp Asp Lys Val Asp Glu Gln His Gly Met His Val Ala Gly Ile
        275                 280                 285
Ile Gly Ala Asn Gly Thr Gly Asp Asp Pro Ala Lys Ser Val Val Gly
    290                 295                 300
Val Ala Pro Glu Ala Gln Leu Leu Ala Met Lys Val Phe Ser Asn Ser
305                 310                 315                 320
Asp Thr Ser Ala Lys Thr Gly Ser Ala Thr Val Val Ser Ala Ile Glu
                325                 330                 335
Asp Ser Ala Lys Ile Gly Ala Asp Val Leu Asn Met Ser Leu Gly Ser
            340                 345                 350
Asn Ser Gly Asn Gln Thr Leu Glu Asp Pro Glu Leu Ala Ala Val Gln
        355                 360                 365
Asn Ala Asn Glu Ser Gly Thr Ala Ala Val Ile Ser Ala Gly Asn Ser
    370                 375                 380
Gly Thr Ser Gly Ser Ala Thr Glu Gly Val Asn Lys Asp Tyr Tyr Gly
385                 390                 395                 400
Leu Gln Asp Asn Glu Met Val Gly Ser Pro Gly Thr Ser Arg Gly Ala
                405                 410                 415
Thr Thr Val Ala Ser Ala Glu Asn Thr Asp Val Ile Thr Gln Ala Val
            420                 425                 430
Thr Ile Thr Asp Gly Thr Gly Leu Gln Leu Gly Pro Glu Thr Ile Gln
        435                 440                 445
Leu Ser Ser His Asp Phe Thr Gly Ser Phe Asp Gln Lys Lys Phe Tyr
    450                 455                 460
Ile Val Lys Asp Ala Ser Gly Asn Leu Ser Lys Gly Ala Leu Ala Asp
465                 470                 475                 480
Tyr Thr Ala Asp Ala Lys Gly Lys Ile Ala Ile Val Lys Arg Gly Glu
                485                 490                 495
Phe Ser Phe Asp Asp Lys Gln Lys Tyr Ala Gln Ala Ala Gly Ala Ala
            500                 505                 510
Gly Leu Ile Ile Val Asn Thr Asp Gly Thr Ala Thr Pro Met Thr Ser
        515                 520                 525
Ile Ala Leu Thr Thr Thr Phe Pro Thr Phe Gly Leu Ser Ser Val Thr
    530                 535                 540
Gly Gln Lys Leu Val Asp Trp Val Thr Ala His Pro Asp Asp Ser Leu
545                 550                 555                 560
Gly Val Lys Ile Thr Leu Ala Met Leu Pro Asn Gln Lys Tyr Thr Glu
                565                 570                 575
Asp Lys Met Ser Asp Phe Thr Ser Tyr Gly Pro Val Ser Asn Leu Ser
```

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            580                 585                 590
Phe Lys Pro Asp Ile Thr Ala Pro Gly Gly Asn Ile Trp Ser Thr Gln
        595                 600                 605
Asn Asn Asn Gly Tyr Thr Asn Met Ser Gly Thr Ser Met Ala Ser Pro
    610                 615                 620
Phe Ile Ala Gly Ser Gln Ala Leu Leu Lys Gln Ala Leu Asn Asn Lys
625                 630                 635                 640
Asn Asn Pro Phe Tyr Ala Tyr Tyr Lys Gln Leu Lys Gly Thr Ala Leu
                645                 650                 655
Thr Asp Phe Leu Lys Thr Val Glu Met Asn Thr Ala Gln Pro Ile Asn
            660                 665                 670
Asp Ile Asn Tyr Asn Asn Val Ile Val Ser Pro Arg Arg Gln Gly Ala
        675                 680                 685
Gly Leu Val Asp Val Lys Ala Ala Ile Asp Ala Leu Glu Lys Asn Pro
    690                 695                 700
Ser Thr Val Val Ala Glu Asn Gly Tyr Pro Ala Val Glu Leu Lys Asp
705                 710                 715                 720
Phe Thr Ser Thr Asp Lys Thr Phe Lys Leu Thr Phe Thr Asn Arg Thr
                725                 730                 735
Thr His Glu Leu Thr Tyr Gln Met Asp Ser Asn Thr Asp Thr Asn Ala
            740                 745                 750
Val Tyr Thr Ser Ala Thr Asp Pro Asn Ser Gly Val Leu Tyr Asp Lys
        755                 760                 765
Lys Ile Asp Gly Ala Ala Ile Lys Ala Gly Ser Asn Ile Thr Val Pro
    770                 775                 780
Ala Gly Lys Thr Ala Gln Ile Glu Phe Thr Leu Ser Leu Pro Lys Ser
785                 790                 795                 800
Phe Asp Gln Gln Gln Phe Val Glu Gly Phe Leu Asn Phe Lys Gly Ser
                805                 810                 815
Asp Gly Ser Arg Leu Asn Leu Pro Tyr Met Gly Phe Phe Gly Asp Trp
            820                 825                 830
Asn Asp Gly Lys Ile Val Asp Ser Leu Asn Gly Ile Thr Tyr Ser Pro
        835                 840                 845
Ala Gly Gly Asn Phe Gly Thr Val Pro Leu Leu Lys Asn Lys Asn Thr
    850                 855                 860
Gly Thr Gln Tyr Tyr Gly Gly Met Val Thr Asp Ala Asp Gly Asn Lys
865                 870                 875                 880
Thr Val Asp Asp Gln Ala Ile Ala Phe Ser Ser Asp Lys Asn Ala Leu
                885                 890                 895
Tyr Asn Asp Ile Ser Met Lys Tyr Tyr Leu Leu Arg Asn Ile Ser Asn
            900                 905                 910
Val Gln Val Asp Ile Leu Asp Gly Gln Gly Asn Lys Val Thr Thr Leu
        915                 920                 925
Ser Ser Ser Thr Asn Arg Lys Lys Thr Tyr Tyr Asn Ala His Ser Gln
    930                 935                 940
Gln Tyr Ile Tyr Tyr Asn Ala Pro Ala Trp Asp Gly Thr Tyr Tyr Asp
945                 950                 955                 960
Gln Arg Asp Gly Asn Ile Lys Thr Ala Asp Asp Gly Ser Tyr Thr Tyr
                965                 970                 975
Arg Ile Ser Gly Val Pro Glu Gly Gly Asp Lys Arg Gln Val Phe Asp
            980                 985                 990
Val Pro Phe Lys Leu Asp Ser Lys Ala Pro Thr Val Arg His Val Ala
        995                 1000                1005
Leu Ser Ala Lys Thr Glu Asn Gly Lys Thr Gln Tyr Tyr Leu Thr Ala
    1010                1015                1020
Glu Ala Lys Asp Asp Leu Ser Gly Leu Asp Ala Thr Lys Ser Val Lys
1025                1030                1035                1040
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```
Thr Glu Ile Asn Glu Val Thr Asn Leu Asp Ala Thr Phe Thr Asp Ala
                1045                1050                1055
Gly Thr Thr Ala Asp Gly Tyr Thr Lys Ile Glu Thr Pro Leu Ser Asp
            1060                1065                1070
Glu Gln Ala Gln Ala Leu Gly Asn Gly Asp Asn Ser Ala Glu Leu Tyr
        1075                1080                1085
Leu Thr Asp Asn Ala Ser Asn Ala Thr Asp Gln Asp Ala Ser Val Gln
    1090                1095                1100
Lys Pro Gly Ser Thr Ser Phe Asp Leu Ile Val Asn Gly Gly Gly Ile
1105                1110                1115                1120
Pro Asp Lys Ile Ser Ser Thr Thr Thr Gly Tyr Glu Ala Asn Thr Gln
                1125                1130                1135
Gly Gly Gly Thr Tyr Thr Phe Ser Gly Thr Tyr Pro Ala Ala Val Asp
            1140                1145                1150
Gly Thr Tyr Thr Asp Ala Gln Gly Lys Lys His Asp Leu Asn Thr Thr
        1155                1160                1165
Tyr Asp Ala Ala Thr Asn Ser Phe Thr Ala Ser Met Pro Val Thr Asn
    1170                1175                1180
Ala Asp Tyr Ala Ala Gln Val Asp Leu Tyr Ala Asp Lys Ala His Thr
1185                1190                1195                1200
Gln Leu Leu Lys His Phe Asp Thr Lys Val Arg Leu Met Ala Pro Thr
                1205                1210                1215
Phe Thr Asp Leu Lys Phe Asn Asn Gly Ser Asp Gln Thr Ser Glu Ala
            1220                1225                1230
Thr Ile Lys Val Thr Gly Thr Val Ser Ala Asp Thr Lys Thr Val Asn
        1235                1240                1245
Val Gly His Thr Val Ala Ala Leu Asp Ala Gln His His Phe Ser Val
    1250                1255                1260
Asp Val Pro Val Asn Tyr Gly Asp Asn Thr Ile Lys Val Thr Ala Thr
1265                1270                1275                1280
Asp Lys Asp Gly Asn Thr Thr Thr Glu Gln Lys Thr Ile Thr Ser Ser
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(Furin-1) S08.048

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    50                  55                  60
Asp Glu Gln Gln Thr Ile Ile Glu Cys Asp Ile Gly Asn Phe Asn Phe
65                  70                  75                  80
Asp Cys Asn Leu Phe Lys Thr Ser Phe Leu Thr Gln His Lys Gln Lys
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Val His Thr Trp Gly Glu Ser Pro Gln Gly Asn Trp Gln Leu Glu Ile
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Leu Asn Glu Thr Phe Cys Tyr Ala Tyr Val Val Arg Ser Thr Gly Met
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Ala Ser Val Val Asp Ile Ser Lys Met Asp Asp Arg Asp Thr Gln Gln
995 1000 1005
Tyr Met Thr Gly Thr Thr Val Leu Leu Leu Val Ser Val Ile Phe Thr

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    1010                1015                1020
Leu Met Gly Val Ala Val Ala Gly Gly Ile Val Tyr His Arg Arg Ala
1025                1030                1035                1040
Met Ala Arg Ser Asn Glu Leu Tyr Ser Arg Val Ser Leu Val Pro Gly
                1045                1050                1055
Asp Glu Ser Asp Ser Asp Glu Asp Glu Leu Phe Thr Ala His Phe Pro
            1060                1065                1070
Ala Arg Lys Ser Gly Val Asn Ile Tyr Arg Asp Glu Ala Pro Ser Glu
        1075                1080                1085
Lys Ile Phe Glu Glu Asp Glu Ile Ser His Leu Val Pro
    1090                1095                1100
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<210> 324
<211> 3781
<212> DNA
<213> Drosophila melanogaster

<220>
<223> Furin-like protease 1, isoform 1-CRR precursor
(Furin-1) S08.048

<400> 324

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gtggcaactg cggcatcatc ggcaggcggc tcatcgccgg cagctccatc atctgcgccc 720
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aacaaccaca tcgtcggaca ctatacccac acctgggcgg tgcacatacc aaacggcgat 960
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catgtgccct ggtactcgga gaagtgcagc tccacgctgg ccaccaccta cagcagcggc 1920
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ccggagcagc agcggtgcga gattaacgct ccccatgtcg acaaggtcat tccacctcgt 2280
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<210> 325
<211> 814
<212> PRT
<213> Saccharomyces cerevisiae

<220>
<223> Kexin precursor (KEX2 protease) S08.048

<400> 325

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Thr Ser Ala Leu Val Ser Ser Gln Gln Ile Pro Leu Lys Asp His Thr
            20                  25                  30
Ser Arg Gln Tyr Phe Ala Val Glu Ser Asn Glu Thr Leu Ser Arg Leu
        35                  40                  45
Glu Glu Met His Pro Asn Trp Lys Tyr Glu His Asp Val Arg Gly Leu
    50                  55                  60
Pro Asn His Tyr Val Phe Ser Lys Glu Leu Leu Lys Leu Gly Lys Arg
65                  70                  75                  80
Ser Ser Leu Glu Glu Leu Gln Gly Asp Asn Asn Asp His Ile Leu Ser
                85                  90                  95
Val His Asp Leu Phe Pro Arg Asn Asp Leu Phe Lys Arg Leu Pro Val
            100                 105                 110
Pro Ala Pro Pro Met Asp Ser Ser Leu Leu Pro Val Lys Glu Ala Glu
        115                 120                 125
```

```
Asp Lys Leu Ser Ile Asn Asp Pro Leu Phe Glu Arg Gln Trp His Leu
    130                 135                 140
Val Asn Pro Ser Phe Pro Gly Ser Asp Ile Asn Val Leu Asp Leu Trp
145                 150                 155                 160
Tyr Asn Asn Ile Thr Gly Ala Gly Val Val Ala Ala Ile Val Asp Asp
                165                 170                 175
Gly Leu Asp Tyr Glu Asn Glu Asp Leu Lys Asp Asn Phe Cys Ala Glu
            180                 185                 190
Gly Ser Trp Asp Phe Asn Asp Asn Thr Asn Leu Pro Lys Pro Arg Leu
        195                 200                 205
Ser Asp Asp Tyr His Gly Thr Arg Cys Ala Gly Glu Ile Ala Ala Lys
    210                 215                 220
Lys Gly Asn Asn Phe Cys Gly Val Gly Val Gly Tyr Asn Ala Lys Ile
225                 230                 235                 240
Ser Gly Ile Arg Ile Leu Ser Gly Asp Ile Thr Thr Glu Asp Glu Ala
                245                 250                 255
Ala Ser Leu Ile Tyr Gly Leu Asp Val Asn Asp Ile Tyr Ser Cys Ser
            260                 265                 270
Trp Gly Pro Ala Asp Asp Gly Arg His Leu Gln Gly Pro Ser Asp Leu
        275                 280                 285
Val Lys Lys Ala Leu Val Lys Gly Val Thr Glu Gly Arg Asp Ser Lys
    290                 295                 300
Gly Ala Ile Tyr Val Phe Ala Ser Gly Asn Gly Gly Thr Arg Gly Asp
305                 310                 315                 320
Asn Cys Asn Tyr Asp Gly Tyr Thr Asn Ser Ile Tyr Ser Ile Thr Ile
                325                 330                 335
Gly Ala Ile Asp His Lys Asp Leu His Pro Pro Tyr Ser Glu Gly Cys
            340                 345                 350
Ser Ala Val Met Ala Val Thr Tyr Ser Ser Gly Ser Gly Glu Tyr Ile
        355                 360                 365
His Ser Ser Asp Ile Asn Gly Arg Cys Ser Asn Ser His Gly Gly Thr
    370                 375                 380
Ser Ala Ala Ala Pro Leu Ala Ala Gly Val Tyr Thr Leu Leu Leu Glu
385                 390                 395                 400
Ala Asn Pro Asn Leu Thr Trp Arg Asp Val Gln Tyr Leu Ser Ile Leu
                405                 410                 415
Ser Ala Val Gly Leu Glu Lys Asn Ala Asp Gly Asp Trp Arg Asp Ser
            420                 425                 430
Ala Met Gly Lys Lys Tyr Ser His Arg Tyr Gly Phe Gly Lys Ile Asp
        435                 440                 445
Ala His Lys Leu Ile Glu Met Ser Lys Thr Trp Glu Asn Val Asn Ala
    450                 455                 460
Gln Thr Trp Phe Tyr Leu Pro Thr Leu Tyr Val Ser Gln Ser Thr Asn
465                 470                 475                 480
Ser Thr Glu Glu Thr Leu Glu Ser Val Ile Thr Ile Ser Glu Lys Ser
                485                 490                 495
Leu Gln Asp Ala Asn Phe Lys Arg Ile Glu His Val Thr Val Thr Val
            500                 505                 510
Asp Ile Asp Thr Glu Ile Arg Gly Thr Thr Thr Val Asp Leu Ile Ser
        515                 520                 525
Pro Ala Gly Ile Ile Ser Asn Leu Gly Val Val Arg Pro Arg Asp Val
    530                 535                 540
Ser Ser Glu Gly Phe Lys Asp Trp Thr Phe Met Ser Val Ala His Trp
545                 550                 555                 560
Gly Glu Asn Gly Val Gly Asp Trp Lys Ile Lys Val Lys Thr Thr Glu
                565                 570                 575
Asn Gly His Arg Ile Asp Phe His Ser Trp Arg Leu Lys Leu Phe Gly
```

```
            580                 585                 590
Glu Ser Ile Asp Ser Ser Lys Thr Glu Thr Phe Val Phe Gly Asn Asp
        595                 600                 605
Lys Glu Glu Val Glu Pro Ala Ala Thr Glu Ser Thr Val Ser Gln Tyr
    610                 615                 620
Ser Ala Ser Ser Thr Ser Ile Ser Ile Ser Ala Thr Ser Thr Ser Ser
625                 630                 635                 640
Ile Ser Ile Gly Val Glu Thr Ser Ala Ile Pro Gln Thr Thr Thr Ala
                645                 650                 655
Ser Thr Asp Pro Asp Ser Asp Pro Asn Thr Pro Lys Lys Leu Ser Ser
            660                 665                 670
Pro Arg Gln Ala Met His Tyr Phe Leu Thr Ile Phe Leu Ile Gly Ala
        675                 680                 685
Thr Phe Leu Val Leu Tyr Phe Met Phe Phe Met Lys Ser Arg Arg Arg
    690                 695                 700
Ile Arg Arg Ser Arg Ala Glu Thr Tyr Glu Phe Asp Ile Ile Asp Thr
705                 710                 715                 720
Asp Ser Glu Tyr Asp Ser Thr Leu Asp Asn Gly Thr Ser Gly Ile Thr
                725                 730                 735
Glu Pro Glu Glu Val Glu Asp Phe Asp Phe Asp Leu Ser Asp Glu Asp
            740                 745                 750
His Leu Ala Ser Leu Ser Ser Ser Glu Asn Gly Asp Ala Glu His Thr
        755                 760                 765
Ile Asp Ser Val Leu Thr Asn Glu Asn Pro Phe Ser Asp Pro Ile Lys
    770                 775                 780
Gln Lys Phe Pro Asn Asp Ala Asn Ala Glu Ser Ala Ser Asn Lys Leu
785                 790                 795                 800
Gln Glu Leu Gln Pro Asp Val Pro Pro Ser Ser Gly Arg Ser
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<210> 326
<211> 2848
<212> DNA
<213> Saccharomyces cerevisiae

<220>
<223> Kexin precursor (KEX2 protease) S08.048

<400> 326
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ttgttttttg gcctcgtcac ataattataa actactaacc cattatcaga tgaaagtgag 180
gaaatatatt actttatgct tttggtgggc cttttcaaca tccgctcttg tatcatcaca 240
acaaattcca ttgaaggacc atacgtcacg acagtatttt gctgtagaaa gcaatgaaac 300
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accaaaccat tatgtttttt caaaagagtt gctaaaattg ggcaaaagat catcattaga 420
agagttacag ggggataaca acgaccacat attatctgtc catgatttat tcccgcgtaa 480
cgacctattt aagagactac cggtgcctgc tccaccaatg gactcaagct tgttaccggt 540
aaaagaagct gaggataaac tcagcataaa tgatccgctt tttgagaggc agtggcactt 600
ggtcaatcca agttttcctg gcagtgatat aaatgttctt gatctgtggt acaataatat 660
tacaggcgca ggggtcgtgg ctgccattgt tgatgatggc cttgactacg aaaatgaaga 720
cttgaaggat aatttttgcg ctgaaggttc ttgggatttc aacgacaata ccaatttacc 780
taaaccaaga ttatctgatg actaccatgg tacgagatgt gcaggtgaaa tagctgccaa 840
aaaaggtaac aatttttgcg gtgtcggggt aggttacaac gctaaaatct caggcataag 900
aatcttatcc ggtgatatca ctacggaaga tgaagctgcg tccttgattt atggtctaga 960
```

```
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ccctagtgac ctggtgaaaa aggctttagt aaaaggtgtt actgagggaa gagattccaa 1080
aggagcgatt tacgtttttg ccagtggaaa tggtggaact cgtggtgata attgcaatta 1140
cgacggctat actaattcca tatattctat tactattggg gctattgatc acaaagatct 1200
acatcctcct tattccgaag gttgttccgc cgtcatggca gtcacgtatt cttcaggttc 1260
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cgctgacgga gattggagag atagcgccat ggggaagaaa tactctcatc gctatggctt 1500
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<210> 327
<211> 794
<212> PRT
<213> Homo sapiens

<220>
<223> Furin precursor S08.071

<400> 327

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            20                  25                  30
Thr Trp Ala Val Arg Ile Pro Gly Gly Pro Ala Val Ala Asn Ser Val
        35                  40                  45
Ala Arg Lys His Gly Phe Leu Asn Leu Gly Gln Ile Phe Gly Asp Tyr
    50                  55                  60
Tyr His Phe Trp His Arg Gly Val Thr Lys Arg Ser Leu Ser Pro His
65                  70                  75                  80
Arg Pro Arg His Ser Arg Leu Gln Arg Glu Pro Gln Val Gln Trp Leu
                85                  90                  95
Glu Gln Gln Val Ala Lys Arg Arg Thr Lys Arg Asp Val Tyr Gln Glu
            100                 105                 110
Pro Thr Asp Pro Lys Phe Pro Gln Gln Trp Tyr Leu Ser Gly Val Thr
```

```
        115                 120                 125
Gln Arg Asp Leu Asn Val Lys Ala Ala Trp Ala Gln Gly Tyr Thr Gly
    130                 135                 140
His Gly Ile Val Val Ser Ile Leu Asp Asp Gly Ile Glu Lys Asn His
145                 150                 155                 160
Pro Asp Leu Ala Gly Asn Tyr Asp Pro Gly Ala Ser Phe Asp Val Asn
                165                 170                 175
Asp Gln Asp Pro Asp Pro Gln Pro Arg Tyr Thr Gln Met Asn Asp Asn
            180                 185                 190
Arg His Gly Thr Arg Cys Ala Gly Glu Val Ala Ala Val Ala Asn Asn
        195                 200                 205
Gly Val Cys Gly Val Gly Val Ala Tyr Asn Ala Arg Ile Gly Gly Val
    210                 215                 220
Arg Met Leu Asp Gly Glu Val Thr Asp Ala Val Glu Ala Arg Ser Leu
225                 230                 235                 240
Gly Leu Asn Pro Asn His Ile His Ile Tyr Ser Ala Ser Trp Gly Pro
                245                 250                 255
Glu Asp Asp Gly Lys Thr Val Asp Gly Pro Ala Arg Leu Ala Glu Glu
            260                 265                 270
Ala Phe Phe Arg Gly Val Ser Gln Gly Arg Gly Gly Leu Gly Ser Ile
        275                 280                 285
Phe Val Trp Ala Ser Gly Asn Gly Gly Arg Glu His Asp Ser Cys Asn
    290                 295                 300
Cys Asp Gly Tyr Thr Asn Ser Ile Tyr Thr Leu Ser Ile Ser Ser Ala
305                 310                 315                 320
Thr Gln Phe Gly Asn Val Pro Trp Tyr Ser Glu Ala Cys Ser Ser Thr
                325                 330                 335
Leu Ala Thr Thr Tyr Ser Ser Gly Asn Gln Asn Glu Lys Gln Ile Val
            340                 345                 350
Thr Thr Asp Leu Arg Gln Lys Cys Thr Glu Ser His Thr Gly Thr Ser
        355                 360                 365
Ala Ser Ala Pro Leu Ala Ala Gly Ile Ile Ala Leu Thr Leu Glu Ala
    370                 375                 380
Asn Lys Asn Leu Thr Trp Arg Asp Met Gln His Leu Val Val Gln Thr
385                 390                 395                 400
Ser Lys Pro Ala His Leu Asn Ala Asn Asp Trp Ala Thr Asn Gly Val
                405                 410                 415
Gly Arg Lys Val Ser His Ser Tyr Gly Tyr Gly Leu Leu Asp Ala Gly
            420                 425                 430
Ala Met Val Ala Leu Ala Gln Asn Trp Thr Thr Val Ala Pro Gln Arg
        435                 440                 445
Lys Cys Ile Ile Asp Ile Leu Thr Glu Pro Lys Asp Ile Gly Lys Arg
    450                 455                 460
Leu Glu Val Arg Lys Thr Val Thr Ala Cys Leu Gly Glu Pro Asn His
465                 470                 475                 480
Ile Thr Arg Leu Glu His Ala Gln Ala Arg Leu Thr Leu Ser Tyr Asn
                485                 490                 495
Arg Arg Gly Asp Leu Ala Ile His Leu Val Ser Pro Met Gly Thr Arg
            500                 505                 510
Ser Thr Leu Leu Ala Ala Arg Pro His Asp Tyr Ser Ala Asp Gly Phe
        515                 520                 525
Asn Asp Trp Ala Phe Met Thr Thr His Ser Trp Asp Glu Asp Pro Ser
    530                 535                 540
Gly Glu Trp Val Leu Glu Ile Glu Asn Thr Ser Glu Ala Asn Asn Tyr
545                 550                 555                 560
Gly Thr Leu Thr Lys Phe Thr Leu Val Leu Tyr Gly Thr Ala Pro Glu
                565                 570                 575
```

```
Gly Leu Pro Val Pro Pro Glu Ser Ser Gly Cys Lys Thr Leu Thr Ser
            580                 585                 590
Ser Gln Ala Cys Val Val Cys Glu Glu Gly Phe Ser Leu His Gln Lys
        595                 600                 605
Ser Cys Val Gln His Cys Pro Pro Gly Phe Ala Pro Gln Val Leu Asp
    610                 615                 620
Thr His Tyr Ser Thr Glu Asn Asp Val Glu Thr Ile Arg Ala Ser Val
625                 630                 635                 640
Cys Ala Pro Cys His Ala Ser Cys Ala Thr Cys Gln Gly Pro Ala Leu
                645                 650                 655
Thr Asp Cys Leu Ser Cys Pro Ser His Ala Ser Leu Asp Pro Val Glu
            660                 665                 670
Gln Thr Cys Ser Arg Gln Ser Gln Ser Ser Arg Glu Ser Pro Pro Gln
        675                 680                 685
Gln Gln Pro Pro Arg Leu Pro Pro Glu Val Glu Ala Gly Gln Arg Leu
    690                 695                 700
Arg Ala Gly Leu Leu Pro Ser His Leu Pro Glu Val Val Ala Gly Leu
705                 710                 715                 720
Ser Cys Ala Phe Ile Val Leu Val Phe Val Thr Val Phe Leu Val Leu
                725                 730                 735
Gln Leu Arg Ser Gly Phe Ser Phe Arg Gly Val Lys Val Tyr Thr Met
            740                 745                 750
Asp Arg Gly Leu Ile Ser Tyr Lys Gly Leu Pro Pro Glu Ala Trp Gln
        755                 760                 765
Glu Glu Cys Pro Ser Asp Ser Glu Glu Asp Glu Gly Arg Gly Glu Arg
    770                 775                 780
Thr Ala Phe Ile Lys Asp Gln Ser Ala Leu
785                 790
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<210> 328
<211> 4180
<212> DNA
<213> Homo sapiens

<220>
<223> Furin precursor S08.071

<400> 328

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<210> 329
<211> 969
<212> PRT

<213> Homo sapiens

<220>
<223> Subtilisin/kexin-like protease PACE4 S08.075

<400> 329

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Ala Gly Gly Ala Gly Gly Pro Gly Phe Arg Pro Leu Ala Pro Arg Pro
        35                  40                  45
Trp Arg Trp Leu Leu Leu Leu Ala Leu Pro Ala Ala Cys Ser Ala Pro
    50                  55                  60
Pro Pro Arg Pro Val Tyr Thr Asn His Trp Ala Val Gln Val Leu Gly
65                  70                  75                  80
Gly Pro Ala Glu Ala Asp Arg Val Ala Ala Ala His Gly Tyr Leu Asn
                85                  90                  95
Leu Gly Gln Ile Gly Asn Leu Glu Asp Tyr Tyr His Phe Tyr His Ser
            100                 105                 110
Lys Thr Phe Lys Arg Ser Thr Leu Ser Ser Arg Gly Pro His Thr Phe
        115                 120                 125
Leu Arg Met Asp Pro Gln Val Lys Trp Leu Gln Gln Gln Glu Val Lys
    130                 135                 140
Arg Arg Val Lys Arg Gln Val Arg Ser Asp Pro Gln Ala Leu Tyr Phe
145                 150                 155                 160
Asn Asp Pro Ile Trp Ser Asn Met Trp Tyr Leu His Cys Gly Asp Lys
                165                 170                 175
Asn Ser Arg Cys Arg Ser Glu Met Asn Val Gln Ala Ala Trp Lys Arg
            180                 185                 190
Gly Tyr Thr Gly Lys Asn Val Val Val Thr Ile Leu Asp Asp Gly Ile
        195                 200                 205
Glu Arg Asn His Pro Asp Leu Ala Pro Asn Tyr Asp Ser Tyr Ala Ser
    210                 215                 220
Tyr Asp Val Asn Gly Asn Asp Tyr Asp Pro Ser Pro Arg Tyr Asp Ala
225                 230                 235                 240
Ser Asn Glu Asn Lys His Gly Thr Arg Cys Ala Gly Glu Val Ala Ala
                245                 250                 255
Ser Ala Asn Asn Ser Tyr Cys Ile Val Gly Ile Ala Tyr Asn Ala Lys
            260                 265                 270
Ile Gly Gly Ile Arg Met Leu Asp Gly Asp Val Thr Asp Val Val Glu
        275                 280                 285
Ala Lys Ser Leu Gly Ile Arg Pro Asn Tyr Ile Asp Ile Tyr Ser Ala
    290                 295                 300
Ser Trp Gly Pro Asp Asp Asp Gly Lys Thr Val Asp Gly Pro Gly Arg
305                 310                 315                 320
Leu Ala Lys Gln Ala Phe Glu Tyr Gly Ile Lys Lys Gly Arg Gln Gly
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Leu Gly Ser Ile Phe Val Trp Ala Ser Gly Asn Gly Gly Arg Glu Gly
            340                 345                 350
Asp Tyr Cys Ser Cys Asp Gly Tyr Thr Asn Ser Ile Tyr Thr Ile Ser
        355                 360                 365
Val Ser Ser Ala Thr Glu Asn Gly Tyr Lys Pro Trp Tyr Leu Glu Glu
    370                 375                 380
Cys Ala Ser Thr Leu Ala Thr Thr Tyr Ser Ser Gly Ala Phe Tyr Glu
385                 390                 395                 400
Arg Lys Ile Val Thr Thr Asp Leu Arg Gln Arg Cys Thr Asp Gly His
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                405                 410                 415
Thr Gly Thr Ser Val Ser Ala Pro Met Val Ala Gly Ile Ile Ala Leu
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Leu Val Lys Thr Ser Arg Pro Ala His Leu Lys Ala Ser Asp Trp Lys
    450                 455                 460
Val Asn Gly Ala Gly His Lys Val Ser His Phe Tyr Gly Phe Gly Leu
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Val Asp Ala Glu Ala Leu Val Val Glu Ala Lys Lys Trp Thr Ala Val
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Pro Ser Gln His Met Cys Val Ala Ala Ser Asp Lys Arg Pro Arg Ser
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Arg Thr Ser Ile Ser His Pro Arg Arg Gly Asp Leu Gln Ile Tyr Leu
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Val Ser Pro Ser Gly Thr Lys Ser Gln Leu Leu Ala Lys Arg Leu Leu
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Cys Trp Gly Glu Lys Ala Glu Gly Gln Trp Thr Leu Glu Ile Gln Asp
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Leu Pro Ser Gln Val Arg Asn Pro Glu Lys Gln Gly Lys Leu Lys Glu
    610                 615                 620
Trp Ser Leu Ile Leu Tyr Gly Thr Ala Glu His Pro Tyr His Thr Phe
625                 630                 635                 640
Ser Ala His Gln Ser Arg Ser Arg Met Leu Glu Leu Ser Ala Pro Glu
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Leu Glu Pro Pro Lys Ala Ala Leu Ser Pro Ser Gln Val Glu Val Pro
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Glu Asp Glu Glu Asp Tyr Thr Ala Gln Ser Thr Pro Gly Ser Ala Asn
        675                 680                 685
Ile Leu Gln Thr Ser Val Cys His Pro Glu Cys Gly Asp Lys Gly Cys
    690                 695                 700
Asp Gly Pro Asn Ala Asp Gln Cys Leu Asn Cys Val His Phe Ser Leu
705                 710                 715                 720
Gly Ser Val Lys Thr Ser Arg Lys Cys Val Ser Val Cys Pro Leu Gly
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Tyr Phe Gly Asp Thr Ala Ala Arg Arg Cys Arg Arg Cys His Lys Gly
            740                 745                 750
Cys Glu Thr Cys Ser Ser Arg Ala Ala Thr Gln Cys Leu Ser Cys Arg
        755                 760                 765
Arg Gly Phe Tyr His His Gln Glu Met Asn Thr Cys Val Thr Leu Cys
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Pro Ala Gly Phe Tyr Ala Asp Glu Ser Gln Lys Asn Cys Leu Lys Cys
785                 790                 795                 800
His Pro Ser Cys Lys Lys Cys Val Asp Glu Pro Glu Lys Cys Thr Val
                805                 810                 815
Cys Lys Glu Gly Phe Ser Leu Ala Arg Gly Ser Cys Ile Pro Asp Cys
            820                 825                 830
Glu Pro Gly Thr Tyr Phe Asp Ser Glu Leu Ile Arg Cys Gly Glu Cys
        835                 840                 845
His His Thr Cys Gly Thr Cys Val Gly Pro Gly Arg Glu Glu Cys Ile
    850                 855                 860
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His Cys Ala Lys Asn Phe His Phe His Asp Trp Lys Cys Val Pro Ala
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Cys Gly Glu Gly Phe Tyr Pro Glu Glu Met Pro Gly Leu Pro His Lys
                885                 890                 895
Val Cys Arg Arg Cys Asp Glu Asn Cys Leu Ser Cys Ala Gly Ser Ser
            900                 905                 910
Arg Asn Cys Ser Arg Cys Lys Thr Gly Phe Thr Gln Leu Gly Thr Ser
        915                 920                 925
Cys Ile Thr Asn His Thr Cys Ser Asn Ala Asp Glu Thr Phe Cys Glu
    930                 935                 940
Met Val Lys Ser Asn Arg Leu Cys Glu Arg Lys Leu Phe Ile Gln Phe
945                 950                 955                 960
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<210> 330
<211> 4403
<212> DNA
<213> Homo sapiens

<220>
<223> Subtilisin/kexin-like protease PACE4 S08.075

<400> 330

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<210> 331
<211> 662
<212> PRT
<213> Anabaena variabilis

<220>
<223> Calcium-dependent protease precursor (Trypsin)
S08.79

<400> 331
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Leu Ile Ser Asp Arg Pro Phe Glu Ala Ala Pro Val Ser Pro Gln Ala
        35                  40                  45
Arg Asn Ile Leu Asn Gln Phe Glu Leu Ser Thr Arg Phe Ser Gln Ala
    50                  55                  60
Gly Val Glu Val Leu His Val Lys Glu Pro Ser His Asp Gly Ala Leu
65                  70                  75                  80
Arg Asp Thr Ala Arg Glu Ile Leu Asn Gln Glu Pro Glu Val Gln Phe
                85                  90                  95
Ala Gly Arg Val Leu Ile Asp Pro Val Ser Gln Gln Pro Ile Val Tyr
            100                 105                 110
Thr Glu Asn Leu Phe Val Lys Phe Asp His Glu Glu Asp Val Ser Phe
        115                 120                 125
Cys Gln Glu Ile Leu Gly Arg Tyr Gly Leu Thr Ile Lys Arg Gln Leu
    130                 135                 140
Glu Tyr Ala Arg Asn Ala Tyr Phe Val Ser Ala Pro Ser Asn Thr Gly
145                 150                 155                 160
Leu Ala Ile Phe Asp Ile Ser Glu Arg Leu Leu Asn Glu Glu Ser Val
                165                 170                 175
Glu Leu Cys His Pro Glu Leu Val Arg Glu Phe Arg Gln Arg Gln Ala
            180                 185                 190
Phe Pro Pro Gln Trp His Leu Lys Gln Thr Thr Ile Gly Gly Lys Thr
        195                 200                 205
Ile Asn Ala His Ala Asn Val Glu Ala Ala Trp Lys Leu Ser Asp Gly
    210                 215                 220
Thr Gly Thr Ile Ile Ala Ile Ile Asp Asp Gly Val Asp Ile Asp His
225                 230                 235                 240
Glu Glu Phe Arg Ser Ser Gly Lys Ile Val Ala Pro Arg Asp Val Thr
                245                 250                 255
Arg Lys Thr Asn Phe Pro Thr Pro Gly Asn Arg Asp Asn His Gly Thr
            260                 265                 270
Ala Cys Ala Gly Val Ala Cys Gly Asn Gly Asn Phe Gly Ala Ser Gly
        275                 280                 285
Val Ala Pro Gly Ala Lys Leu Met Pro Ile Arg Phe Val Ser Ala Leu
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Gly Ser Gln Asp Glu Ala Asp Ser Phe Val Trp Ala Ala Gln Asn Gly
305                 310                 315                 320
Ala Asp Val Ile Ser Cys Ser Trp Gly Pro Pro Asp Gly Thr Trp Trp
                325                 330                 335
Asp Asp Lys Asp Pro Leu His Lys Gln Lys Val Pro Leu Pro Asp Ser
            340                 345                 350
Thr Arg Leu Ala Met Asp Tyr Ala Ile Asn Lys Gly Arg Asn Gly Lys
        355                 360                 365
Gly Cys Val Ile Leu Phe Ala Ala Gly Asn Gly Asn Glu Ser Val Asp
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Asn Asp Gly Tyr Ala Ser Tyr Glu Lys Val Ile Ala Val Ala Ala Cys
385                 390                 395                 400
Asn Asp Phe Gly Thr Arg Ser Ala Tyr Ser Asp Phe Gly Thr Ala Val
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Trp Cys Ala Phe Pro Ser Asn Asn Gly Asn Pro Ser Gln Thr Pro Gly
            420                 425                 430
Ile Trp Thr Ala Asp Arg Thr Gly Val Val Gly Tyr Asn Ser Gly Asn
        435                 440                 445
Thr Asn Leu Gly Asp Gln Ala Gly Asn Tyr Thr Asn Ser Phe Gly Gly
    450                 455                 460
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                485                 490                 495
Arg Ser Cys Asp Arg Ile Asp Pro Val Gly Gly Asn Tyr Asn Ala Glu
            500                 505                 510
Gly Arg Ser Pro Phe Tyr Gly Tyr Gly Arg Ile Asn Ala Leu Lys Ala
        515                 520                 525
Val Glu Leu Ala Leu Pro Ala Gln Pro Glu Pro Val Ser Ile Phe Thr
    530                 535                 540
Ala Val Gln Asp Val Pro Ile Asn Asp Leu Gln Ile Ser Gln Leu Ser
545                 550                 555                 560
Leu Ala Ile Ala Asn Thr Asn Pro Ile Lys Ser Ile Lys Val Thr Val
                565                 570                 575
Asp Ile Glu His Thr Tyr Ile Gly Asp Leu Val Val Ser Leu Asn Pro
            580                 585                 590
Pro Ala Glu Ser Gly Val Leu Pro Ile Ile Leu His Asp Arg Lys Gly
        595                 600                 605
Gly Gly Ala Asp Asp Ile Lys Gln Thr Tyr Asp Glu Val Ser Thr Pro
    610                 615                 620
Gly Leu Thr Ala Leu Lys Gly Lys Ile Pro Gln Gly Thr Trp Thr Leu
625                 630                 635                 640
Glu Val Ala Asp Lys Ala Gln Ala Asp Thr Gly Lys Ile Arg Ser Leu
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Thr Ile Glu Leu Gly Phe
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<210> 332
<211> 2187
<212> DNA
<213> Anabaena variabilis

<220>
<223> Calcium-dependent protease precursor
(Trypsin) S08.79

<400> 332
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<213> Rattus norvegicus

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<223> Caspase-1 precursor C14.001

<400> 333

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Gly Pro Arg Ala Ser Gln Met Phe Ile Thr Tyr Ile Cys Asn Glu Asp
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Cys Tyr Leu Ala Glu Ile Leu Glu Leu Gln Ser Gly Pro Ser Ala Glu
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Glu Thr Lys Glu Lys Leu Asn Lys Glu Gly Gly Ala Phe Pro Gly Pro
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Ser Gly Ser Leu Lys Phe Cys Pro Leu Glu Ile Ala Gln Lys Leu Trp
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Lys Glu Asn His Ser Glu Ile Tyr Pro Ile Met Lys Thr Pro Thr Arg
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Thr Arg Leu Ala Leu Ile Ile Cys Asn Thr Asp Phe Gln His Leu Ser
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Val Asp Thr Ile Phe Gln Met Met Asn Thr Leu Lys Cys Pro Ser Leu
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Lys Asp Lys Pro Lys Val Ile Ile Ile Gln Ala Cys Arg Gly Glu Lys
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Gln Gly Val Val Leu Leu Lys Asp Ser Val Gly Asn Ser Glu Glu Gly
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Phe Leu Thr Asp Ala Ile Phe Glu Asp Asp Gly Ile Lys Lys Ala His
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<212> DNA
<213> Rattus norvegicus

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<212> PRT
<213> Caenorhabditis elegans

<220>
<223> Cell death protein 3 precursor C14.002

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50 55 60
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65 70 75 80
His Glu Gly Leu Ala Glu Val Leu Glu Pro Leu Ala Arg Ser Val Asp
85 90 95
Ser Asn Ala Val Glu Phe Glu Cys Pro Met Ser Pro Ala Ser His Arg
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Ser Asp Arg His Asn Tyr Ser Ser Pro Pro Val Asn Ala Phe Pro Ser
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Tyr Ser Ser Ser Arg Asn Arg Ser Phe Ser Lys Ala Ser Gly Pro Thr
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305 310 315 320
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Gln Val Gln Gln Val Trp Arg Lys Lys Pro Ser Gln Ala Asp Ile Leu
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Arg Gly Ser Trp Phe Ile Gln Ala Val Cys Glu Val Phe Ser Thr His
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<212> DNA
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<220>
<223> Cell death protein 3 precursor C14.002

<400> 336

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gcccagtata tatgtatgta ctatgcttct atcaacaaaa tagtttcata gatcatcacc 7380
ccaaccccac caacctaccg taccatattc atttttgccg ggaatcaatt tcgattaatt 7440
ttaacctatt ttttcgccac aaaaaatcta atatttgaat taacgaatag cattcccatc 7500
tctcccgtgc cggaatgcct cccggccttt taaagttcgg aacatttggc aattatgtat 7560
aaatttgtag gtccccccca tcatttcccg cccatcatct caaattgcat tctttttcg 7620
ccgtgatatc ccgattctgg tcagcaaaga tct                          7653
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<210> 337
<211> 277
<212> PRT
<213> Homo sapiens

<220>
<223> Caspase-3 precursor C14.003

<400> 337
Met Glu Asn Thr Glu Asn Ser Val Asp Ser Lys Ser Ile Lys Asn Leu
 1   5   10   15
Glu Pro Lys Ile Ile His Gly Ser Glu Ser Met Asp Ser Gly Ile Ser
            20   25   30
Leu Asp Asn Ser Tyr Lys Met Asp Tyr Pro Glu Met Gly Leu Cys Ile
        35   40   45
Ile Ile Asn Asn Lys Asn Phe His Lys Ser Thr Gly Met Thr Ser Arg
    50   55   60
Ser Gly Thr Asp Val Asp Ala Ala Asn Leu Arg Glu Thr Phe Arg Asn
65   70   75   80
Leu Lys Tyr Glu Val Arg Asn Lys Asn Asp Leu Thr Arg Glu Glu Ile
                85   90   95
Val Glu Leu Met Arg Asp Val Ser Lys Glu Asp His Ser Lys Arg Ser
            100   105   110
Ser Phe Val Cys Val Leu Leu Ser His Gly Glu Glu Gly Ile Ile Phe
        115   120   125
Gly Thr Asn Gly Pro Val Asp Leu Lys Lys Ile Thr Asn Phe Phe Arg
    130   135   140
Gly Asp Arg Cys Arg Ser Leu Thr Gly Lys Pro Lys Leu Phe Ile Ile
145   150   155   160
Gln Ala Cys Arg Gly Thr Glu Leu Asp Cys Gly Ile Glu Thr Asp Ser
                165   170   175
Gly Val Asp Asp Asp Met Ala Cys His Lys Ile Pro Val Glu Ala Asp
            180   185   190
Phe Leu Tyr Ala Tyr Ser Thr Ala Pro Gly Tyr Tyr Ser Trp Arg Asn
        195   200   205
Ser Lys Asp Gly Ser Trp Phe Ile Gln Ser Leu Cys Ala Met Leu Lys
    210   215   220
Gln Tyr Ala Asp Lys Leu Glu Phe Met His Ile Leu Thr Arg Val Asn
225   230   235   240
Arg Lys Val Ala Thr Glu Phe Glu Ser Phe Ser Phe Asp Ala Thr Phe
                245   250   255
His Ala Lys Lys Gln Ile Pro Cys Ile Val Ser Met Leu Thr Lys Glu
            260   265   270
Leu Tyr Phe Tyr His
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<210> 338
<211> 2635
<212> DNA
<213> Homo sapiens

<220>
<223> Caspase-3 precursor   C14.003

<400> 338
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aggccgtgag gagttagcga gccctgctca cactcggcgc tctggttttc ggtgggtgtg 180
ccctgcacct gcctcttccc ccattctcat taataaaggt atccatggag aacactgaaa 240
actcagtgga ttcaaaatcc attaaaaatt tggaaccaaa gatcatacat ggaagcgaat 300
caatggactc tggaatatcc ctggacaaca gttataaaat ggattatcct gagatgggtt 360
tatgtataat aattaataat aagaattttc ataaaagcac tggaatgaca tctcggtctg 420

gtacagatgt cgatgcagca aacctcaggg aaacattcag aaacttgaaa tatgaagtca 480
ggaataaaaa tgatcttaca cgtgaagaaa ttgtggaatt gatgcgtgat gtttctaaag 540
aagatcacag caaaaggagc agttttgttt gtgtgcttct gagccatggt gaagaaggaa 600
taatttttgg aacaaatgga cctgttgacc tgaaaaaaat aacaaacttt ttcagagggg 660
atcgttgtag aagtctaact ggaaaaccca aacttttcat tattcaggcc tgccgtggta 720
cagaactgga ctgtggcatt gagacagaca gtggtgttga tgatgacatg gcgtgtcata 780
aaataccagt ggatgccgac ttcttgtatg catactccac agcacctggt tattattctt 840
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<210> 339
<211> 303
<212> PRT
<213> Homo sapiens

<220>

<400> 339
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Ala Asn Glu Asp Ser Val Asp Ala Lys Pro Asp Arg Ser Ser Phe Val
            20   25   30
Pro Ser Leu Phe Ser Lys Lys Lys Lys Asn Val Thr Met Arg Ser Ile
        35   40   45
Lys Thr Thr Arg Asp Arg Val Pro Thr Tyr Gln Tyr Asn Met Asn Phe
    50   55   60
Glu Lys Leu Gly Lys Cys Ile Ile Ile Asn Asn Lys Asn Phe Asp Lys
65   70   75   80
Val Thr Gly Met Gly Val Arg Asn Gly Thr Asp Lys Asp Ala Glu Ala

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                85                  90                  95
Leu Phe Lys Cys Phe Arg Ser Leu Gly Phe Asp Val Ile Val Tyr Asn
            100                 105                 110
Asp Cys Ser Cys Ala Lys Met Gln Asp Leu Leu Lys Lys Ala Ser Glu
        115                 120                 125
Glu Asp His Thr Asn Ala Ala Cys Phe Ala Cys Ile Leu Leu Ser His
    130                 135                 140
Gly Glu Glu Asn Val Ile Tyr Gly Lys Asp Gly Val Thr Pro Ile Lys
145                 150                 155                 160
Asp Leu Thr Ala His Phe Arg Gly Asp Arg Cys Lys Thr Leu Leu Glu
                165                 170                 175
Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Arg Gly Thr Glu Leu Asp
            180                 185                 190
Asp Gly Ile Gln Ala Asp Ser Gly Pro Ile Asn Asp Thr Asp Ala Asn
        195                 200                 205
Pro Arg Tyr Lys Ile Pro Val Glu Ala Asp Phe Leu Phe Ala Tyr Ser
    210                 215                 220
Thr Val Pro Gly Tyr Tyr Ser Trp Arg Ser Pro Gly Arg Gly Ser Trp
225                 230                 235                 240
Phe Val Gln Ala Leu Cys Ser Ile Leu Glu Glu His Gly Lys Asp Leu
                245                 250                 255
Glu Ile Met Gln Ile Leu Thr Arg Val Asn Asp Arg Val Ala Arg His
            260                 265                 270
Phe Glu Ser Gln Ser Asp Asp Pro His Phe His Glu Lys Lys Gln Ile
        275                 280                 285
Pro Cys Val Val Ser Met Leu Thr Lys Glu Leu Tyr Phe Ser Gln
    290                 295                 300
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<210> 340
<211> 912
<212> DNA
<213> Homo sapiens

<220>
<223> Caspase-7 precursor C14.004

<400> 340

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aaaaatgtca ccatgcgatc catcaagacc acccgggacc gagtgcctac atatcagtac 180
aacatgaatt ttgaaaagct gggcaaatgc atcataataa acaacaagaa ctttgataaa 240
gtgacaggta tgggcgttcg aaacggaaca gacaaagatg ccgaggcgct cttcaagtgc 300
ttccgaagcc tgggttttga cgtgattgtc tataatgact gctcttgtgc caagatgcaa 360
gatctgctta aaaaagcttc tgaagaggac catacaaatg ccgcctgctt cgcctgcatc 420
ctcttaagcc atggagaaga aaatgtaatt tatgggaaag atggtgtcac accaataaag 480
gatttgacag cccactttag gggggataga tgcaaaaccc ttttagagaa acccaaactc 540
ttcttcattc aggcttgccg agggaccgag cttgatgatg ccatccaggc cgactcgggg 600
cccatcaatg acacagatgc taatcctcga tacaagatcc cagtggaagc tgacttcctc 660
ttcgcctatt ccacggttcc aggctattac tcgtggagga gcccaggaag aggctcctgg 720
tttgtgcaag ccctctgctc catcctggag gagcacggaa aagacctgga aatcatgcag 780
atcctcacca gggtgaatga cagagttgcc aggcactttg agtctcagtc tgatgaccca 840
cacttccatg agaagaagca gatcccctgt gtggtctcca tgctcaccaa ggaactctac 900
ttcagtcaat ag                                                    912
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<210> 341

<211> 293
<212> PRT
<213> Homo sapiens

<220>
<223> Caspase-6 precursor C14.005

<400> 341
Met Ser Ser Ala Ser Gly Leu Arg Arg Gly His Pro Ala Gly Gly Glu
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Glu Asn Met Thr Glu Thr Asp Ala Phe Tyr Lys Arg Glu Met Phe Asp
20 25 30
Pro Ala Glu Lys Tyr Lys Met Asp His Arg Arg Arg Gly Ile Ala Leu
35 40 45
Ile Phe Asn His Glu Arg Phe Phe Trp His Leu Thr Leu Pro Glu Arg
50 55 60
Arg Gly Thr Cys Ala Asp Arg Asp Asn Leu Thr Arg Arg Phe Ser Asp
65 70 75 80
Leu Gly Phe Glu Val Lys Cys Phe Asn Asp Leu Lys Ala Glu Glu Leu
85 90 95
Leu Leu Lys Ile His Glu Val Ser Thr Val Ser His Ala Asp Ala Asp
100 105 110
Cys Phe Val Cys Val Phe Leu Ser His Gly Glu Gly Asn His Ile Tyr
115 120 125
Ala Tyr Asp Ala Lys Ile Glu Ile Gln Thr Leu Thr Gly Leu Phe Lys
130 135 140
Gly Asp Lys Cys His Ser Leu Val Gly Lys Pro Lys Ile Phe Ile Ile
145 150 155 160
Gln Ala Cys Arg Gly Asn Gln His Asp Val Pro Val Ile Pro Leu Asp
165 170 175
Val Val Asp Asn Gln Thr Glu Lys Leu Asp Thr Asn Ile Thr Glu Val
180 185 190
Asp Ala Ala Ser Val Tyr Thr Leu Pro Ala Gly Ala Asp Phe Leu Met
195 200 205
Cys Tyr Ser Val Ala Glu Gly Tyr Tyr Ser His Arg Glu Thr Val Asn
210 215 220
Gly Ser Trp Tyr Ile Gln Asp Leu Cys Glu Met Leu Gly Lys Tyr Gly
225 230 235 240
Ser Ser Leu Glu Phe Thr Glu Leu Leu Thr Leu Val Asn Arg Lys Val
245 250 255
Ser Gln Arg Arg Val Asp Phe Cys Lys Asp Pro Ser Ala Ile Gly Lys
260 265 270
Lys Gln Val Pro Cys Phe Ala Ser Met Leu Thr Lys Lys Leu His Phe
275 280 285
Phe Pro Lys Ser Asn
290

<210> 342
<211> 1545
<212> DNA
<213> Homo sapiens

<220>
<223> Caspase-6 precursor C14.005

<400> 342
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ggggaagaaa acatgacaga aacagatgcc ttctataaaa gagaaatgtt tgatccggca 180
gaaaagtaca aaatggacca caggaggaga ggaattgctt taatcttcaa tcatgagagg 240
ttcttttggc acttaacact gccagaaagg cggcgcacct gcgcagatag agacaatctt 300
acccgcaggt tttcagatct aggatttgaa gtgaaatgct ttaatgatct taaagcagaa 360
gaactactgc tcaaaattca tgaggtgtca actgttagcc acgcagatgc cgattgcttt 420
gtgtgtgtct tcctgagcca tggcgaaggc aatcacattt atgcatatga tgctaaaatc 480
gaaattcaga cattaactgg cttgttcaaa ggagacaagt gtcacagcct ggttggaaaa 540
cccaagatat ttatcatcca ggcatgtcgg ggaaaccagc acgatgtgcc agtcattcct 600
ttggatgtag tagataatca gacagagaag ttggacacca acataactga ggtggatgca 660
gcctccgttt acacgctgcc tgctggagct gacttcctca tgtgttactc tgttgcagaa 720
ggatattatt ctcaccggga aactgtgaac ggctcatggt acattcaaga tttgtgtgag 780
atgttgggaa aatatggctc ctccttagag ttcacagaac tcctcacact ggtgaacagg 840
aaagtttctc agcgccgagt ggacttttgc aaagacccaa gtgcaattgg aaagaagcag 900
gttccctgtt ttgcctcaat gctaactaaa aagctgcatt tctttccaaa atctaattaa 960
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gttactcaca cctgtaatcc cagcactttg ggagtccaag gtgggcggat cacctgaggt 1080
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aaaaaaattt agctaggcat ggcggcgcat gcctgcaatc ccagctactt ggaaggctga 1200
ggcaggagaa tcacttgaac ccaggaggtg gaggctgcgg tgagccgagc attgcgccat 1260
tgcactccag cctgggcaac gagtgaaact ccgtctcaaa aaaaaagaaa atgtctttct 1320
cttcctttta tataaatatc gttagggtga agcattatgg tctaatgatt caaatgtttt 1380
aaagtttaat gcctagcaga gaactgcctt aaaaaaaaaa agttcatgtt ggccatggtg 1440
aaagggtttg atatggagaa acaaaatcct caggaaatta gataaataaa aatttataag 1500
catttgtatt atttttaat aaactgcagg gttacacaaa aatct 1545

<210> 343
<211> 452
<212> PRT
<213> Mus musculus

<220>
<223> Caspase-2 precursor C14.006

<400> 343
Met Ala Ala Pro Ser Gly Arg Ser Gln Ser Ser Leu His Arg Lys Gly
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Leu Met Ala Ala Asp Arg Arg Ser Arg Ile Leu Ala Val Cys Gly Met
            20   25   30
His Pro Asp His Gln Glu Thr Leu Lys Lys Asn Arg Val Val Leu Ala
        35   40   45
Lys Gln Leu Leu Leu Ser Glu Leu Leu Glu His Leu Leu Glu Lys Asp
    50   55   60
Ile Ile Thr Leu Glu Met Arg Glu Leu Ile Gln Ala Lys Gly Gly Ser
65   70   75   80
Phe Ser Gln Asn Val Glu Leu Leu Asn Leu Leu Pro Lys Arg Gly Pro
                85   90   95
Gln Ala Phe Asp Ala Phe Cys Glu Ala Leu Arg Glu Thr Arg Gln Gly
            100   105   110
His Leu Glu Asp Leu Leu Leu Thr Thr Leu Ser Asp Ile Gln His Val
        115   120   125
Leu Pro Pro Leu Ser Cys Asp Tyr Asp Thr Ser Leu Pro Phe Ser Val
    130   135   140

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Cys Glu Ser Cys Pro Pro His Lys Gln Leu Arg Leu Ser Thr Asp Ala
145                 150                 155                 160
Thr Glu His Ser Leu Asp Asn Gly Asp Gly Pro Pro Cys Leu Leu Val
                165                 170                 175
Lys Pro Cys Thr Pro Glu Phe Tyr Gln Ala His Tyr Gln Leu Ala Tyr
            180                 185                 190
Arg Leu Gln Ser Gln Pro Arg Gly Leu Ala Leu Val Leu Ser Asn Val
        195                 200                 205
His Phe Thr Gly Glu Lys Asp Leu Glu Phe Arg Ser Gly Gly Asp Val
    210                 215                 220
Asp His Thr Thr Leu Val Thr Leu Phe Lys Leu Leu Gly Tyr Asn Val
225                 230                 235                 240
His Val Leu His Asp Gln Thr Ala Gln Glu Met Gln Glu Lys Leu Gln
                245                 250                 255
Asn Phe Ala Gln Leu Pro Ala His Arg Val Thr Asp Ser Cys Val Val
            260                 265                 270
Ala Leu Leu Ser His Gly Val Glu Gly Gly Ile Tyr Gly Val Asp Gly
        275                 280                 285
Lys Leu Leu Gln Leu Gln Glu Val Phe Arg Leu Phe Asp Asn Ala Asn
    290                 295                 300
Cys Pro Ser Leu Gln Asn Lys Pro Lys Met Phe Phe Ile Gln Ala Cys
305                 310                 315                 320
Arg Gly Asp Glu Thr Asp Arg Gly Val Asp Gln Gln Asp Gly Lys Asn
                325                 330                 335
His Thr Gln Ser Pro Gly Cys Glu Glu Ser Asp Ala Gly Lys Glu Glu
            340                 345                 350
Leu Met Lys Met Arg Leu Pro Thr Arg Ser Asp Met Ile Cys Gly Tyr
        355                 360                 365
Ala Cys Leu Lys Gly Asn Ala Ala Met Arg Asn Thr Lys Arg Gly Ser
    370                 375                 380
Trp Tyr Ile Glu Ala Leu Thr Gln Val Phe Ser Glu Arg Ala Cys Asp
385                 390                 395                 400
Met His Val Ala Asp Met Leu Val Lys Val Asn Ala Leu Ile Lys Glu
                405                 410                 415
Arg Glu Gly Tyr Ala Pro Gly Thr Glu Phe His Arg Cys Lys Glu Met
            420                 425                 430
Ser Glu Tyr Cys Ser Thr Leu Cys Gln Gln Leu Tyr Leu Phe Pro Gly
        435                 440                 445
Tyr Pro Pro Thr
    450
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<210> 344
<211> 3395
<212> DNA
<213> Mus musculus

<220>
<223> Caspase-2 precursor C14.006

<400> 344
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acactgaaaa agaatcgagt ggtgctggcc aagcagctgc tgctgagcga gctgttagaa 180
cacctcctag agaaggacat tatcactttg gaaatgaggg agctcatcca ggccaaaggg 240
ggcagtttca gccagaatgt ggaactcctc aacctgctgc caaagagagg accccaggct 300

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gatgctacgg aacactcctt agataatggt gatggtcctc cctgtcttct ggtgaagcca 540
tgcactcctg agttttacca ggcacactac cagctggcct ataggttgca atctcagccc 600
cgtggcttgg cactggtgct gagcaatgtg cacttcactg gagagaaaga cctggaattc 660
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aatgtccatg tgctacatga ccagaccgca caggaaatgc aagagaaact tcagaatttt 780
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gctattatag tgtacagttc aattagtata tgggtttttt tttccaggtg ttttatttt 3120
atccactgtt ttgttgttgt ttttttatat tttctacata tcacgtgtga gacaacttct 3180
ttcacatctc catagtgccc agcaaatttg aggcctatgg tagttgaggt gctcaactaa 3240
tgtttgttgt atgaaccaag tggtttgaag acttgctgcc aaattctgcc ttttgggtca 3300
gtataggatg cataagtggt agaatcttca cacttcccac tgccaagatt ttgtattgcc 3360
atcaggtgcc aaataaatgt tgatacttat tactg                          3395
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<210> 345
<211> 377

<212> PRT
<213> Homo sapiens

<220>
<223> Caspase-4 precursor C14.007

<400> 345
Met Ala Glu Gly Asn His Arg Lys Lys Pro Leu Lys Val Leu Glu Ser
1 5 10 15
Leu Gly Lys Asp Phe Leu Thr Gly Val Leu Asp Asn Leu Val Glu Gln
20 25 30
Asn Val Leu Asn Trp Lys Glu Glu Glu Lys Lys Lys Tyr Tyr Asp Ala
35 40 45
Lys Thr Glu Asp Lys Val Arg Val Met Ala Asp Ser Met Gln Glu Lys
50 55 60
Gln Arg Met Ala Gly Gln Met Leu Leu Gln Thr Phe Phe Asn Ile Asp
65 70 75 80
Gln Ile Ser Pro Asn Lys Lys Ala His Pro Asn Met Glu Ala Gly Pro
85 90 95
Pro Glu Ser Gly Glu Ser Thr Asp Ala Leu Lys Leu Cys Pro His Glu
100 105 110
Glu Phe Leu Arg Leu Cys Lys Glu Arg Ala Glu Glu Ile Tyr Pro Ile
115 120 125
Lys Glu Arg Asn Asn Arg Thr Arg Leu Ala Leu Ile Ile Cys Asn Thr
130 135 140
Glu Phe Asp His Leu Pro Pro Arg Asn Gly Ala Asp Phe Asp Ile Thr
145 150 155 160
Gly Met Lys Glu Leu Leu Glu Gly Leu Asp Tyr Ser Val Asp Val Glu
165 170 175
Glu Asn Leu Thr Ala Arg Asp Met Glu Ser Ala Leu Arg Ala Phe Ala
180 185 190
Thr Arg Pro Glu His Lys Ser Ser Asp Ser Thr Phe Leu Val Leu Met
195 200 205
Ser His Gly Ile Leu Glu Gly Ile Cys Gly Thr Val His Asp Glu Lys
210 215 220
Lys Pro Asp Val Leu Leu Tyr Asp Thr Ile Phe Gln Ile Phe Asn Asn
225 230 235 240
Arg Asn Cys Leu Ser Leu Lys Asp Lys Pro Lys Val Ile Ile Val Gln
245 250 255
Ala Cys Arg Gly Ala Asn Arg Gly Glu Leu Trp Val Arg Asp Ser Pro
260 265 270
Ala Ser Leu Glu Val Ala Ser Ser Gln Ser Ser Glu Asn Leu Glu Glu
275 280 285
Asp Ala Val Tyr Lys Thr His Val Glu Lys Asp Phe Ile Ala Phe Cys
290 295 300
Ser Ser Thr Pro His Asn Val Ser Trp Arg Asp Ser Thr Met Gly Ser
305 310 315 320
Ile Phe Ile Thr Gln Leu Ile Thr Cys Phe Gln Lys Tyr Ser Trp Cys
325 330 335
Cys His Leu Glu Glu Val Phe Arg Lys Val Gln Gln Ser Phe Glu Thr
340 345 350
Pro Arg Ala Lys Ala Gln Met Pro Thr Ile Glu Arg Leu Ser Met Thr
355 360 365
Arg Tyr Phe Tyr Leu Phe Pro Gly Asn
370 375

<210> 346
<211> 1291
<212> DNA
<213> Homo sapiens

<220>
<223> Caspase-4 precursor C14.007

<400> 346
gctctttcca acgctgtaaa aaaggacaga ggctgttccc tatggcagaa ggcaaccaca 60
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ataacttggt ggaacaaaat gtactgaact ggaaggaaga ggaaaaaaag aaatattacg 180
atgctaaaac tgaagacaaa gttcgggtca tggcagactc tatgcaagag aagcaacgta 240
tggcaggaca aatgcttctt caaacctttt ttaacataga ccaaatatcc cccaataaaa 300
aagctcatcc gaatatggag gctggaccac ctgagtcagg agaatctaca gatgccctca 360
agctttgtcc tcatgaagaa ttcctgagac tatgtaaaga aagagctgaa gagatctatc 420
caataaagga gagaaacaac cgcacacgcc tggctctcat catatgcaat acagagtttg 480
accatctgcc tccgaggaat ggagctgact ttgacatcac agggatgaag gagctacttg 540
agggtctgga ctatagtgta gatgtagaag agaatctgac agccagggat atggagtcag 600
cgctgagggc atttgctacc agaccagagc acaagtcctc tgacagcaca ttcttggtac 660
tcatgtctca tggcatcctg gagggaatct gcggaactgt gcatgatgag aaaaaaccag 720
atgtgctgct ttatgacacc atcttccaga tattcaacaa ccgcaactgc ctcagtctga 780
aggacaaacc caaggtcatc attgtccagg cctgcagagg tgcaaaccgt ggggaactgt 840
gggtcagaga ctctccagca tccttggaag tggcctcttc acagtcatct gagaacctgg 900
aggaagatgc tgtttacaag acccacgtgg agaaggactt cattgctttc tgctcttcaa 960
cgccacacaa cgtgtcctgg agagacagca caatgggctc tatcttcatc acacaactca 1020
tcacatgctt ccagaaatat tcttggtgct gccacctaga ggaagtattt cggaaggtac 1080
agcaatcatt tgaaactcca agggccaaag ctcaaatgcc caccatagaa cgactgtcca 1140
tgacaagata tttctacctc tttcctggca attgaaaatg gaagccacaa gcagcccagc 1200
cctccttaat caacttcaag gagcaccttc attagtacag cttgcatatt taacattttg 1260
tatttcaata aaagtgaaga caaaaaaaaa a 1291

<210> 347
<211> 418
<212> PRT
<213> Homo sapiens

<220>
<223> Caspase-5 precursor C14.008

<400> 347
Met Phe Lys Gly Ile Leu Gln Ser Gly Leu Asp Asn Phe Val Ile Asn
1 5 10 15
His Met Leu Lys Asn Asn Val Ala Gly Gln Thr Ser Ile Gln Thr Leu
20 25 30
Val Pro Asn Thr Asp Gln Lys Ser Thr Ser Val Lys Lys Asp Asn His
35 40 45
Lys Lys Lys Thr Val Lys Met Leu Glu Tyr Leu Gly Lys Asp Val Leu
50 55 60
His Gly Val Phe Asn Tyr Leu Ala Lys His Asp Val Leu Thr Leu Lys
65 70 75 80
Glu Glu Glu Lys Lys Lys Tyr Tyr Asp Ala Lys Ile Glu Asp Lys Ala
85 90 95
Leu Ile Leu Val Asp Ser Leu Arg Lys Asn Arg Val Ala His Gln Met
100 105 110
Phe Thr Gln Thr Leu Leu Asn Met Asp Gln Lys Ile Thr Ser Val Lys

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        115                 120                 125
Pro Leu Leu Gln Ile Glu Ala Gly Pro Pro Glu Ser Ala Glu Ser Thr
    130                 135                 140
Asn Ile Leu Lys Leu Cys Pro Arg Glu Glu Phe Leu Arg Leu Cys Lys
145                 150                 155                 160
Lys Asn His Asp Glu Ile Tyr Pro Ile Lys Lys Arg Glu Asp Arg Arg
                165                 170                 175
Arg Leu Ala Leu Ile Ile Cys Asn Thr Lys Phe Asp His Leu Pro Ala
            180                 185                 190
Arg Asn Gly Ala His Tyr Asp Ile Val Gly Met Lys Arg Leu Leu Gln
        195                 200                 205
Gly Leu Gly Tyr Thr Val Val Asp Glu Lys Asn Leu Thr Ala Arg Asp
    210                 215                 220
Met Glu Ser Val Leu Arg Ala Phe Ala Ala Arg Pro Glu His Lys Ser
225                 230                 235                 240
Ser Asp Ser Thr Phe Leu Val Leu Met Ser His Gly Ile Leu Glu Gly
                245                 250                 255
Ile Cys Gly Thr Ala His Lys Lys Lys Lys Pro Asp Val Leu Leu Tyr
            260                 265                 270
Asp Thr Ile Phe Gln Ile Phe Asn Asn Arg Asn Cys Leu Ser Leu Lys
        275                 280                 285
Asp Lys Pro Lys Val Ile Ile Val Gln Ala Cys Arg Gly Glu Lys His
    290                 295                 300
Gly Glu Leu Trp Val Arg Asp Ser Pro Ala Ser Leu Ala Val Ile Ser
305                 310                 315                 320
Ser Gln Ser Ser Glu Asn Leu Glu Ala Asp Ser Val Cys Lys Ile His
                325                 330                 335
Glu Glu Lys Asp Phe Ile Ala Phe Cys Ser Ser Thr Pro His Asn Val
            340                 345                 350
Ser Trp Arg Asp Arg Thr Arg Gly Ser Ile Phe Ile Thr Glu Leu Ile
        355                 360                 365
Thr Cys Phe Gln Lys Tyr Ser Cys Cys Cys His Leu Met Glu Ile Phe
    370                 375                 380
Arg Lys Val Gln Lys Ser Phe Glu Val Pro Gln Ala Lys Ala Gln Met
385                 390                 395                 400
Pro Thr Ile Glu Arg Ala Thr Leu Thr Arg Asp Phe Tyr Leu Phe Pro
                405                 410                 415
Gly Asn
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<210> 348
<211> 1400
<212> DNA
<213> Homo sapiens

<220>
<223> Caspase-5 precursor C14.008

<400> 348
cggcaaaaaa aaaaggcgta agaattttga agctatgttc aaaggtatcc ttcagagtgg 60
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ccagacccta gtacctaata cggatcaaaa gtcgaccagt gtaaaaaaag acaaccacaa 180
aaaaaaaaca gttaagatgt tggaatacct gggcaaagat gttcttcatg gtgtttttaa 240
ttatttggca aaacacgatg ttctgacatt gaaggaagag gaaaagaaaa aatattatga 300

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tgccaaaatt gaagacaagg ccctgatctt ggtagactct ttgcgaaaga atcgcgtggc 360
tcatcaaatg tttacccaaa cacttctcaa tatggaccaa aagatcacca gtgtaaaacc 420
tcttctgcaa atcgaggctg gaccacctga gtcagcagaa tctacaaata tactcaaact 480
ttgtcctcgt gaagaattcc tgagactgtg taaaaaaaat catgatgaga tctatccaat 540
aaaaaagaga gaggaccgca gacgcctggc tctcatcata tgcaatacaa agtttgatca 600
cctgcctgca aggaatgggg ctcactatga catcgtgggg atgaaaaggc tgcttcaagg 660
cctgggctac actgtggttg acgaaaagaa tctcacagcc agggatatgg agtcagtgct 720
gagggcattt gctgccagac cagagcacaa gtcctctgac agcacgttct tggtactcat 780
gtctcatggc atcctagagg gaatctgcgg aactgcgcat aaaaagaaaa aaccggatgt 840
gctgctttat gacaccatct tccagatatt caacaaccgc aactgcctca gtctaaagga 900
caaacccaag gtcatcattg tccaggcctg cagaggtgaa aaacatgggg aactctgggt 960
cagagactct ccagcatcct tggcagtcat ctcttcacag tcatctgaga acctggaggc 1020
agattctgtt tgcaagatcc acgaggagaa ggacttcatt gctttctgtt cttcaacacc 1080
acataacgtg tcctggagag accgcacaag gggctccatc ttcattacgg aactcatcac 1140
atgcttccag aaatattctt gctgctgcca cctaatggaa atatttcgga aggtacagaa 1200
atcatttgaa gttccacagg ctaaagccca gatgcccacc atagaacgag caaccttgac 1260
aagagatttc tacctctttc ctggcaattg aaaatgaaac cacaggcagc ccagccctcc 1320
tctgtcaaca tcaaagagca catttaccag tatagcttgc atagtcaata tttggtattt 1380
caataaaagt aaagactgta                                            1400

<210> 349
<211> 479
<212> PRT
<213> Homo sapiens

<220>
<223> Caspase-8 precursor   C14.009

<400>  349
Met Asp Phe Ser Arg Asn Leu Tyr Asp Ile Gly Glu Gln Leu Asp Ser
 1               5                  10                  15
Glu Asp Leu Ala Ser Leu Lys Phe Leu Ser Leu Asp Tyr Ile Pro Gln
            20                  25                  30
Arg Lys Gln Glu Pro Ile Lys Asp Ala Leu Met Leu Phe Gln Arg Leu
        35                  40                  45
Gln Glu Lys Arg Met Leu Glu Glu Ser Asn Leu Ser Phe Leu Lys Glu
    50                  55                  60
Leu Leu Phe Arg Ile Asn Arg Leu Asp Leu Leu Ile Thr Tyr Leu Asn
65                  70                  75                  80
Thr Arg Lys Glu Glu Met Glu Arg Glu Leu Gln Thr Pro Gly Arg Ala
                85                  90                  95
Gln Ile Ser Ala Tyr Arg Val Met Leu Tyr Gln Ile Ser Glu Glu Val
            100                 105                 110
Ser Arg Ser Glu Leu Arg Ser Phe Lys Phe Leu Leu Gln Glu Glu Ile
        115                 120                 125
Ser Lys Cys Lys Leu Asp Asp Asp Met Asn Leu Leu Asp Ile Phe Ile
    130                 135                 140
Glu Met Glu Lys Arg Val Ile Leu Gly Glu Gly Lys Leu Asp Ile Leu
145                 150                 155                 160
Lys Arg Val Cys Ala Gln Ile Asn Lys Ser Leu Leu Lys Ile Ile Asn
                165                 170                 175
Asp Tyr Glu Glu Phe Ser Lys Glu Arg Ser Ser Ser Leu Glu Gly Ser
            180                 185                 190
Pro Asp Glu Phe Ser Asn Gly Glu Glu Leu Cys Gly Val Met Thr Ile
        195                 200                 205
Ser Asp Ser Pro Arg Glu Gln Asp Ser Glu Ser Gln Thr Leu Asp Lys
    210                 215                 220
```

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Val Tyr Gln Met Lys Ser Lys Pro Arg Gly Tyr Cys Leu Ile Ile Asn
225                 230                 235                 240
Asn His Asn Phe Ala Lys Ala Arg Glu Lys Val Pro Lys Leu His Ser
                245                 250                 255
Ile Arg Asp Arg Asn Gly Thr His Leu Asp Ala Gly Ala Leu Thr Thr
            260                 265                 270
Thr Phe Glu Glu Leu His Phe Glu Ile Lys Pro His Asp Asp Cys Thr
        275                 280                 285
Val Glu Gln Ile Tyr Glu Ile Leu Lys Ile Tyr Gln Leu Met Asp His
    290                 295                 300
Ser Asn Met Asp Cys Phe Ile Cys Cys Ile Leu Ser His Gly Asp Lys
305                 310                 315                 320
Gly Ile Ile Tyr Gly Thr Asp Gly Gln Glu Ala Pro Ile Tyr Glu Leu
                325                 330                 335
Thr Ser Gln Phe Thr Gly Leu Lys Cys Pro Ser Leu Ala Gly Lys Pro
            340                 345                 350
Lys Val Phe Phe Ile Gln Ala Cys Gln Gly Asp Asn Tyr Gln Lys Gly
        355                 360                 365
Ile Pro Val Glu Thr Asp Ser Glu Glu Gln Pro Tyr Leu Glu Met Asp
    370                 375                 380
Leu Ser Ser Pro Gln Thr Arg Tyr Ile Pro Asp Glu Ala Asp Phe Leu
385                 390                 395                 400
Leu Gly Met Ala Thr Val Asn Asn Cys Val Ser Tyr Arg Asn Pro Ala
                405                 410                 415
Glu Gly Thr Trp Tyr Ile Gln Ser Leu Cys Gln Ser Leu Arg Glu Arg
            420                 425                 430
Cys Pro Arg Gly Asp Asp Ile Leu Thr Ile Leu Thr Glu Val Asn Tyr
        435                 440                 445
Glu Val Ser Asn Lys Asp Asp Lys Lys Asn Met Gly Lys Gln Met Pro
    450                 455                 460
Gln Pro Thr Phe Thr Leu Arg Lys Lys Leu Val Phe Pro Ser Asp
465                 470                 475
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<210> 350
<211> 2887
<212> DNA
<213> Homo sapiens

<220>
<223> Caspase-8 precursor C14.009

<400> 350
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gattctgcct ttctgctgga gggaagtgtt ttcacaggtt ctcctccttt tatcttttgt 60
gtttttttttc aagccctgct gaatttgcta gtcaactcaa caggaagtga ggccatggag 120
ggaggcagaa gagccagggt ggttattgaa agtagaagaa acttcttcct gggagccttt 180
cccacccccct tccctgctga gcacgtggag ttaggcaggt taggggactc ggagactgcg 240
atggtgccag gaaagggtgg agcggattat attctcctgc cttttaaaaa gatggacttc 300
agcagaaatc tttatgatat tggggaacaa ctggacagtg aagatctggc ctccctcaag 360
ttcctgagcc tggactacat tccgcaaagg aagcaagaac ccatcaagga tgccttgatg 420
ttattccaga gactccagga aaagagaatg ttggaggaaa gcaatctgtc cttcctgaag 480
gagctgctct tccgaattaa tagactggat ttgctgatta cctacctaaa cactagaaag 540
gaggagatgg aaagggaact tcagacacca ggcagggctc aaatttctgc ctacagggtc 600
atgctctatc agatttcaga agaagtgagc agatcagaat tgaggtcttt taagtttctt 660
ttgcaagagg aaatctccaa atgcaaactg gatgatgaca tgaacctgct ggatattttc 720
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atagagatgg agaagagggt catcctggga gaaggaaagt tggacatcct gaaaagagtc 780
tgtgcccaaa tcaacaagag cctgctgaag ataatcaacg actatgaaga attcagcaaa 840
gagagaagca gcagccttga aggaagtcct gatgaatttt caaatgggga ggagttgtgt 900
ggggtaatga caatctcgga ctctccaaga gaacaggata gtgaatcaca gactttggac 960
aaagtttacc aaatgaaaag caaacctcgg ggatactgtc tgatcatcaa caatcacaat 1020
tttgcaaaag cacgggagaa agtgcccaaa cttcacagca ttagggacag gaatggaaca 1080
cacttggatg caggggcttt gaccacgacc tttgaagagc ttcattttga gatcaagccc 1140
cacgatgact gcacagtaga gcaaatctat gagattttga aaatctacca actcatggac 1200
cacagtaaca tggactgctt catctgctgt atcctctccc atggagacaa aggcatcatc 1260
tatggcactg atggacagga ggcccccatc tatgagctga catctcagtt cactggtttg 1320
aagtgccctt cccttgctgg aaaacccaaa gtgtttttta ttcaggcttg tcaggggat 1380
aactaccaga aaggtatacc tgttgagact gattcagagg agcaacccta tttagaaatg 1440
gatttatcat cacctcaaac gagatatatc ccggatgagg ctgactttct gctggggatg 1500
gccactgtga ataactgtgt ttcctaccga aaccctgcag agggaacctg gtacatccag 1560
tcactttgcc agagcctgag agagcgatgt cctcgaggcg atgatattct caccatcctg 1620
actgaagtga actatgaagt aagcaacaag gatgacaaga aaaacatggg gaaacagatg 1680
cctcagccta ctttcacact aagaaaaaaa cttgtcttcc cttctgattg atggtgctat 1740
tttgtttgtt ttgttttgtt ttgttttttt gagacagaat ctcgctctgt cgcccaggct 1800
ggagtgcagt ggcgtgatct cggctcaccg caagctccgc ctcccgggtt cacgccattc 1860
tcctgcctca gcctcccgag tagctgggac tacaggggcc cgccaccaca cctggctaat 1920
tttttaaaaa tatttttagt agagacaggg tttcactgtg ttagccaggg tggtcttgat 1980
ctcctgacct cgtgatccac ccacctcggc ctcccaaagt gctgggatta caggcgtgag 2040
ccaccgcgcc tggccgatgg tactatttag atataacact atgtttattt actaattttc 2100
tagattttct actttattaa ttgttttgca ctttttttata agagctaaag ttaaatagga 2160
tattaacaac aataacactg tctccttttct cttacgctta aggctttggg aatgttttta 2220

gctggtggca ataaatacca gacacgtaca aaatccagct atgaatatag agggcttatg 2280
attcagattg ttatctatca actataagcc cactgttaat attctattaa ctttaattct 2340
ctttcaaagc taaattccac actaccacat taaaaaaatt agaaagtagc cacgtatggt 2400
ggctcatgtc tataatccca gcactttggg aggttgaggt gggaggattt gcttgaaccc 2460
aagaggtcca aggctgcagt gagccatgtt cacaccgctg cactcaagct tgggtgacag 2520
agcaagaccc cgtccccaaa aaaatttttt ttttaataaa cccaaatttg tttgaaaact 2580
tttaaaaatt caaatgattt ttacaagttt taaataagct ctccccaaac ttgctttatg 2640
ccttcttatt gcttttatga tatatatatg cttggctaac tatatttgct ttttgctaac 2700
aatgctctgg ggtcttttta tgcatttgca tttgctcttt catctctgct tggattattt 2760
taaatcatta ggaattaagt tatctttaaa atttaagtat ctttttttcca aaacattttt 2820
taatagaata aaatataatt tgatcttaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2880
aaaaaaa                                                          2887

<210> 351
<211> 416
<212> PRT
<213> Homo sapiens

<220>
<223> Caspase-9 precursor
        C14.010

<400> 351
Met Asp Glu Ala Asp Arg Arg Leu Leu Arg Arg Cys Arg Leu Arg Leu
 1               5                  10                  15
Val Glu Glu Leu Gln Val Asp Gln Leu Trp Asp Ala Leu Leu Ser Arg
            20                  25                  30
Glu Leu Phe Arg Pro His Met Ile Glu Asp Ile Gln Arg Ala Gly Ser
        35                  40                  45
Gly Ser Arg Arg Asp Gln Ala Arg Gln Leu Ile Ile Asp Leu Glu Thr
    50                  55                  60
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Arg Gly Ser Gln Ala Leu Pro Leu Phe Ile Ser Cys Leu Glu Asp Thr
65                  70                  75                  80
Gly Gln Asp Met Leu Ala Ser Phe Leu Arg Thr Asn Arg Gln Ala Ala
                85                  90                  95
Lys Leu Ser Lys Pro Thr Leu Glu Asn Leu Thr Pro Val Val Leu Arg
            100                 105                 110
Pro Glu Ile Arg Lys Pro Glu Val Leu Arg Pro Glu Thr Pro Arg Pro
        115                 120                 125
Val Asp Ile Gly Ser Gly Gly Phe Gly Asp Val Gly Ala Leu Glu Ser
    130                 135                 140
Leu Arg Gly Asn Ala Asp Leu Ala Tyr Ile Leu Ser Met Glu Pro Cys
145                 150                 155                 160
Gly His Cys Leu Ile Ile Asn Asn Val Asn Phe Cys Arg Glu Ser Gly
                165                 170                 175
Leu Arg Thr Arg Thr Gly Ser Asn Ile Asp Cys Glu Lys Leu Arg Arg
            180                 185                 190
Arg Phe Ser Ser Leu His Phe Met Val Glu Val Lys Gly Asp Leu Thr
        195                 200                 205
Ala Lys Lys Met Val Leu Ala Leu Leu Glu Leu Ala Gln Gln Asp His
    210                 215                 220
Gly Ala Leu Asp Cys Cys Val Val Val Ile Leu Ser His Gly Cys Gln
225                 230                 235                 240
Ala Ser His Leu Gln Phe Pro Gly Ala Val Tyr Gly Thr Asp Gly Cys
                245                 250                 255
Pro Val Ser Val Glu Lys Ile Val Asn Ile Phe Asn Gly Thr Ser Cys
            260                 265                 270
Pro Ser Leu Gly Gly Lys Pro Lys Leu Phe Phe Ile Gln Ala Cys Gly
        275                 280                 285
Gly Glu Gln Lys Asp His Gly Phe Glu Val Ala Ser Thr Ser Pro Glu
    290                 295                 300
Asp Glu Ser Pro Gly Ser Asn Pro Glu Pro Asp Ala Thr Pro Phe Gln
305                 310                 315                 320
Glu Gly Leu Arg Thr Phe Asp Gln Leu Asp Ala Ile Ser Ser Leu Pro
                325                 330                 335
Thr Pro Ser Asp Ile Phe Val Ser Tyr Ser Thr Phe Pro Gly Phe Val
            340                 345                 350
Ser Trp Arg Asp Pro Lys Ser Gly Ser Trp Tyr Val Glu Thr Leu Asp
        355                 360                 365
Asp Ile Phe Glu Gln Trp Ala His Ser Glu Asp Leu Gln Ser Leu Leu
    370                 375                 380
Leu Arg Val Ala Asn Ala Val Ser Val Lys Gly Ile Tyr Lys Gln Met
385                 390                 395                 400
Pro Gly Cys Phe Asn Phe Leu Arg Lys Lys Leu Phe Phe Lys Thr Ser
                405                 410                 415
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<210> 352
<211> 1481
<212> DNA
<213> Homo sapiens

<220>
<223> Caspase-9 precursor C14.010

<400> 352
gccatggacg aagcggatcg gcggctcctg cggcggtgcc ggctgcggct ggtggaagag 60

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ctgcaggtgg accagctctg ggacgtcctg ctgagccgcg agctgttcag gccccatatg 120
atcgaggaca tccagcgggc aggctctgga tctcggcggg atcaggccag gcagctgatc 180
atagatctgg agactcgagg gagtcaggct cttcctttgt tcatctcctg cttagaggac 240
acaggccagg acatgctggc ttcgtttctg cgaactaaca ggcaagcagg aaagttgtcg 300
aagccaaccc tagaaaacct taccccagtg gtgctcagac cagagattcg caaaccagag 360
gttctcagac cggaaacacc cagaccagtg gacattggtt ctggaggatt cggtgatgtc 420
ggtgctcttg agagtttgag gggaaatgca gatttggctt acatcctgag catggagccc 480
tgtggccact gcctcattat caacaatgtg aacttctgcc gtgagtccgg gctccgcacc 540
cgcactggct ccaacatcga ctgtgagaag ttgcggcgtc gcttctcctc gctgcatttc 600
atggtggagg tgaagggcga cctgactgcc aagaaaatgg tgctggcttt gctggagctg 660
gcgcggcagg accacggtgc tctggactgc tgcgtggtgg tcattctctc tcacggctgt 720
caggccagcc acctgcagtt cccaggggct gtctacggca cagatggatg ccctgtgtcg 780
gtcgagaaga ttgtgaacat cttcaatggg accagctgcc ccagcctggg agggaagccc 840
aagctctttt tcatccaggc ctgtggtggg gagcagaaag accatgggtt tgaggtggcc 900
tccacttccc ctgaagacga gtcccctggc agtaaccccg agccagatgc caccccgttc 960
caggaaggtt tgaggacctt cgaccagctg gacgccatat ctagtttgcc cacacccagt 1020
gacatctttg tgtcctactc tactttccca ggttttgttt cctggaggga ccccaagagt 1080
ggctcctggt acgttgagac cctggacgac atctttgagc agtgggctca ctctgaagac 1140
ctgcagtccc tcctgcttag ggtcgctaat gctgtttcgg tgaaagggat ttataaacag 1200
atgcctggtt gctttaattt cctccggaaa aaacttttct ttaaaacatc ataaggccag 1260
ggcccctcac cctgccttat cttgcacccc caaagctttc ctgccccagg cctgaaagag 1320
gctgaggcct ggactttcct gcaactcaag gactttgcag ccggcacagg gtctgctctt 1380
tctctgccag tgacagacag gctcttagca gcttccagat tgacgacaag tgctgaacag 1440
tggaggaaga gggacagatg aatgccgtgg attgcacgtg g                      1481
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<210> 353
<211> 521
<212> PRT
<213> Homo sapiens

<220>
<223> Caspase-10 precursor C14.011

<400> 353

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Met Lys Ser Gln Gly Gln His Trp Tyr Ser Ser Ser Asp Lys Asn Cys
 1               5                  10                  15
Lys Val Ser Phe Arg Glu Lys Leu Leu Ile Ile Asp Ser Asn Leu Gly
            20                  25                  30
Val Gln Asp Val Glu Asn Leu Lys Phe Leu Cys Ile Gly Leu Val Pro
        35                  40                  45
Asn Lys Lys Leu Glu Lys Ser Ser Ser Ala Ser Asp Val Phe Glu His
    50                  55                  60
Leu Leu Ala Glu Asp Leu Leu Ser Glu Glu Asp Pro Phe Phe Leu Ala
65                  70                  75                  80
Glu Leu Leu Tyr Ile Ile Arg Gln Lys Lys Leu Leu Gln His Leu Asn
                85                  90                  95
Cys Thr Lys Glu Glu Val Glu Arg Leu Leu Pro Thr Arg Gln Arg Val
            100                 105                 110
Ser Leu Phe Arg Asn Leu Leu Tyr Glu Leu Ser Glu Gly Ile Asp Ser
        115                 120                 125
Glu Asn Leu Lys Asp Met Ile Phe Leu Leu Lys Asp Ser Leu Pro Lys
    130                 135                 140
Thr Glu Met Thr Ser Leu Ser Phe Leu Ala Phe Leu Glu Lys Gln Gly
145                 150                 155                 160
Lys Ile Asp Glu Asp Asn Leu Thr Cys Leu Glu Asp Leu Cys Lys Thr
                165                 170                 175
Val Val Pro Lys Leu Leu Arg Asn Ile Glu Lys Tyr Lys Arg Glu Lys
```

```
            180                 185                 190
Ala Ile Gln Ile Val Thr Pro Pro Val Asp Lys Glu Ala Glu Ser Tyr
        195                 200                 205
Gln Gly Glu Glu Glu Leu Val Ser Gln Thr Asp Val Lys Thr Phe Leu
    210                 215                 220
Glu Ala Leu Pro Gln Glu Ser Trp Gln Asn Lys His Ala Gly Ser Asn
225                 230                 235                 240
Gly Asn Arg Ala Thr Asn Gly Ala Pro Ser Leu Val Ser Arg Gly Met
                245                 250                 255
Gln Gly Ala Ser Ala Asn Thr Leu Asn Ser Glu Thr Ser Thr Lys Arg
            260                 265                 270
Ala Ala Val Tyr Arg Met Asn Arg Asn His Arg Gly Leu Cys Val Ile

        275                 280                 285
Val Asn Asn His Ser Phe Thr Ser Leu Lys Asp Arg Gln Gly Thr His
    290                 295                 300
Lys Asp Ala Glu Ile Leu Ser His Val Phe Gln Trp Leu Gly Phe Thr
305                 310                 315                 320
Val His Ile His Asn Asn Val Thr Lys Val Glu Met Glu Met Val Leu
                325                 330                 335
Gln Lys Gln Lys Cys Asn Pro Ala His Ala Asp Gly Asp Cys Phe Val
            340                 345                 350
Phe Cys Ile Leu Thr His Gly Arg Phe Gly Ala Val Tyr Ser Ser Asp
        355                 360                 365
Glu Ala Leu Ile Pro Ile Arg Glu Ile Met Ser His Phe Thr Ala Leu
    370                 375                 380
Gln Cys Pro Arg Leu Ala Glu Lys Pro Lys Leu Phe Phe Ile Gln Ala
385                 390                 395                 400
Cys Gln Gly Glu Glu Ile Gln Pro Ser Val Ser Ile Glu Ala Asp Ala
                405                 410                 415
Leu Asn Pro Glu Gln Ala Pro Thr Ser Leu Gln Asp Ser Ile Pro Ala
            420                 425                 430
Glu Ala Asp Phe Leu Leu Gly Leu Ala Thr Val Pro Gly Tyr Val Ser
        435                 440                 445
Phe Arg His Val Glu Glu Gly Ser Trp Tyr Ile Gln Ser Leu Cys Asn
    450                 455                 460
His Leu Lys Lys Leu Val Pro Arg Met Leu Lys Phe Leu Glu Lys Thr
465                 470                 475                 480
Met Glu Ile Arg Gly Arg Lys Arg Thr Val Trp Gly Ala Lys Gln Ile
                485                 490                 495
Ser Ala Thr Ser Leu Pro Thr Ala Ile Ser Ala Gln Thr Pro Arg Pro
            500                 505                 510
Pro Met Arg Arg Trp Ser Ser Val Ser
        515                 520
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<210> 354
<211> 3536
<212> DNA
<213> Homo sapiens

<220>
<223> Caspase-10 precursor C14.011

<400> 354
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tggtggagct tgatctgaag gctggccatg aaatctcaag gtcaacattg gtattccagt 180
tcagataaaa actgtaaagt gagctttcgt gagaagcttc tgattattga ttcaaacctg 240
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ctggagaagt ccagctcagc ctcagatgtt tttgaacatc tcttggcaga ggatctgctg 360
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ctgcagcacc tcaactgtac caaagaggaa gtggagcgac tgctgcccac ccgacaaagg 480
gtttctctgt ttagaaacct gctctacgaa ctgtcagaag gcattgactc agagaactta 540
aaggacatga tcttccttct gaaagactcg cttcccaaaa ctgaaatgac ctccctaagt 600
ttcctggcat ttctagagaa acaaggtaaa atagatgaag ataatctgac atgcctggag 660
gacctctgca aaacagttgt acctaaactt ttgagaaaca tagagaaata caaaagagag 720
aaagctatcc agatagtgac acctcctgta gacaaggaag ccgagtcgta tcaaggagag 780
gaagaactag tttcccaaac agatgttaag acattcttgg aagccttacc gagggcagct 840
gtgtacagga tgaatcggaa ccacagaggc ctctgtgtca ttgtcaacaa ccacagcttt 900
acctccctga aggacagaca aggaacccat aaagatgctg agatcctgag tcatgtgttc 960
cagtggcttg ggttcacagt gcatatacac aataatgtga cgaaagtgga aatggagatg 1020
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attctgaccc atgggagatt tggagctgtc tactcttcgg atgaggccct cattcccatt 1140
cgggagatca tgtctcactt cacagccctg cagtgcccta gactggctga aaaacctaaa 1200
ctctttttca tccaggcctg ccaaggtgaa gagatacagc cttccgtatc catcgaagca 1260
gatgctctga accctgagca ggcacccact tccctgcagg acagtattcc tgccgaggct 1320
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ggcagctggt atattcagtc tctgtgtaat catctgaaga aattggtccc aagacatgaa 1440
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ggaacaaaga aacagatgcc ccagcctgct ttcacactaa ggaaaaaact agtattccct 1560
gtgcccctgg atgcactttc aatatagcag agagtttttg ttggttctta gacctcaaac 1620
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cagactggag tgcaggggggg caatcacggc tcactgtagt ctcgacctcc caggctcaag 1860
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ggtctatgcc aggcccattt cctgcttttg tgtaaggaag gtgctcacat aggaagtttt 2340
tatttggtta gagacaggtt tccctgtagg aagatgatgg ctcatttaca ctcagctgct 2400
ctgcaagcag aaactttaca acctgatgtc atattccatt ttggactggg tgcggtgact 2460
catgcctgta atcccagtac tctgggaagc caaggcaggc agatcacttg aggtcaggag 2520
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gttgccattg acagaacacc caattcaaat tgactgaagc aaagaaggga atttattgcc 2820
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aggcatgagg agagaggctg tgtcagaaac tgaagctgtt ctcaggatca ctgggctctt 3060
cttggcagag gggatgtctg gcttgcctga agggagtggc tctgtaagga cgccttgatg 3120
ctttcttcat taagattttg agcatttta cgtacttgag cttttttttt ttttttttc 3180
aatttctaga ggaacttttt ctctgttaat tcctggaact gtattttgaa tccttaaagg 3240
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gccaggtgaa ctggaatgcc ttggggcgtg gaagggcatt aggagtgttt catttgatat 3420
gtgaatgctc ataaaaaaat gtcaaggaat gaagaacaac aactctcagt ggtgcctgca 3480

tttataatta tttatgtgaa agtcaaattc atgtacagta aatttgttat aagaat 3536

<210> 355
<211> 373
<212> PRT
<213> Mus musculus

<220>
<223> Caspase-11 C14.012

<400> 355

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Met Ala Glu Asn Lys His Pro Asp Lys Pro Leu Lys Val Leu Glu Gln
 1               5                  10                  15
Leu Gly Lys Glu Val Leu Thr Glu Tyr Leu Glu Lys Leu Val Gln Ser
            20                  25                  30
Asn Val Leu Lys Leu Lys Glu Glu Asp Lys Gln Lys Phe Asn Asn Ala
        35                  40                  45
Glu Arg Ser Asp Lys Arg Trp Val Phe Val Asp Ala Met Lys Lys Lys
    50                  55                  60
His Ser Lys Val Gly Glu Met Leu Leu Gln Thr Phe Phe Ser Val Asp
65                  70                  75                  80
Pro Gly Ser His His Gly Glu Ala Asn Leu Glu Met Glu Glu Pro Glu
                85                  90                  95
Glu Ser Leu Asn Thr Leu Lys Leu Cys Ser Pro Glu Glu Phe Thr Arg
            100                 105                 110
Leu Cys Arg Glu Lys Thr Gln Glu Ile Tyr Pro Ile Lys Glu Ala Asn
        115                 120                 125
Gly Arg Thr Arg Lys Ala Leu Ile Ile Cys Asn Thr Glu Phe Lys His
    130                 135                 140
Leu Ser Leu Arg Tyr Gly Ala Lys Phe Asp Ile Ile Gly Met Lys Gly
145                 150                 155                 160
Leu Leu Glu Asp Leu Gly Tyr Asp Val Val Val Lys Glu Glu Leu Thr
                165                 170                 175
Ala Glu Gly Met Glu Ser Glu Met Lys Asp Phe Ala Ala Leu Ser Glu
            180                 185                 190
His Gln Thr Ser Asp Ser Thr Phe Leu Val Leu Met Ser His Gly Thr
        195                 200                 205
Leu His Gly Ile Cys Gly Thr Met His Ser Glu Lys Thr Pro Asp Val
    210                 215                 220
Leu Gln Tyr Asp Thr Ile Tyr Gln Ile Phe Asn Asn Cys His Cys Pro
225                 230                 235                 240
Gly Leu Arg Asp Lys Pro Lys Val Ile Ile Val Gln Ala Cys Arg Gly
                245                 250                 255
Gly Asn Ser Gly Glu Met Trp Ile Arg Glu Ser Ser Lys Pro Gln Leu
            260                 265                 270
Cys Arg Gly Val Asp Leu Pro Arg Asn Met Glu Ala Asp Ala Val Lys
        275                 280                 285
Leu Ser His Val Glu Lys Asp Phe Ile Ala Phe Tyr Ser Thr Thr Pro
    290                 295                 300
His His Leu Ser Tyr Arg Asp Lys Thr Gly Gly Ser Tyr Phe Ile Thr
305                 310                 315                 320
Arg Leu Ile Ser Cys Phe Arg Lys His Ala Cys Ser Cys His Leu Phe
                325                 330                 335
Asp Ile Phe Leu Lys Val Gln Gln Ser Phe Glu Lys Ala Ser Ile His
            340                 345                 350
```

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Ser Gln Met Pro Thr Ile Asp Arg Ala Thr Leu Thr Arg Tyr Phe Tyr
        355                 360                 365
Leu Phe Pro Gly Asn
    370
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<210> 356
<211> 1350
<212> DNA
<213> Mus musculus

<220>
<223> Caspase-11 C14.012

<400> 356

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accacttaag gtgttggaac agctgggcaa agaagtcctt acggagtacc tagaaaaatt 120
agtacaaagc aatgtactga aattaaagga ggaagataaa caaaaattta acaatgctga 180
acgcagtgac aagcgttggg tttttgtaga tgccatgaaa aagaaacaca gcaaagtagg 240
tgaaatgctt ctccagacat tcttcagtgt ggacccaggc agccaccatg gtgaagctaa 300
tctggaaatg gaggaaccag aagaatcatt gaacactctc aagctttgtt cccctgaaga 360
gttcacaagg ctttgcagag aaaagacaca agaaatttac ccaataaagg aggccaatgg 420
ccgtacacga aaggctctta tcatatgcaa tacagagttc aaacatctct cactgaggta 480
tggggctaaa tttgacatca ttggtatgaa aggccttctt gaagacttag gctacgatgt 540
ggtggtgaaa gaggagctta cagcagaggg catggagtca gagatgaaag actttgctgc 600
actctcagaa caccagacat cagacagcac attcctggtg ctaatgtctc atggcacact 660
gcatggcatt tgtggaacaa tgcacagtga aaaaactcca gatgtgctac agtatgatac 720
catctatcag atattcaaca attgccactg tccaggtcta cgagacaaac ccaaagtcat 780
cattgtgcag gcctgcagag gtgggaactc tggagaaatg tggatcagag agtcttcaaa 840
accccagttg tgcagaggtg tagatctacc taggaatatg gaagctgatg ctgtcaagct 900
gagccacgtg gagaaggact tcattgcctt ctactctaca accccacatc acttgtccta 960
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aagtattcat tcccagatgc ccaccattga tcgggcaacc ttgacaagat atttctacct 1140
ctttcctggc aactgagaac aaagcaacaa gcaactgaat ctcatttctt cagcttgaag 1200
aagtgatctt ggccaaggat cacattctat tcctgaaatt ccagaactag tgaaattaag 1260
gaaagaatac ttatgaattc aagaccagcc taagcaacac agtgggattc tgttccatag 1320
acaagcaaac aagcaaaaat aaaaaaaaaa                                  1350
```

<210> 357
<211> 419
<212> PRT
<213> Mus musculus

<220>
<223> Caspase-12 precursor
C14.013

<400> 357

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Met Ala Ala Arg Arg Thr His Glu Arg Asp Pro Ile Tyr Lys Ile Lys
 1               5                  10                  15
Gly Leu Ala Lys Asp Met Leu Asp Gly Val Phe Asp Asp Leu Val Glu
            20                  25                  30
Lys Asn Val Leu Asn Gly Asp Glu Leu Leu Lys Ile Gly Glu Ser Ala
        35                  40                  45
Ser Phe Ile Leu Asn Lys Ala Glu Asn Leu Val Glu Asn Phe Leu Glu
```

```
     50                  55                  60
Lys Thr Asp Met Ala Gly Lys Ile Phe Ala Gly His Ile Ala Asn Ser
65                  70                  75                  80
Gln Glu Gln Leu Ser Leu Gln Phe Ser Asn Asp Glu Asp Asp Gly Pro
                85                  90                  95
Gln Lys Ile Cys Thr Pro Ser Ser Pro Ser Glu Ser Lys Arg Lys Val
            100                 105                 110
Glu Asp Asp Glu Met Glu Val Asn Ala Gly Leu Ala His Glu Ser His
        115                 120                 125
Leu Met Leu Thr Ala Pro His Gly Leu Gln Ser Ser Glu Val Gln Asp
    130                 135                 140
Thr Leu Lys Leu Cys Pro Arg Asp Gln Phe Cys Lys Ile Lys Thr Glu
145                 150                 155                 160
Arg Ala Lys Glu Ile Tyr Pro Val Met Glu Lys Glu Gly Arg Thr Arg
                165                 170                 175
Leu Ala Leu Ile Ile Cys Asn Lys Lys Phe Asp Tyr Leu Phe Asp Arg
            180                 185                 190
Asp Asn Ala Asp Thr Asp Ile Leu Asn Met Gln Glu Leu Leu Glu Asn
        195                 200                 205
Leu Gly Tyr Ser Val Val Leu Lys Glu Asn Leu Thr Ala Gln Glu Met
    210                 215                 220
Glu Thr Glu Leu Met Gln Phe Ala Gly Arg Pro Glu His Gln Ser Ser
225                 230                 235                 240
Asp Ser Thr Phe Leu Val Phe Met Ser His Gly Ile Leu Glu Gly Ile
                245                 250                 255
Cys Gly Val Lys His Arg Asn Lys Lys Pro Asp Val Leu His Asp Asp
            260                 265                 270
Thr Ile Phe Lys Ile Phe Asn Asn Ser Asn Cys Arg Ser Leu Arg Asn
        275                 280                 285
Lys Pro Lys Ile Leu Ile Met Gln Ala Cys Arg Gly Arg Tyr Asn Gly
    290                 295                 300
Thr Ile Trp Val Ser Thr Asn Lys Gly Ile Ala Thr Ala Asp Thr Asp
305                 310                 315                 320
Glu Glu Arg Val Leu Ser Cys Lys Trp Asn Asn Ser Ile Thr Lys Ala
                325                 330                 335
His Val Glu Thr Asp Phe Ile Ala Phe Lys Ser Ser Thr Pro His Asn
            340                 345                 350
Ile Ser Trp Lys Val Gly Lys Thr Gly Ser Leu Phe Ile Ser Lys Leu
        355                 360                 365
Ile Asp Cys Phe Lys Lys Tyr Cys Trp Cys Tyr His Leu Glu Glu Ile
    370                 375                 380
Phe Arg Lys Val Gln His Ser Phe Glu Val Pro Gly Glu Leu Thr Gln
385                 390                 395                 400
Met Pro Thr Ile Glu Arg Val Ser Met Thr Arg Tyr Phe Tyr Leu Phe
                405                 410                 415
Pro Gly Asn
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<210> 358
<211> 2228
<212> DNA
<213> Mus musculus

<220>
<223> Caspase-12 precursor C14.013

<400> 358
ggcacgagcg gcacgagcgg cacgagcaca gccatggcgg ccaggaggac acatgaaaga 60
gatccaatct acaagatcaa aggtttggcc aaggacatgc tggatggggt ttttgatgac 120
ctggtggaga agaatgtttt aaatggagat gagttactca aaatagggga aagtgcgagt 180
ttcatcctga acaaggctga gaatctggtt gagaacttct tagagaaaac agacatggca 240
ggaaaaatat ttgctggcca cattgccaat tcccaggaac agctgagttt acaattttct 300
aatgatgagg atgatggacc tcagaagata tgtacacctt cttctccatc agaatccaag 360
agaaaagtag aggatgatga aatggaggta aatgctggat tggcccatga atcacatcta 420
atgctgacag ctcctcatgg actccagagc tcagaagtcc aagatacact gaagctttgt 480
ccacgtgatc agttttgtaa gataaagaca gaaagggcaa aagagatata tccagtgatg 540
gagaaggagg gacgaacacg tctggctctc atcatctgca acaaaaagtt tgactacctt 600
tttgatagag ataatgctga tactgacatt ttgaacatgc aagaactact tgaaaatctt 660
ggatactctg tggtgttaaa ggaaaacctt acagctcagg aaatggagac agagttaatg 720
cagtttgctg gccgtccaga gcaccagtcc tcagacagca cattcctggt gtttatgtcc 780
catggcatcc tggaaggaat ctgtggggtg aagcaccgaa acaaaaagcc agatgttctt 840
catgatgaca ctatcttcaa aattttcaac aactctaact gtcggagtct gagaaacaaa 900
cccaagattc tcatcatgca ggcctgcaga ggcagatata atggaactat ttgggtatcc 960
acaaacaaag ggatagccac tgctgataca gatgaggaac gtgtgttgag ctgtaaatgg 1020
aataatagta taacaaaggc ccatgtggag acagatttca ttgctttcaa atcttctacc 1080
ccacataata tttcttggaa ggtaggcaag actggttccc tcttcatttc caaactcatt 1140
gactgcttca aaaagtactg ttggtgttat catttggagg aaatttttcg aaaggttcaa 1200
cactcatttg aggtcccagg tgaactgacc cagatgccca ctattgagag agtatccatg 1260
acacgctatt tctacctttt tcccgggaat tagcacaggc aactctcatg cagttcccag 1320
tcaagtattg ctgtagctga gaagaaaaga aaattccaag atcccaggat ttttaaatgt 1380
gtaaaacttt tcagttagat attttataca atatcataag gctagataat ttccataggt 1440
tatttttagg ggaaacctga tacgtaaaat tttgcatgaa aagtatagat tcgttccttc 1500
cttccaaatc tgctcatctt ttactttatt ttattaaatt tatatttgca cattttttgta 1560
aaatgaataa aggaaaaaga cactaaagaa catgtctgaa catatcctgg aacttcttct 1620
ttgtaaaatg aataaaggaa aaagacacta aagaacaaag atgatacacc ttttgatgaa 1680
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ataaagaggt ttatgtccac tgtttgtctc tggcatacat ggttttcatg cctagtggct 1860
acctaccatt cctttcaatc aatttcttag gatataattg acaaatttat gctatgttta 1920
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tatgtgatga agcccaccta ccactatttt tgtcatcttg aggatgttat atcattattt 2160
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aaaaaaaa 2228

<210> 359
<211> 339
<212> PRT
<213> Drosophila melanogaster

<220>
<223> Caspase precursor (insect)
C14.015

<400> 359
Met Asp Ala Thr Asn Asn Gly Glu Ser Ala Asp Gln Val Gly Ile Arg
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Val Gly Asn Pro Glu Gln Pro Asn Asp His Thr Asp Ala Leu Gly Ser
20 25 30
Val Gly Ser Gly Gly Ala Gly Ser Ser Gly Leu Val Ala Gly Ser Ser
35 40 45

```
His Pro Tyr Gly Ser Gly Ala Ile Gly Gln Leu Ala Asn Gly Tyr Ser
     50                  55                  60
Ser Pro Ser Ser Ser Tyr Arg Lys Asn Val Ala Lys Met Val Thr Asp
65                  70                  75                  80
Arg His Ala Ala Glu Tyr Asn Met Arg His Lys Asn Arg Gly Met Ala
                85                  90                  95
Leu Ile Phe Asn His Glu His Phe Glu Val Pro Thr Leu Lys Ser Arg
            100                 105                 110
Ala Gly Thr Asn Val Asp Cys Glu Asn Leu Thr Arg Val Leu Lys Gln
        115                 120                 125
Leu Asp Phe Glu Val Thr Val Tyr Lys Asp Cys Arg Tyr Lys Asp Ile
    130                 135                 140
Leu Arg Thr Ile Glu Tyr Ala Ala Ser Gln Asn His Ser Asp Ser Asp
145                 150                 155                 160
Cys Ile Leu Val Ala Ile Leu Ser His Gly Glu Met Gly Tyr Ile Tyr
                165                 170                 175
Ala Lys Asp Thr Gln Tyr Lys Leu Asp Asn Ile Trp Ser Phe Phe Thr
            180                 185                 190
Ala Asn His Cys Pro Ser Leu Ala Gly Lys Pro Lys Leu Phe Phe Ile
        195                 200                 205
Gln Ala Cys Gln Gly Asp Arg Leu Asp Gly Gly Val Thr Met Gln Arg
    210                 215                 220
Ser Gln Thr Glu Thr Asp Gly Asp Ser Ser Met Ser Tyr Lys Ile Pro
225                 230                 235                 240
Val His Ala Asp Phe Leu Ile Ala Tyr Ser Thr Val Pro Gly Phe Tyr
                245                 250                 255
Ser Trp Arg Asn Thr Thr Arg Gly Ser Trp Phe Met Gln Ser Leu Cys
            260                 265                 270
Ala Glu Leu Ala Ala Asn Gly Lys Arg Leu Asp Ile Leu Thr Leu Leu
        275                 280                 285
Thr Phe Val Cys Gln Arg Val Ala Val Asp Phe Glu Ser Cys Thr Pro
    290                 295                 300
Asp Thr Pro Glu Met His Gln Gln Lys Gln Ile Pro Cys Ile Thr Thr
305                 310                 315                 320
Met Leu Thr Arg Ile Leu Arg Phe Ser Asp Lys Gln Leu Ala Pro Ala

                325                 330                 335
Gly Arg Val
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<210> 360
<211> 1020
<212> DNA
<213> Drosophila melanogaster

<220>
<223> Caspase precursor (insect) C14.015

<400> 360
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agcggcctgg tcgcaggatc ctcgcatcct tacggcagcg gagccattgg gcagctggcc 180
aacgggtaca gctcaccctc gtccagctac cgaaagaatg tagccaaaat ggtcaccgac 240
cgccatgcag ccgagtacaa catgcgccac aagaaccgcg gaatggcact gatcttcaac 300
catgagcact tcgaggtgcc caccttgaag tcccgcgcgg gaaccaatgt ggactgcgag 360

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aatctgactc gggtgctcaa gcagctggac ttcgaagtga ccgtgtacaa ggactgccgc 420
tacaaggaca ttttgaggac aatcgagtat tcagcgtcgc agaatcacag cgatagtgat 480
tgcatcctgg tcgccatcct gtcgcacggc gagatgggct acatctacgc caaggacaca 540
cagtacaagc tggataacat ctggagcttc ttcacggcca atcactgccc ctcgctagcc 600
ggcaaaccca agttgttctt catacaggcc tgccagggcg acagattgga tggcggagtg 660
accatgcagc gttctcagac ggaaaccgat ggcgactcct cgatgagcta caagattcca 720
gtgcacgccg actttctgat cgcctactcg acggttcctg gattctattc gtggcgcaac 780
accacccgcg gcacgtggtt catgcagagc ctgtgcgccg aactggcggc caatggcaag 840
cggctggaca tcctgaccct gctcacattc gtgtgccagc gggtggccgt ggactttgag 900
tcctgcaccc cggacactcc ggagatgcac cagcagaagc agataccctg catcaccacc 960
atgctgacgc gcattctgcg tttcagcgac aagcagttgg ctccagccgg acgggtttga 1020
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<210> 361
<211> 323
<212> PRT
<213> Drosophila melanogaster

<220>
<223> Caspase-1 precursor (insect)
C14.016

<400> 361

```
Met Thr Asp Glu Cys Val Thr Arg Asn Tyr Gly Val Gly Ile Arg Ser
 1               5                  10                  15
Pro Asn Gly Ser Glu Asn Arg Gly Ser Phe Ile Met Ala Asp Asn Thr
            20                  25                  30
Asp Ala Lys Gly Cys Thr Pro Glu Ser Leu Val Val Gly Gly Ala Thr
        35                  40                  45
Ala Ala Ser Pro Leu Pro Ala Asn Lys Phe Val Ala Arg Met Pro Val
    50                  55                  60
Glu Arg Tyr Ala Ser Glu Tyr Asn Met Ser His Lys His Arg Gly Val
65                  70                  75                  80
Ala Leu Ile Phe Asn His Glu Phe Phe Asp Ile Pro Ser Leu Lys Ser
                85                  90                  95
Arg Thr Gly Thr Asn Val Asp Ala Gln Glu Leu Lys Lys Ala Phe Glu
            100                 105                 110
Asn Leu Gly Phe Ala Val Ser Val His Lys Asp Cys Lys Leu Arg Asp
        115                 120                 125
Ile Leu Lys His Val Gly Lys Ala Ala Glu Leu Asp His Thr Asp Asn
    130                 135                 140
Asp Cys Leu Ala Val Ala Ile Leu Ser His Gly Glu His Gly Tyr Leu
145                 150                 155                 160
Tyr Ala Lys Asp Thr Gln Tyr Lys Leu Asp Asn Ile Trp His Tyr Phe
                165                 170                 175
Thr Ala Thr Phe Cys Pro Ser Leu Ala Gly Lys Pro Lys Leu Phe Phe
            180                 185                 190
Ile Gln Ala Cys Gln Gly Asp Arg Leu Asp Gly Gly Ile Thr Leu Glu
        195                 200                 205
Lys Gly Val Thr Glu Thr Asp Gly Glu Ser Ser Thr Ser Tyr Lys Ile
    210                 215                 220
Pro Ile His Ala Asp Phe Leu Phe Ser Tyr Ser Thr Ile Pro Gly Tyr
225                 230                 235                 240
Phe Ser Trp Arg Asn Ile Asn Asn Gly Ser Trp Tyr Met Gln Ser Leu
                245                 250                 255
Ile Arg Glu Leu Asn Ala Asn Gly Lys Lys Tyr Asp Leu Leu Thr Leu
            260                 265                 270
```

```
Leu Thr Phe Val Asn Gln Arg Val Ala Leu Asp Phe Glu Ser Asn Val
        275                 280                 285
Pro Ala Thr Pro Met Met Asp Arg Gln Lys Gln Ile Pro Cys Leu Thr
    290                 295                 300
Ser Met Leu Thr Arg Ile Leu Arg Phe Gly Asp Lys Pro Asn Gly Asn
305                 310                 315                 320
Lys Ala Gly
```

<210> 362
<211> 1757
<212> DNA
<213> Drosophila melanogaster

<220>
<223> Caspase-1 precursor (insect) C14.016

<400> 362

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cgactgtgag ccataaaagg acattcgctc gatcgaaagc cgacaaaagc tggctgagaa 120
gcgcaaaaca gctgcgctgc gcaaagtttg gccaacgcag agcaatagaa aacagaagca 180
gtgtcagaat aaaacaagaa tcagaccaaa aagggcgcaa caactgcgga gagagaaaag 240
gaaggaaaga gcagcgcgtg acgagggagg agcaggaggg agcgaacaaa aggcaagagg 300
aaacacaagg agaaacgcaa acaatcaaaa caagaactta agcaagaaaa ggggcgcaag 360
atgaccgacg agtgcgtaac cagaaactac ggagtaggca ttcgcagccc aaatggatcg 420
gaaaatcggg gcagctttat aatggctgat aataccgatg ccaagggctg tacgccggag 480
tctcttgttg ttggtggtgc aactgcagcg agccccttgc cggccaacaa gtttgtggct 540
cgaatgcccg tggaacgata tgcaagcgaa tacaacatga gtcacaagca ccgcggagtt 600
gcgctgatct tcaaccacga attcttcgac ataccctcgc tgaagagccg caccggaaca 660
aatgtcgatg cccaagagct gaaaaaggcc tttgaaaacc tgggattcgc ggtgtccgtg 720
cacaaggact gcaagttgag ggacatcctg aagcacgtgg ggaaggccgc cgagttggac 780
cacacggaca acgactgcct tgcggtggcc atactctcgc acggggagca cggctacctg 840
tacgccaagg atacgcagta caagctggac aacatctggc actacttcac tgccaccttc 900
tgcccctcgc tggcgggcaa gccgaagctg ttcttcatcc aagcctgcca gggcgatcgc 960
ttggacggag gcatcactct ggagaagggc gttaccgaga cggacgggga gtcctcgacg 1020
agctacaaga tacccataca cgccgacttt ctcttctcct actcgaccat tccgggctac 1080
ttctcctggc gcaacatcaa caatggctcc tggtacatgc aatcgctgat ccgcgagctg 1140
aacgccaatg gcaaaaagta cgacctgctc accctgctta cattcgttaa ccagcgcgta 1200
gccctagact ttgagtcgaa cgtgcccgcc acaccgatga tggatcgcca gaagcaaata 1260
ccgtgcctca cctccatgct gacgcgcata ctgcgcttcg gcgacaagcc gaacggcaat 1320
aaggctggct aggaagagat ctcccttcga agaagaactt tcaacagagg ttgtacaacc 1380
atcgcccgca atcattcacg ttggattcca attcacttca agtttagttt tagctgacgc 1440
gtgcgattaa cccgatggat attgaagcac ccgactccct ttcattcatt cccctgcctt 1500
tcccatgccc atttcggcct tatcattgac gaaattcgtt acccatttac ccactagatg 1560
acttccgtat gcataagcga gaccttgcca atagaaaacc cacaaatttg agataagata 1620
atacaatgaa gatttataca tacatacata cttttatgta cacgcaaaca tttatatttg 1680
atatgaataa aaatgaatta aaaacataaa aaaaaaaaaa aaaaaaaaaa aaaaaacaaa 1740
aaaaaaaaaa aaaaaaa                                                1757
```

<210> 363
<211> 377
<212> PRT
<213> Bos taurus

<220>
<223> Caspase-13 precursor C14.017

<400> 363
Met Ala Glu Asp Lys His Asn Lys Asn Pro Leu Lys Met Leu Glu Ser
1 5 10 15
Leu Gly Lys Glu Leu Ile Ser Gly Leu Leu Asp Asp Phe Val Glu Lys
20 25 30
Asn Val Leu Lys Leu Glu Glu Glu Glu Lys Lys Lys Ile Tyr Asp Ala
35 40 45
Lys Leu Gln Asp Lys Ala Arg Val Leu Val Asp Ser Ile Arg Gln Lys
50 55 60
Asn Gln Glu Ala Gly Gln Val Phe Val Gln Thr Phe Leu Asn Ile Asp
65 70 75 80
Lys Asn Ser Thr Ser Ile Lys Ala Pro Glu Glu Thr Val Ala Gly Pro
85 90 95
Asp Glu Ser Val Gly Ser Ala Ala Thr Leu Lys Leu Cys Pro His Glu
100 105 110
Glu Phe Leu Lys Leu Cys Lys Glu Arg Ala Gly Glu Ile Tyr Pro Ile
115 120 125
Lys Glu Arg Lys Asp Arg Thr Arg Leu Ala Leu Ile Ile Cys Asn Thr
130 135 140
Glu Phe Asp His Met Pro Pro Arg Asn Gly Ala Ala Leu Asp Ile Leu
145 150 155 160
Gly Met Lys Gln Leu Leu Glu Gly Leu Gly Tyr Thr Val Glu Val Glu
165 170 175
Glu Lys Leu Thr Ala Arg Asp Met Glu Ser Val Leu Trp Lys Phe Ala
180 185 190
Ala Arg Glu Glu His Lys Ser Ser Asp Ser Thr Phe Leu Val Phe Met
195 200 205
Ser His Gly Ile Leu Asp Gly Ile Cys Gly Thr Met His Ser Glu Glu
210 215 220
Glu Pro Asp Val Leu Pro Tyr Asp Thr Ile Phe Arg Thr Phe Asn Asn
225 230 235 240
Arg Asn Cys Leu Ser Leu Lys Asp Lys Pro Lys Val Ile Ile Val Gln
245 250 255
Ala Cys Arg Gly Ala Asn Arg Gly Glu Leu Trp Val Ser Asp Ser Pro
260 265 270
Pro Ala Leu Ala Asp Ser Phe Ser Gln Ser Ser Glu Asn Leu Glu Glu
275 280 285
Asp Ala Val Tyr Lys Thr His Val Glu Lys Asp Phe Ile Ala Phe Cys
290 295 300
Ser Ser Thr Pro His Asn Val Ser Trp Arg Asp Ile Lys Lys Gly Ser
305 310 315 320
Leu Phe Ile Thr Arg Leu Ile Thr Cys Phe Gln Lys Tyr Ala Trp Cys
325 330 335
Cys His Leu Glu Glu Val Phe Arg Lys Val Gln Gln Ser Phe Glu Lys
340 345 350
Pro Asn Val Lys Ala Gln Met Pro Thr Val Glu Arg Leu Ser Met Thr
355 360 365
Arg Tyr Phe Tyr Leu Phe Pro Gly Asn
370 375

<210> 364
<211> 2060
<212> DNA

<213> Homo sapiens

<220>
<223> Caspase-13 precursor C14.017

<400> 364
ccacgcgtcc gcggacgcgt gggctccttc aaggcagtag gaagatacta agcttattat 60
ctatggctga agacaaacac aacaaaaacc cacttaagat gttggaatct ttgggcaaag 120
aactcatttc tggccttttg gatgactttg tggaaaaaaa tgtcctgaaa ttggaggaag 180
aggagaagaa aaaaatttat gatgccaaac ttcaagacaa agcccgggtc ttggttgatt 240
ctatacgaca gaaaaaccaa gaggcaggtc aagtctttgt tcaaactttc ctaaacatag 300
acaaaaattc caccagtata aaagctcctg aggaaactgt ggctggacca gatgagtcag 360
tgggatctgc agctaccctc aagctttgcc ctcatgaaga attcctgaaa ctgtgtaaag 420
aaagggctgg agagatctat ccaataaagg agagaaagga ccgcactcgt ctggctctca 480
tcatatgcaa cacagagttt gatcatatgc ctcccaggaa tggggctgcc cttgacatcc 540
ttggaatgaa gcagctgctt gagggtcttg gctacactgt ggaagtggaa gagaaactca 600
cagccaggga catggaatca gtgctgtgga aatttgctgc acgtgaagag cacaaatcct 660
cagacagtac attcttggtg ttcatgtctc atggcatcct ggatgggatc tgtgggacta 720
tgcacagtga ggaagaacca gatgtgttac cttatgatac catcttccgg acattcaaca 780
accgtaattg cctcagtcta aaggacaaac ctaaagtcat cattgtccag gcctgcagag 840
gtgcaaatcg tggggaattg tgggtcagtg actctccacc agccttggca gacagctttt 900
cacagtcatc cgagaacctg gaagaggatg ctgtttacaa gacccatgta gagaaggact 960
tcattgcttt ctgttcctca actccacata atgtgtcctg gagagacata aaaaaaggtt 1020
ctctcttcat tacacgactc atcacatgct tccaaaaata tgcttggtgc tgtcatcttg 1080
aggaagtatt taggaaggta caacaatcat ttgaaaaacc aaatgttaaa gcccagatgc 1140
ccactgttga acgactctct atgacaagat atttctacct ctttcctggc aactgaaaat 1200

aaaaatcaca ggaaattcaa ccatttatca gcttcaagaa gcatttttat cagcacagca 1260
tccatgttta acctttttgtc tttcattaaa gtgaaaacat atgaactgtt ctttggggtc 1320
ctctaagaaa gaatagaatt tcaattaaaa caatggatgg atggaaataa agtagaagaa 1380
gaaaactgga ttttcttgtt atattgcata taatgcctgc actttactga gtgaagagaa 1440
ctagtcatga cttgccctca gcagcagggt gaaaggagat ggtgcacatc tggagacaag 1500
gaccaaaaac tgggtcacct gctcctttga tcactcatca aaccttgcaa ctagaattat 1560
ttggaagaat atttctaatt tattatttaa ccaacatcat aggtcaagtt caatttttt 1620
tcagaaagtt gttatggtac ctatgcatct ttcttcttat ccataaatta atttgctttc 1680
ttgttgatga tttttcattc cagatttcca agcttcagga aaattttgtt atttagcaaa 1740
cacttggtaa ttgtctaaaa taaattgggc ctttgattta agatggtata attgggtgtg 1800
cttgtataga aagacagaca ttattagata cagaacatcc aagagtgtgg gaaatgtcag 1860
caatgggaaa gaaaatgtta aattttctgg aaagtgaatg tcagtagagg aattttagca 1920
acatggccat ctgagccact gactaaggag atgtaccact tcaattacat acatgcagaa 1980
tgctgaatag atatatcagg acatgctgaa ctgtattaca aataaaatga ttctctagat 2040
atcaaaaaaa aaaaaaaaaa 2060

<210> 365
<211> 242
<212> PRT
<213> Homo sapiens

<220>
<223> Caspase-14 precursor C14.018

<400> 365
Met Ser Asn Pro Arg Ser Leu Glu Glu Glu Lys Tyr Asp Met Ser Gly
 1 5 10 15
Ala Arg Leu Ala Leu Ile Leu Cys Val Thr Lys Ala Arg Glu Gly Ser
 20 25 30

```
Glu Glu Asp Leu Asp Ala Leu Glu His Met Phe Arg Gln Leu Arg Phe
        35                  40                  45
Glu Ser Thr Met Lys Arg Asp Pro Thr Ala Glu Gln Phe Gln Glu Glu
    50                  55                  60
Leu Glu Lys Phe Gln Gln Ala Ile Asp Ser Arg Glu Asp Pro Val Ser
65                  70                  75                  80
Cys Ala Phe Val Val Leu Met Ala His Gly Arg Glu Gly Phe Leu Lys
                85                  90                  95
Gly Glu Asp Gly Glu Met Val Lys Leu Glu Asn Leu Phe Glu Ala Leu
            100                 105                 110
Asn Asn Lys Asn Cys Gln Ala Leu Arg Ala Lys Pro Lys Val Tyr Ile
        115                 120                 125
Ile Gln Ala Cys Arg Gly Glu Gln Arg Asp Pro Gly Glu Thr Val Gly
    130                 135                 140
Gly Asp Glu Ile Val Met Val Ile Lys Asp Ser Pro Gln Thr Ile Pro
145                 150                 155                 160
Thr Tyr Thr Asp Ala Leu His Val Tyr Ser Thr Val Glu Gly Tyr Ile
                165                 170                 175
Ala Tyr Arg His Asp Gln Lys Gly Ser Cys Phe Ile Gln Thr Leu Val
            180                 185                 190
Asp Val Phe Thr Lys Arg Lys Gly His Ile Leu Glu Leu Leu Thr Glu
        195                 200                 205
Val Thr Arg Arg Met Ala Glu Ala Glu Leu Val Gln Glu Gly Lys Ala
    210                 215                 220
Arg Lys Thr Asn Pro Glu Ile Gln Ser Thr Leu Arg Lys Arg Leu Tyr
225                 230                 235                 240
Leu Gln
```

<210> 366
<211> 777
<212> DNA
<213> Homo sapiens

<220>
<223> Caspase-14 precursor C14.018

<400> 366
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aggatcagac aagggtgctg agagccggga ctcacaacca aaggagaaat gagcaatccg 60
cggtctttgg aagaggagaa atatgatatg tcaggtgccc gcctggccct aatactgtgt 120
gtcaccaaag cccgggaagg ttccgaagaa gacctggatg ctctggaaca catgtttcgg 180
cagctgagat tcgaaagcac catgaaaaga gaccccactg ccgagcaatt ccaggaagag 240
ctggaaaaat tccagcaggc catcgattcc cgggaagatc ccgtcagttg tgccttcgtg 300
gtactcatgg ctcacgggag ggaaggcttc ctcaagggag aagatgggga gatggtcaag 360
ctggagaatc tcttcgaggc cctgaacaac aagaactgcc aggccctgcg agctaagccc 420
aaggtgtaca tcatacaggc ctgtcgagga gaacaaaggg accccggtga aacagtaggt 480
ggagatgaga ttgtgatggt catcaaagac agcccacaaa ccatcccaac atacacagat 540
gccttgcacg tttattccac ggtagaggga tacatcgcct accgacatga tcagaaaggc 600
tcatgcttta tccagaccct ggtggatgtg ttcacgaaga ggaaaggaca tatcttggaa 660
cttctgacag aggtgacccg gcggatggca gaagcagagc tggttcaaga aggaaaagca 720
aggaaaacga accctgaaat ccaaagcacc ctccggaaac ggctgtatct gcagtag    777
```

<210> 367
<211> 450
<212> PRT

<213> Drosophila melanogaster

<220>
<223> Caspase Nc precursor
C14.019

<400> 367

```
Met Gln Pro Pro Glu Leu Glu Ile Gly Met Pro Lys Arg His Arg Glu
 1               5                  10                  15
His Ile Arg Lys Asn Leu Asn Ile Leu Val Glu Trp Thr Asn Tyr Glu
            20                  25                  30
Arg Leu Ala Met Glu Cys Val Gln Gln Gly Ile Leu Thr Val Gln Met
        35                  40                  45
Leu Arg Asn Thr Gln Asp Leu Asn Gly Lys Pro Phe Asn Met Asp Glu
    50                  55                  60
Lys Asp Val Arg Val Glu Gln His Arg Arg Leu Leu Leu Lys Ile Thr
65                  70                  75                  80
Gln Arg Gly Pro Thr Ala Tyr Asn Leu Leu Ile Asn Ala Leu Arg Asn
                85                  90                  95
Ile Asn Cys Leu Asp Ala Ala Val Leu Leu Glu Ser Val Asp Glu Ser
            100                 105                 110
Asp Ser Arg Pro Pro Phe Ile Ser Leu Asn Glu Arg Arg Thr Ser Arg
        115                 120                 125
Lys Ser Ala Asp Ile Val Asp Thr Pro Ser Pro Glu Ala Ser Glu Gly
    130                 135                 140
Pro Cys Val Ser Lys Leu Arg Asn Glu Pro Leu Gly Ala Leu Thr Pro
145                 150                 155                 160
Tyr Val Gly Val Val Asp Gly Pro Glu Val Lys Lys Ser Lys Lys Ile
                165                 170                 175
His Gly Gly Asp Ser Ala Ile Leu Gly Thr Tyr Lys Met Gln Ser Arg
            180                 185                 190
Phe Asn Arg Gly Val Leu Leu Met Val Asn Ile Met Asp Tyr Pro Asp
        195                 200                 205
Gln Asn Arg Arg Arg Ile Gly Ala Glu Lys Asp Ser Lys Ser Leu Ile
    210                 215                 220
His Leu Phe Gln Glu Leu Asn Phe Thr Ile Phe Pro Tyr Gly Asn Val
225                 230                 235                 240
Asn Gln Asp Gln Phe Phe Lys Leu Leu Thr Met Val Thr Ser Ser Ser
                245                 250                 255
Tyr Val Gln Asn Thr Glu Cys Phe Val Met Val Leu Met Thr His Gly
            260                 265                 270
Asn Ser Val Glu Gly Lys Glu Lys Val Glu Phe Cys Asp Gly Ser Val
        275                 280                 285
Val Asp Met Gln Lys Ile Lys Asp His Phe Gln Thr Ala Lys Cys Pro
    290                 295                 300
Tyr Leu Val Asn Lys Pro Lys Val Leu Met Phe Pro Phe Cys Arg Gly
305                 310                 315                 320
Asp Glu Tyr Asp Leu Gly His Pro Lys Asn Gln Gly Asn Leu Met Glu
                325                 330                 335
Pro Val Tyr Thr Ala Gln Glu Glu Lys Trp Pro Asp Thr Gln Thr Glu
            340                 345                 350
Gly Ile Pro Ser Pro Ser Thr Asn Val Pro Ser Leu Ala Asp Thr Leu
        355                 360                 365
Val Cys Tyr Ala Asn Thr Pro Gly Tyr Val Thr His Arg Asp Leu Asp
    370                 375                 380
Thr Gly Ser Trp Tyr Ile Gln Lys Phe Cys Gln Val Met Ala Asp His
385                 390                 395                 400
```

```
Ala His Asp Thr Asp Leu Glu Asp Ile Leu Lys Lys Thr Ser Glu Ala
                405                 410                 415
Val Gly Asn Lys Arg Thr Lys Lys Gly Ser Met Gln Thr Gly Ala Tyr
            420                 425                 430
Asp Asn Leu Gly Phe Asn Lys Lys Leu Tyr Phe Asn Pro Gly Phe Phe
        435                 440                 445
Asn Glu
    450
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<210> 368
<211> 2090
<212> DNA
<213> Drosophila melanogaster

<220>
<223> Caspase Nc precursor C14.019

<400> 368

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cccgatcctt gctaggatca tctagtgcaa tatatagact agttaattta cttttggaaa 120
aataaggaca ccagcagggc cgccgatttg tgccccttc ttgaaagtcg caaaacaaaa 180
acaacgacga caacaacaaa gcggagacaa agaatcgaca agtagcgata aacgaaatca 240
ttcccgggaa aaccttggag acgggtgatt cactgccaat accactgcca attggagact 300
gatcacggca gccatccttg gcgcgcccaa taagcggagt caccggaacg cgtggaagcc 360
atatccggaa tgcagccgcc ggagctcgag attggaatgc cgaagaggca tcgcgagcat 420
atacgcaaga atctgaatat actggttgaa tggacgaact acgagcgtct ggccatggag 480
tgcgtgcaac agggcatcct aaccgttcag atgctaagaa atacgcagga tctcaatggc 540
aagccattca acatggacga gaaggatgtg cgtgtggagc agcatcgtag gctcctattg 600
aagatcaccc agcgtggtcc caccgcctat aacctgctga tcaatgcact gcgcaatatc 660
aattgtctgg atgcggccgt tctattggaa tccgtcgatg agtccgattc aaggccaccc 720
tttatctcgc taaacgaacg gagaaccagc cggaagtcgg ccgatattgt ggacacaccc 780
tcacccgaag cctccgaagg accctgcgtt agcaagctcc ggaatgagcc gctgggagca 840
ctcacccctt atgtgggtgt cgttgacggt cccgaggtaa aaaaatcgaa aaagatacat 900
ggtggggata gtgccatatt gggcacatat aagatgcaat cacgtttcaa ccgaggcgtt 960
ttgctaatgg ttaacataat ggactatccg gatcaaaacc gtcgacggat cggagccgaa 1020
aaggacagca agtcgttgat acacttgttt caagaactga attttacgat tttcccctat 1080
gggaacgtga atcaggatca gttctttaaa cttctgacaa tggtgacctc ctcgtcgtat 1140
gtgcagaata ccgagtgttt cgtaatggta ctgatgacac acggcaacag tgtggaggga 1200
aaagagaagg tggagttttg cgatggatct gtggtcgata tgcagaagat caaggaccat 1260
ttccagacgg ccaaatgtcc ttatttggtg aacaagccga aggtgcttat gtttcccttt 1320
tgccgcggcg atgaatatga tttgggccat ccaaagaatc aaggcaatct catggagcca 1380
gtgtatacgg cgcaagagga gaagtggcct gacacccaga cggagggcat acccagcccg 1440
agcaccaatg tgccaagtct tgccgacact ctggtctgct atgctaatac gccgggctat 1500
gttacccacc gcgatctcga cacgggcagc tggtacatcc agaagttttg ccaagtgatg 1560
gccgatcatg cccacgacac agaccttgag gatatcctaa agaagacgag cgaagccgtg 1620
ggtaataagc gcaccaagaa gggttccatg cagacaggtg cctatgataa tcttggcttt 1680
aataagaaac tctacttcaa tcccgggttt ttcaacgaat agttgccgcc actggacatt 1740
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ttttagatta tgtgttctgt gctcgcgtgc tataaaatgt ttatattgta acaaatactc 1860
attcaagtat tcttctaata cgtattgcat acctcattta aaggtacgaa attatgtaat 1920
ttatgtgata actgccagaa atctacaaat attataatac agagttccag tatatacaca 1980
gccagatttt tgaaatcgaa catttaggca aaatgtaaag caattttcca gtctgatttt 2040
tgagtgtgta cacttacaaa ataaacgatg atatttcaca aggcccaaag            2090
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<210> 369

<211> 824
<212> PRT
<213> Homo sapiens

<220>
<223> MALT lymphoma translocation protein 1
(paracaspase)
C14.026

<400> 369
Met Ser Leu Leu Gly Asp Pro Leu Gln Ala Leu Pro Pro Ser Ala Ala
1 5 10 15
Pro Thr Gly Pro Leu Leu Ala Pro Pro Ala Gly Ala Thr Leu Asn Arg
20 25 30
Leu Arg Glu Pro Leu Leu Arg Arg Leu Ser Glu Leu Leu Asp Gln Ala
35 40 45
Pro Glu Gly Arg Gly Trp Arg Arg Leu Ala Glu Leu Ala Gly Ser Arg
50 55 60
Gly Arg Leu Arg Leu Ser Cys Leu Asp Leu Glu Gln Cys Ser Leu Lys
65 70 75 80
Val Leu Glu Pro Glu Gly Ser Pro Ser Leu Cys Leu Leu Lys Leu Met
85 90 95
Gly Glu Lys Gly Cys Thr Val Thr Glu Leu Ser Asp Phe Leu Gln Ala
100 105 110
Met Glu His Thr Glu Val Leu Gln Leu Leu Ser Pro Pro Gly Ile Lys
115 120 125
Ile Thr Val Asn Pro Glu Ser Lys Ala Val Leu Ala Gly Gln Phe Val
130 135 140
Lys Leu Cys Cys Arg Ala Thr Gly His Pro Phe Val Gln Tyr Gln Trp
145 150 155 160
Phe Lys Met Asn Lys Glu Ile Pro Asn Gly Asn Thr Ser Glu Leu Ile
165 170 175
Phe Asn Ala Val His Val Lys Asp Ala Gly Phe Tyr Val Cys Arg Val
180 185 190
Asn Asn Asn Phe Thr Phe Glu Phe Ser Gln Trp Ser Gln Leu Asp Val
195 200 205
Cys Asp Ile Pro Glu Ser Phe Gln Arg Ser Val Asp Gly Val Ser Glu
210 215 220
Ser Lys Leu Gln Ile Cys Val Glu Pro Thr Ser Gln Lys Leu Met Pro
225 230 235 240
Gly Ser Thr Leu Val Leu Gln Cys Val Ala Val Gly Ser Pro Ile Pro
245 250 255
His Tyr Gln Trp Phe Lys Asn Glu Leu Pro Leu Thr His Glu Thr Lys
260 265 270
Lys Leu Tyr Met Val Pro Tyr Val Asp Leu Glu His Gln Gly Thr Tyr
275 280 285
Trp Cys His Val Tyr Asn Asp Arg Asp Ser Gln Asp Ser Lys Lys Val
290 295 300
Glu Ile Ile Ile Gly Arg Thr Asp Glu Ala Val Glu Cys Thr Glu Asp
305 310 315 320
Glu Leu Asn Asn Leu Gly His Pro Asp Asn Lys Glu Gln Thr Thr Asp
325 330 335
Gln Pro Leu Ala Lys Asp Lys Val Ala Leu Leu Ile Gly Asn Met Asn
340 345 350
Tyr Arg Glu His Pro Lys Leu Lys Ala Pro Leu Val Asp Val Tyr Glu
355 360 365
Leu Thr Asn Leu Leu Arg Gln Leu Asp Phe Lys Val Val Ser Leu Leu

```
    370                 375                 380
Asp Leu Thr Glu Tyr Glu Met Arg Asn Ala Val Asp Glu Phe Leu Leu
385                 390                 395                 400
Leu Leu Asp Lys Gly Val Tyr Gly Leu Leu Tyr Tyr Ala Gly His Gly
                405                 410                 415
Tyr Glu Asn Phe Gly Asn Ser Phe Met Val Pro Val Asp Ala Pro Asn
            420                 425                 430
Pro Tyr Arg Ser Glu Asn Cys Leu Cys Val Gln Asn Ile Leu Lys Leu
        435                 440                 445
Met Gln Glu Lys Glu Thr Gly Leu Asn Val Phe Leu Leu Asp Met Cys
    450                 455                 460
Arg Lys Arg Asn Asp Tyr Asp Asp Thr Ile Pro Ile Leu Asp Ala Leu
465                 470                 475                 480
Lys Val Thr Ala Asn Ile Val Phe Gly Tyr Ala Thr Cys Gln Gly Ala
                485                 490                 495
Glu Ala Phe Glu Ile Gln His Ser Gly Leu Ala Asn Gly Ile Phe Met
            500                 505                 510
Lys Phe Leu Lys Asp Arg Leu Leu Glu Asp Lys Lys Ile Thr Val Leu
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545                 550                 555                 560
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Asn Leu Gln Trp Ala Lys Ala His Glu Leu Pro Glu Ser Met Cys Leu
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Lys Phe Asp Cys Gly Val Gln Ile Gln Leu Gly Phe Ala Ala Glu Phe
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Ser Asn Val Met Ile Ile Tyr Thr Ser Ile Val Tyr Lys Pro Pro Glu
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Ile Ile Met Cys Asp Ala Tyr Val Thr Asp Phe Pro Leu Asp Leu Asp
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Tyr Leu Val Ser Lys Asp Leu Pro Lys His Cys Leu Tyr Thr Arg Leu
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Ser Ser Leu Gln Lys Leu Lys Glu His Leu Val Phe Thr Val Cys Leu
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Ser Tyr Gln Tyr Ser Gly Leu Glu Asp Thr Val Glu Asp Lys Gln Glu
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Val Asn Val Gly Lys Pro Leu Ile Ala Lys Leu Asp Met His Arg Gly
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Tyr Gln Ser Ser Ala Ala Thr Ser Gly Gly Ala Gly His Tyr His Ser
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Leu Gln Asp Pro Phe His Gly Val Tyr His Ser His Pro Gly Asn Pro
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Ser Asn Val Thr Pro Ala Asp Ser Cys His Cys Ser Arg Thr Pro Asp
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Ala Phe Ile Ser Ser Phe Ala His His Ala Ser Cys His Phe Ser Arg
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<212> PRT
<213> Homo sapiens

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(c-FLIP)
C14.971

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35 40 45
Lys Leu Ser Val Gly Asp Leu Ala Glu Leu Leu Tyr Arg Val Arg Arg
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Phe Asp Leu Leu Lys Arg Ile Leu Lys Met Asp Arg Lys Ala Val Glu
65 70 75 80
Thr His Leu Leu Arg Asn Pro His Leu Val Ser Asp Tyr Arg Val Leu
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Ile Phe Leu Met Lys Asp Tyr Met Gly Arg Gly Lys Ile Ser Lys Glu
115 120 125
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Ser Leu Lys Asp Pro Ser Asn Asn Phe Arg Leu His Asn Gly Arg Ser
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Glu Glu Arg Tyr Lys Met Lys Ser Lys Pro Leu Gly Ile Cys Leu Ile
245 250 255
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260 265 270
Ser Leu Gly Tyr Glu Val Gln Lys Phe Leu His Leu Ser Met His Gly
275 280 285
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Tyr Asp Ser Phe Val Cys Val Leu Val Ser Arg Gly Gly Ser Gln Ser
305 310 315 320

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(c-FLIP) C14.971

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<220>

<223> PBR322

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<210> 378
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<212> PRT
<213> Artificial Sequence

<220>
<223> wildtype RCL sequence from P4-P1

<400> 378
Val Ser Ala Arg Met
1 5

<210> 379
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> mutant RCL sequence from P4-P1'

<400> 379
Arg Arg Ala Arg Met
1 5

<210> 380
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> RRARM mutagenic primer

<400> 380
ccacagctgt cataaggagg gccagaatgg cccccgagga gatc 44

<210> 381
<211> 18
<212> DNA
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<220>
<223> primer 535

<400> 381
cagctatcgc gattgcag 18

<210> 382
<211> 17

<212> DNA
<213> Artificial Sequence

<220>
<223> primer 5542

<400> 382
gtgcgcagcc atcccgg 17

<210> 383
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<221> variation
<222> 8
<223> n = a, g, c, or t

<220>
<221> variation
<222> 9
<223> n = a, g, c, or t

<220>
<221> variation
<222> 10
<223> s = g or c

<220>
<223> Primer TC30

<400> 383
gccctggnns gcggccatc 19

<210> 384
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<221> variation
<222> 8
<223> n = a, g, c, or t

<220>
<221> variation
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<220>
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<220>
<223> Primer TC155

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<210> 385
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<220>
<223> Primer 717

<400> 385
tttcagtgtg gccaaaag 18

<210> 386
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer 718

<400> 386
cagagtcttt tggccaca 18

<210> 387
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer 850

<400> 387
ggggtaccgc caccatgaga gccctgctgg cgcgc 35

<210> 388
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer 851

<400> 388
gctctagatc atcagagggc caggccattc tct 33

<210> 389
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> mutant P4-P1' RCL loop sequence

<400> 389
Pro Phe Gly Arg Ser
1 5

<210> 390
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> PFGRS mutagenesis primer

<400> 390
ccacagctgt cataccttc ggcagaagcg cccccgagga gatc 44

<210> 391
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> mature chymotrypsin

<400> 391
Cys Gly Val Pro Ala Ile His Pro Val Leu Ser Gly Leu Ser Arg Ile
1 5 10 15
Val Asn Gly Glu Asp Ala Val Pro Gly Ser Trp Pro Trp Gln Val Ser
20 25 30
Leu Gln Asp Lys Thr Gly Phe His Phe Cys Gly Gly Ser Leu Ile Ser
35 40 45
Glu Asp Trp Val Val Thr Ala Ala His Cys Gly Val Arg Thr Ser Asp
50 55 60
Val Val Val Ala Gly Glu Phe Asp Gln Gly Ser Asp Glu Glu Asn Ile
65 70 75 80
Gln Val Leu Lys Ile Ala Lys Val Phe Lys Asn Pro Lys Phe Ser Ile
85 90 95
Leu Thr Val Asn Asn Asp Ile Thr Leu Leu Lys Leu Ala Thr Pro Ala
100 105 110
Arg Phe Ser Gln Thr Val Ser Ala Val Cys Leu Pro Ser Ala Asp Asp

115 120 125
Asp Phe Pro Ala Gly Thr Leu Cys Ala Thr Thr Gly Trp Gly Lys Thr
130 135 140
Lys Tyr Asn Ala Asn Lys Thr Pro Asp Lys Leu Gln Gln Ala Ala Leu
145 150 155 160
Pro Leu Leu Ser Asn Ala Glu Cys Lys Lys Ser Trp Gly Arg Arg Ile
165 170 175
Thr Asp Val Met Ile Cys Ala Gly Ala Ser Gly Val Ser Ser Cys Met
180 185 190
Gly Asp Ser Gly Gly Pro Leu Val Cys Gln Lys Asp Gly Ala Trp Thr
195 200 205
Leu Val Gly Ile Val Ser Trp Gly Ser Asp Thr Cys Ser Thr Ser Ser
210 215 220
Pro Gly Val Tyr Ala Arg Val Thr Lys Leu Ile Pro Trp Val Gln Lys

225 230 235 240
Ile Leu Ala Ala Asn
245

<210> 392
<211> 10
<212> DNA
<213> Artificial Sequence

<220>
<223> AATTCTATGG

<400> 392
aattctatgg 10

<210> 393
<211> 10
<212> DNA
<213> Artificial Sequence

<220>
<223> tgcaccatag

<400> 393
tgcaccatag 10

<210> 394
<211> 13
<212> DNA
<213> Artificial Sequence

<220>
<223> ATGGAACCCTGAA

<400> 394
atggaaccct gaa 13

<210> 395
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> AGCTTCAGGGTTCCATCAC-

<400> 395
agcttcaggg ttccatcac 19

<210> 396
<211> 380
<212> PRT
<213> Artificial Sequence

<220>
<223> PAI-I with MET as cloned into pPAIST7HS

<400> 396
Met Val His His Pro Pro Ser Tyr Val Ala His Leu Ala Ser Asp Phe
1 5 10 15
Gly Val Arg Val Phe Gln Gln Val Ala Gln Ala Ser Lys Asp Arg Asn
20 25 30
Val Val Phe Ser Pro Tyr Gly Val Ala Ser Val Leu Ala Met Leu Gln
35 40 45
Leu Thr Thr Gly Gly Glu Thr Gln Gln Gln Ile Gln Ala Ala Met Gly
50 55 60
Phe Lys Ile Asp Asp Lys Gly Met Ala Pro Ala Leu Arg His Leu Tyr
65 70 75 80
Lys Glu Leu Met Gly Pro Trp Asn Lys Asp Glu Ile Ser Thr Thr Asp
85 90 95
Ala Ile Phe Val Gln Arg Asp Leu Lys Leu Val Gln Gly Phe Met Pro
100 105 110
His Phe Phe Arg Leu Phe Arg Ser Thr Val Lys Gln Val Asp Phe Ser
115 120 125
Glu Val Glu Arg Ala Arg Phe Ile Ile Asn Asp Trp Val Lys Thr His
130 135 140
Thr Lys Gly Met Ile Ser Asn Leu Leu Gly Lys Gly Ala Val Asp Gln
145 150 155 160
Leu Thr Arg Leu Val Leu Val Asn Ala Leu Tyr Phe Asn Gly Gln Trp
165 170 175
Lys Thr Pro Phe Pro Asp Ser Ser Thr His Arg Arg Leu Phe His Lys
180 185 190
Ser Asp Gly Ser Thr Val Ser Val Pro Met Met Ala Gln Thr Asn Lys
195 200 205
Phe Asn Tyr Thr Glu Phe Thr Thr Pro Asp Gly His Tyr Tyr Asp Ile
210 215 220
Leu Glu Leu Pro Tyr His Gly Asp Thr Leu Ser Met Phe Ile Ala Ala
225 230 235 240
Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala Leu Thr Asn Ile Leu Ser
245 250 255
Ala Gln Leu Ile Ser His Trp Lys Gly Asn Met Thr Arg Leu Pro Arg
260 265 270
Leu Leu Val Leu Pro Lys Phe Ser Leu Glu Thr Glu Val Asp Leu Arg
275 280 285
Lys Pro Leu Glu Asn Leu Gly Met Thr Asp Met Phe Arg Gln Phe Gln
290 295 300
Ala Asp Phe Thr Ser Leu Ser Asp Gln Glu Pro Leu His Val Ala Gln
305 310 315 320
Ala Leu Gln Lys Val Lys Ile Glu Val Asn Glu Ser Gly Thr Val Ala
325 330 335
Ser Ser Ser Thr Ala Val Ile Val Ser Ala Arg Met Ala Pro Glu Glu
340 345 350
Ile Ile Met Asp Arg Pro Phe Leu Phe Val Val Arg His Asn Pro Thr
355 360 365
Gly Thr Val Leu Phe Met Gly Gln Val Met Glu Pro
370 375 380

<210> 397
<211> 21
<212> PRT
<213> Artificial Sequence

<220>

<223> Manduca sexta serpin 1B RSL loop

<400> 397
Glu Gly Ala Glu Ala Ala Ala Ala Asn Ala Phe Gly Ile Val Pro Lys
 1   5   10   15
Ser Leu Ile Leu Tyr
            20

<210> 398
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Manduca sexta serpin 1K RSL loop

<400> 398
Glu Gly Ala Glu Ala Ala Ala Ala Asn Ala Phe Lys Ile Thr Thr Tyr
 1   5   10   15
Ser Phe His Phe Val
            20

<210> 399
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> 1-antichymotrypsin RSL loop

<400> 399
Glu Gly Thr Glu Ala Ser Ala Ala Thr Ala Val Lys Ile Thr Leu Leu
 1   5   10   15
Ser Ala Leu Val Glu
            20

<210> 400
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Antithrombin-III RSL loop

<400> 400
Glu Gly Ser Glu Ala Ala Ala Ser Thr Ala Val Val Ile Ala Gly Arg
 1   5   10   15
Ser Leu Asn Pro Asn
            20

<210> 401
<211> 21
<212> PRT

<213> Artificial Sequence

<220>
<223> PAI-II RSL loop

<400> 401
Glu Gly Thr Glu Ala Ala Ala Gly Thr Gly Gly Val Met Thr Gly Arg
 1   5   10   15
Thr Gly His Gly Gly
            20

<210> 402
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> 1-antitrypsin RSL loop

<400> 402
Lys Gly Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met
 1   5   10   15
Ser Ile Pro Pro Glu
            20

<210> 403
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> PAI-I RSL loop

<400> 403
Ser Gly Thr Val Ala Ser Ser Ser Thr Ala Val Ile Val Ser Ala Arg
 1   5   10   15
Met Ala Pro Glu Glu
            20

<210> 404
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> PAI-III RSL loop

<400> 404
Ser Gly Thr Arg Ala Ala Ala Ala Thr Gly Thr Ile Phe Thr Phe Arg
 1   5   10   15
Ser Ala Arg Leu Asn
            20

<210> 405
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Ovalbumin RSL loop

<400> 405
Ala Gly Arg Glu Val Val Gly Ser Ala Glu Ala Gly Val Asp Ala Ala
1 5 10 15
Ser Val Ser Glu Glu
20

<210> 406
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> TNF- alpha cleavage sequence

<400> 406
Ala Glu Ala Lys
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<210> 407
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> TNF-R1 cleavage sequence (1)

<400> 407
Glu Asn Val Lys
1

<210> 408
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> TNF-R1 cleavage sequence (2)

<400> 408
Gly Thr Glu Asp
1

<210> 409
<211> 4
<212> PRT

<213> Artificial Sequence

<220>
<223> TNF-R2 cleavage sequence (1)

<400> 409
Ser Pro Thr Arg
 1

<210> 410
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> TNF-R2 cleavage sequence (2)

<400> 410
Val Ser Thr Arg
 1

<210> 411
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> TNF-R2 cleavage sequence (3)

<400> 411
Ser Thr Ser Phe
 1

<210> 412
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> HER-2 cleavage sequence (1)

<400> 412
Lys Phe Pro Asp
 1

<210> 413
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> HER-2 cleavage sequence (2)

<400> 413
Ala Glu Gln Arg
1

<210> 414
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR cleavage sequence (1)

<400> 414
Lys Tyr Ala Asp
1

<210> 415
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR cleavage sequence (2)

<400> 415
Asn Gly Pro Lys
1

<210> 416
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> VEGFR-1 cleavage sequence (1)

<400> 416
Ser Ser Ala Tyr
1

<210> 417
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> VEGFR-1 cleavage sequence (2)

<400> 417
Gly Thr Ser Asp
1

<210> 418
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> VEGFR-2 cleavage sequence (1)

<400> 418
Ala Gln Glu Lys
1

<210> 419
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> VEGFR-2 cleavage sequence (2)

<400> 419
Arg Ile Asp Tyr
1

<210> 420
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C3 cleavage sequence (1)

<400> 420
Arg Glu Phe Lys
1

<210> 421
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C3 cleavage sequence (2)

<400> 421
Gly Leu Ala Arg
1

<210> 422
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C3 cleavage sequence (3)

<400> 422
Arg Leu Gly Arg
 1

<210> 423
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C3 cleavage sequence (4)

<400> 423
Ala Glu Gly Lys
 1

<210> 424
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C3 cleavage sequence (5)

<400> 424
Gln His Ala Arg
 1

<210> 425
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C3 cleavage sequence (6)

<400> 425
Leu Pro Ser Arg
 1

<210> 426
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C3 cleavage sequence (7)

<400> 426

Ser Leu Leu Arg
1

<210> 427
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C3 cleavage sequence (8)

<400> 427
Leu Gly Leu Ala
1

<210> 428
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C3 cleavage sequence (9)

<400> 428
Leu Ser Val Val
1

<210> 429
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C4 cleavage sequence (1)

<400> 429
His Arg Gly Arg
1

<210> 430
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C2 cleavage sequence (1)

<400> 430
Gly Ala Thr Arg
1

<210> 431

<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C2 cleavage sequence (2)

<400> 431

Ser Leu Gly Arg
 1

<210> 432
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> C2 cleavage sequence (3)

<400> 432
Val Phe Ala Lys
 1

<210> 433
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> urokinase plasminogen activator (uPA) preproprotein

<400> 433
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1   5   10   15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20   25   30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35   40   45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50   55   60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65   70   75   80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85   90   95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100   105   110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115   120   125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130   135   140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145   150   155   160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165   170   175

```
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 434
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR73 F173I; F30I (CHYM SYSTEM)

<400> 434

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
```

```
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Ile Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 435
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR81 L224A, I240V; L73A, I89V (CHYM SYSTEM)

<400> 435

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
```

```
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 436
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR1 L224P; L73P (CHYM SYSTEM)

<400> 436

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
```

```
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Pro
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 437
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR3 R378C; R217C (CHYM SYSTEM)

<400> 437

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Cys Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 438

<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR4 L312P; L155P (CHYM SYSTEM)

<400> 438
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
1 5 10 15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
20 25 30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
35 40 45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
50 55 60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65 70 75 80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
85 90 95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
100 105 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
115 120 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
130 135 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145 150 155 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
165 170 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
180 185 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
195 200 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
210 215 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225 230 235 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
245 250 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
260 265 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
275 280 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
290 295 300
Asp Tyr Leu Tyr Pro Glu Gln Pro Lys Met Thr Val Val Lys Leu Ile
305 310 315 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
325 330 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
340 345 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
355 360 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
370 375 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg

385 390 395 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
405 410

<210> 439
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR7 S226P, I240V, I298T; S75P, I89V, I138T (CHYM SYSTEM)

<400> 439
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
1 5 10 15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
20 25 30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
35 40 45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
50 55 60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65 70 75 80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
85 90 95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
100 105 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
115 120 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
130 135 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145 150 155 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
165 170 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
180 185 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
195 200 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
210 215 220
Asn Pro Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225 230 235 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
245 250 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
260 265 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
275 280 285
Phe Gly Thr Ser Cys Glu Thr Thr Gly Phe Gly Lys Glu Asn Ser Thr
290 295 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305 310 315 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
325 330 335

```
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 440
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR32 E294G; E137G (CHYM SYSTEM)

<400> 440

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
```

```
Phe Gly Thr Ser Cys Gly Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 441
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR36 R223G, L312P; R72G, L155P (CHYM SYSTEM)

<400> 441

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Gly Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
```

```
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Pro Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 442
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR37 G290D; G133D (CHYM SYSTEM)

<400> 442

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
```

```
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Asp Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 443
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR66 V317A; V160A (CHYM SYSTEM)

<400> 443

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
```

```
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Ala Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 444
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR24 V185D; V38D (CHYM SYSTEM)

<400> 444

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
```

```
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Asp Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 445
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> AR85 F289L, V317A; F132L, V160A (CHYM SYSTEM)

<400> 445

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
```

```
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
     50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu

                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Leu Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Ala Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 446
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF2 F173T, L224A, I240V; F30T, L73A, I189V (CHYM SYSTEM)

<400> 446
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
1 5 10 15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
20 25 30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
35 40 45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
50 55 60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65 70 75 80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
85 90 95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
100 105 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
115 120 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
130 135 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145 150 155 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Thr Ala Ala Ile
165 170 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
180 185 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
195 200 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
210 215 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225 230 235 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
245 250 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
260 265 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
275 280 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
290 295 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305 310 315 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
325 330 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
340 345 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
355 360 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
370 375 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385 390 395 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
405 410

<210> 447
<211> 411

<212> PRT
<213> Artificial Sequence

<220>
<223> ARF6 F173L, L224A, I240V; F30L, L73A, I189V (CHYM SYSTEM)

<400> 447
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
1 5 10 15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
20 25 30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
35 40 45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
50 55 60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65 70 75 80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
85 90 95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
100 105 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
115 120 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
130 135 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145 150 155 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Leu Ala Ala Ile
165 170 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
180 185 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
195 200 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
210 215 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225 230 235 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
245 250 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
260 265 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
275 280 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
290 295 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305 310 315 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
325 330 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
340 345 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
355 360 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
370 375 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385 390 395 400

```
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410


<210> 448
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF11 F173V, L224A, I240V; F30V, L73A, I189V  (CHYM SYSTEM)

<400> 448
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
```

```
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 449
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF17 F173G, L224A, I240V; F30G, L73A, I189V (CHYM SYSTEM)

<400> 449

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Gly Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
```

```
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410


<210> 450
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF16 F173L, L224A, I240V; F30L, L73A, I189V  (CHYM SYSTEM)

<400> 450
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125

His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Leu Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
```

```
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 451
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF33 L224A, I240V, L312V; L155V, L73A, I189V (CHYM SYSTEM)

<400> 451

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
```

```
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Val Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 452
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF35 F173M, L224A, I240V; F30M, L73A, I189V (CHYM SYSTEM)

<400> 452

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
```

```
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Met Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 453
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF36 L224A, L312M; L155M, L73A, I189V (CHYM SYSTEM)

<400> 453

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
```

```
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Met Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 454
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF37 F173M, L224A, I240V; F30M, L73A, I189V (CHYM SYSTEM)

<400> 454

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
```

```
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Met Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 455
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF43 F173L, L224A, I240V; F30L, L73A, I189V (CHYM SYSTEM)

<400> 455
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly

```
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Leu Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 456
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF47 F173V, L224A, I240V; F30V, L73A, I189V (CHYM SYSTEM)

<400> 456

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 457
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF48 F173L, L224A, I240V, L312M; F30L, L155M, L73A, I189V (CHYM SYSTEM)

<400> 457
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
1 5 10 15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
20 25 30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
35 40 45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
50 55 60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65 70 75 80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
85 90 95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
100 105 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
115 120 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
130 135 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145 150 155 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Leu Ala Ala Ile
165 170 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
180 185 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
195 200 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
210 215 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225 230 235 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
245 250 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
260 265 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
275 280 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
290 295 300
Asp Tyr Leu Tyr Pro Glu Gln Met Lys Met Thr Val Val Lys Leu Ile
305 310 315 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
325 330 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
340 345 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
355 360 365

```
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 458
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF103 F173L, L224A, I240V; F30L, L73A, I189V (CHYM SYSTEM)

<400> 458

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Leu Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
```

```
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410


<210> 459
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> ARF115 F173G, L224A, I240V, L312M; F30G, L155M, L73A, I189V  (CHYM SYSTEM)

<400> 459
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys

        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Gly Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Ala
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
```

```
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Met Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 460
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/Ia F164V; F21V (CHYM SYSTEM)

<400> 460

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Val Thr Thr Ile Glu Asn Gln Pro Trp Phe Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
```

```
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 461
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/Ib I167L; I24L (CHYM SYSTEM)

<400> 461

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Leu Glu Asn Gln Pro Trp Phe Ala Ala Ile
```

```
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 462
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/Ic F173V; F30V (CHYM SYSTEM)

<400> 462

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
```

```
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu

    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 463
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/Id F173L; F30L (CHYM SYSTEM)

<400> 463

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
```

```
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Leu Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 464
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/IIa F173V, Y209H; F30V, Y61aH (CHYM SYSTEM)

<400> 464

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
```

```
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
His Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 465
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/IIb F173V, K233E; F30V, K82E (CHYM SYSTEM)

<400> 465
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
1 5 10 15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
20 25 30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
35 40 45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
50 55 60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65 70 75 80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
85 90 95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
100 105 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
115 120 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
130 135 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145 150 155 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
165 170 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
180 185 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
195 200 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
210 215 220
Asn Ser Asn Thr Gln Gly Glu Met Glu Phe Glu Val Glu Asn Leu Ile
225 230 235 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
245 250 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
260 265 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
275 280 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
290 295 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305 310 315 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
325 330 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
340 345 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
355 360 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
370 375 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385 390 395 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
405 410

<210> 466
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/IIc F173V, K313T; F30V, K156T (CHYM SYSTEM)

<400> 466
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1   5   10   15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20   25   30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35   40   45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50   55   60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65   70   75   80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85   90   95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100   105   110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115   120   125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130   135   140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145   150   155   160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165   170   175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180   185   190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195   200   205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210   215   220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225   230   235   240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245   250   255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260   265   270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275   280   285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290   295   300
Asp Tyr Leu Tyr Pro Glu Gln Leu Thr Met Thr Val Val Lys Leu Ile
305   310   315   320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325   330   335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340   345   350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355   360   365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp

```
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 467
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/IIIa F173V, K233E, V316A; F30V, K82E, V159A
(CHYM SYSTEM)

<400> 467

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Glu Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Ala Val Lys Leu Ile
305                 310                 315                 320
```

```
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 468
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/IIIb F173V, K233E, T186A, V316A; F30V, K82E, 39A, V159A (CHYM SYSTEM)

<400> 468

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Ala Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Glu Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
```

```
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Ala Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 469
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/IIIc F173V, K233E, T315A, V316A; F30V, K82E, T158A, V159A (CHYM SYSTEM)

<400> 469

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1                5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
```

```
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Glu Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Ala Ala Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 470
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/IIId F173V, Y209H, K243E; F173V, Y61aH, K92E
(CHYM SYSTEM)

```
<400> 470
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
```

```
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
His Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val Glu Asn Leu Ile
225                 230                 235                 240
Leu His Glu Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 471
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/IVa F173V, K233E, V316A, G231E, I240V, K348E; F173V, K82E, V159A, E80G, I89V, K187E (CHYM SYSTEM)

<400> 471

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
```

```
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Gly Met Glu Phe Glu Val Glu Asn Leu Val

225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Ala Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Glu Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 472
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> uPA/IVb F173V, K233E, V316A, G231E, E235K, I240V,
K348E; F173V, K82E, V159A, E80G, E89K, I89V, K187E
(CHYM SYSTEM)

<400> 472

```
Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp Cys Leu Asn Gly
 1               5                  10                  15
```

```
Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile His Trp Cys Asn
            20                  25                  30
Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile Asp Lys Ser Lys
        35                  40                  45
Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly Lys Ala Ser Thr
    50                  55                  60
Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser Ala Thr Val Leu
65                  70                  75                  80
Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu Gln Leu Gly Leu
                85                  90                  95
Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg Arg Arg Pro Trp
            100                 105                 110
Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln Glu Cys Met Val
        115                 120                 125
His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro Pro Glu Glu Leu
    130                 135                 140
Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg Phe Lys Ile Ile
145                 150                 155                 160
Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp Val Ala Ala Ile
                165                 170                 175
Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val Cys Gly Gly Ser
            180                 185                 190
Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His Cys Phe Ile Asp
        195                 200                 205
Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly Arg Ser Arg Leu
    210                 215                 220
Asn Ser Asn Thr Gln Gly Gly Met Glu Phe Lys Val Glu Asn Leu Val
225                 230                 235                 240
Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His His Asn Asp Ile
                245                 250                 255
Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys Ala Gln Pro Ser
            260                 265                 270
Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr Asn Asp Pro Gln
        275                 280                 285
Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys Glu Asn Ser Thr
    290                 295                 300
Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Ala Val Lys Leu Ile
305                 310                 315                 320
Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly Ser Glu Val Thr
                325                 330                 335
Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Glu Thr Asp Ser Cys
            340                 345                 350
Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu Gln Gly Arg Met
        355                 360                 365
Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys Ala Leu Lys Asp
    370                 375                 380
Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu Pro Trp Ile Arg
385                 390                 395                 400
Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
                405                 410
```

<210> 473
<211> 299
<212> PRT
<213> Autographa californica nucleopolyhedrovirus

<220>
<223> P35 peptide

<400> 473
Met Cys Val Ile Phe Pro Val Glu Ile Asp Val Ser Gln Thr Ile Ile
 1   5   10   15
Arg Asp Cys Gln Val Asp Lys Gln Thr Arg Glu Leu Val Tyr Ile Asn
            20   25   30
Lys Ile Met Asn Thr Gln Leu Thr Lys Pro Val Leu Met Met Phe Asn
        35   40   45
Ile Ser Gly Pro Ile Arg Ser Val Thr Arg Lys Asn Asn Asn Leu Arg
    50   55   60
Asp Arg Ile Lys Ser Lys Val Asp Glu Gln Phe Asp Gln Leu Glu Arg
65   70   75   80
Asp Tyr Ser Asp Gln Met Asp Gly Phe His Asp Ser Ile Lys Tyr Phe
                85   90   95
Lys Asp Glu His Tyr Ser Val Ser Cys Gln Asn Gly Ser Val Leu Lys
            100   105   110
Ser Lys Phe Ala Lys Ile Leu Lys Ser His Asp Tyr Thr Asp Lys Lys
        115   120   125
Ser Ile Glu Ala Tyr Glu Lys Tyr Cys Leu Pro Lys Leu Val Asp Glu
    130   135   140
Arg Asn Asp Tyr Tyr Val Ala Val Cys Val Leu Lys Pro Gly Phe Glu
145   150   155   160
Asn Gly Ser Asn Gln Val Leu Ser Phe Glu Tyr Asn Pro Ile Gly Asn
                165   170   175
Lys Val Ile Val Pro Phe Ala His Glu Ile Asn Asp Thr Gly Leu Tyr
            180   185   190
Glu Tyr Asp Val Val Ala Tyr Val Asp Ser Val Gln Phe Asp Gly Glu
        195   200   205
Gln Phe Glu Glu Phe Val Gln Ser Leu Ile Leu Pro Ser Ser Phe Lys
    210   215   220
Asn Ser Glu Lys Val Leu Tyr Tyr Asn Glu Ala Ser Lys Asn Lys Ser
225   230   235   240
Met Ile Tyr Lys Ala Leu Glu Phe Thr Thr Glu Ser Ser Trp Gly Lys
                245   250   255
Ser Glu Lys Tyr Asn Trp Lys Ile Phe Cys Asn Gly Phe Ile Tyr Asp
            260   265   270
Lys Lys Ser Lys Val Leu Tyr Val Lys Leu His Asn Val Thr Ser Ala
        275   280   285
Leu Asn Lys Asn Val Ile Leu Asn Thr Ile Lys
    290   295

<210> 474
<211> 2105
<212> DNA
<213> Homo sapiens

<220>
<223> Full length u-PA

<400> 474
atgagagccc tgctggcgcg cctgcttctc tgcgtcctgg tcgtgagcga ctccaaaggc 60
agcaatgaac ttcatcaagt tccatcgaac tgtgactgtc taaatggagg aacatgtgtg 120
tccaacaagt acttctccaa cattcactgg tgcaactgcc caaagaaatt cggagggcag 180
cactggtgaa atagataagt caaaaacctg ctatgagggg aatggtcact tttaccgagg 240
aaaggccagc actgacacca gttgccggcc ctgcctgccc tggaactctg ccactgtcct 300

tcagcaaacg taccatgccc acagatctga tgctcttcag ctgggcctgg ggaaacataa 360
ttactgcagg aacccagaca accggaggcg accctggtgc tatgtgcagg tgggcctaaa 420
gccgcttgtc caagagtgca tggtgcatga ctgcgcagat ggaaaaaagc cctcctctcc 480
tccagaagaa ttaaaatttc agtgtggcca aaagactctg aggccccgct ttgagattat 540
tgggggagaa ttcaccacca tcgagaacca gccctggttt gcggccatct acaggaggca 600
ccgggggggc tctgtcacct acgtgtgtgg aggcagcctc atcagccctt gctgggtgat 660
cagcgccaca cactgcttca ttgattaccc aaagaaggag gactacatcg tctacctggg 720
tcgctcaagg cttaactcca acacgcaagg ggagatgaag tttgaggtgg aaaacctcat 780
cctacacaag gactacagcg ctgacacgct tgctcaccac aacgacattg ccttgctgaa 840
gatccgttcc aaggagggca ggtgtgcgca gccatcccgg actatacaga ccatctgcct 900
gccctcgatg tataacgatc cccagtttgg cacaagctgt gagatcactg gctttggaaa 960
agagaattct accgactatc tctatccgga gcagctgaaa atgactgttg tgaagctgat 1020
ttcccaccgg gagtgtcagc agccccacta ctacggctct gaagtcacca ccaaaatgct 1080
atgtgctgct gacccccaat ggaaaacaga ttcctgccag ggagactcag ggggacccct 1140
cgtctgttcc ctccaaggcc gcatgacttt gactggaatt gtgagctggg gccgtggatg 1200
tgccctgaag gacaagccag gcgtctacac gagagtctca cacttcttac cctggatccg 1260
cagtcacacc aaggaagaga atggcctggc cctctgaggg ttttcagtgt ggccaaaaga 1320
ctctgaggcc ccgctttaag attattgggg gagaattcac caccatcgag aaccagccct 1380
ggtttgcggc catctacagg aggcaccggg ggggctctgt cacctacgtg tgtggaggca 1440
gcctcatcag cccttgctgg gtgatcagcg ccacacactg cttcattgat tacccaaaga 1500
aggaggacta catcgtctac ctgggtcgct caaggcttaa ctccaacacg caaggggaga 1560
tgaagtttga ggtggaaaac ctcatcctac acaaggacta cagcgctgac acgcttgctc 1620
accacaacga cattgccttg ctgaagatcc gttccaagga gggcaggtgt gcgcagccat 1680
cccggactat acagaccatc tgcctgccct cgatgtataa cgatccccag tttggcacaa 1740
gctgtgagat cactggcttt ggaaaagaga attctaccga ctatctctat ccggagcagc 1800
tgaaaatgac tgttgtgaag ctgatttccc accgggagtg tcagcagccc cactactacg 1860
gctctgaagt caccaccaaa atgctatgtg ctgctgaccc ccaatggaaa acagattcct 1920
gccagggaga ctcaggggga cccctcgtct gttccctcca aggccgcatg actttgactg 1980
gaattgtgag ctggggccgt ggatgtgccc tgaaggacaa gccaggcgtc tacacgagag 2040
tctcacactt cttaccctgg atccgcagtc acaccaagga agagaatggc ctgccctctg 2100
agggt 2105

<210> 475
<211> 804
<212> DNA
<213> Homo sapiens

<220>
<223> uPA protease domain

<400> 475
tttcagtgtg gccaaaagac tctgaggccc cgctttaaga ttattggggg agaattcacc 60
accatcgaga accagccctg gtttgcggcc atctacagga ggcaccgggg gggctctgtc 120
acctacgtgt gtggaggcag cctcatcagc ccttgctggg tgatcagcgc cacacactgc 180
ttcattgatt acccaaagaa ggaggactac atcgtctacc tgggtcgctc aaggcttaac 240
tccaacacgc aaggggagat gaagtttgag gtggaaaacc tcatcctaca caaggactac 300
agcgctgaca cgcttgctca ccacaacgac attgccttgc tgaagatccg ttccaaggag 360
ggcaggtgtg cgcagccatc ccggactata cagaccatct gcctgccctc gatgtataac 420
gatccccagt ttggcacaag ctgtgagatc actggctttg gaaaagagaa ttctaccgac 480
tatctctatc cggagcagct gaaaatgact gttgtgaagc tgatttccca ccgggagtgt 540
cagcagcccc actactacgg ctctgaagtc accaccaaaa tgctatgtgc tgctgacccc 600
caatggaaaa cagattcctg ccagggagac tcaggggac ccctcgtctg ttccctccaa 660
ggccgcatga ctttgactgg aattgtgagc tggggccgtg gatgtgccct gaaggacaag 720
ccaggcgtct acacgagagt ctcacacttc ttaccctgga tccgcagtca caccaaggaa 780
gagaatggcc tgccctctga gggt 804

<210> 476

<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer UPAF1

<400> 476
atgagagccc tgctggcgcg cc 22

<210> 477
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer UPAF2

<400> 477
ggaaaagaga attctaccg 19

<210> 478
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 478
Ile Ala Gly Arg Ser Leu
1 5

<210> 479
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 479
Ser Leu Gly Arg Lys Ile
1 5

<210> 480
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 480
Val Leu Lys Asp

1

<210> 481
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 481
Leu Val Glu Asp
1

<210> 482
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 482
Trp Phe Lys Asp
1

<210> 483
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 483
Arg Ile Tyr Asp
1

<210> 484
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 484
Lys Val Gly Arg
1

<210> 485
<211> 4

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 485
Arg Val Arg Lys
 1

<210> 486
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 486
Arg Lys Thr Lys
 1

<210> 487
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 487
Lys Thr Lys Lys
 1

<210> 488
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 488
Thr Lys Lys Arg
 1

<210> 489
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site

<400> 489
Arg Arg Val Arg
1

<210> 490
<211> 1474
<212> PRT
<213> Homo sapiens

<220>
<223> Alpha-2-macroglobulin precursor (Alpha-2-M)

<400> 490
Met Gly Lys Asn Lys Leu Leu His Pro Ser Leu Val Leu Leu Leu Leu
1 5 10 15
Val Leu Leu Pro Thr Asp Ala Ser Val Ser Gly Lys Pro Gln Tyr Met
20 25 30
Val Leu Val Pro Ser Leu Leu His Thr Glu Thr Thr Glu Lys Gly Cys
35 40 45
Val Leu Leu Ser Tyr Leu Asn Glu Thr Val Thr Val Ser Ala Ser Leu
50 55 60
Glu Ser Val Arg Gly Asn Arg Ser Leu Phe Thr Asp Leu Glu Ala Glu
65 70 75 80
Asn Asp Val Leu His Cys Val Ala Phe Ala Val Pro Lys Ser Ser Ser
85 90 95
Asn Glu Glu Val Met Phe Leu Thr Val Gln Val Lys Gly Pro Thr Gln
100 105 110
Glu Phe Lys Lys Arg Thr Thr Val Met Val Lys Asn Glu Asp Ser Leu
115 120 125
Val Phe Val Gln Thr Asp Lys Ser Ile Tyr Lys Pro Gly Gln Thr Val
130 135 140
Lys Phe Arg Val Val Ser Met Asp Glu Asn Phe His Pro Leu Asn Glu
145 150 155 160
Leu Ile Pro Leu Val Tyr Ile Gln Asp Pro Lys Gly Asn Arg Ile Ala
165 170 175
Gln Trp Gln Ser Phe Gln Leu Glu Gly Gly Leu Lys Gln Phe Ser Phe
180 185 190
Pro Leu Ser Ser Glu Pro Phe Gln Gly Ser Tyr Lys Val Val Val Gln
195 200 205
Lys Lys Ser Gly Gly Arg Thr Glu His Pro Phe Thr Val Glu Glu Phe
210 215 220
Val Leu Pro Lys Phe Glu Val Gln Val Thr Val Pro Lys Ile Ile Thr
225 230 235 240
Ile Leu Glu Glu Glu Met Asn Val Ser Val Cys Gly Leu Tyr Thr Tyr
245 250 255
Gly Lys Pro Val Pro Gly His Val Thr Val Ser Ile Cys Arg Lys Tyr
260 265 270
Ser Asp Ala Ser Asp Cys His Gly Glu Asp Ser Gln Ala Phe Cys Glu
275 280 285
Lys Phe Ser Gly Gln Leu Asn Ser His Gly Cys Phe Tyr Gln Gln Val
290 295 300
Lys Thr Lys Val Phe Gln Leu Lys Arg Lys Glu Tyr Glu Met Lys Leu
305 310 315 320
His Thr Glu Ala Gln Ile Gln Glu Glu Gly Thr Val Val Glu Leu Thr
325 330 335

```
Gly Arg Gln Ser Ser Glu Ile Thr Arg Thr Ile Thr Lys Leu Ser Phe
            340                 345                 350
Val Lys Val Asp Ser His Phe Arg Gln Gly Ile Pro Phe Phe Gly Gln
        355                 360                 365
Val Arg Leu Val Asp Gly Lys Gly Val Pro Ile Pro Asn Lys Val Ile
    370                 375                 380
Phe Ile Arg Gly Asn Glu Ala Asn Tyr Tyr Ser Asn Ala Thr Thr Asp
385                 390                 395                 400
Glu His Gly Leu Val Gln Phe Ser Ile Asn Thr Thr Asn Val Met Gly
                405                 410                 415
Thr Ser Leu Thr Val Arg Val Asn Tyr Lys Asp Arg Ser Pro Cys Tyr
            420                 425                 430
Gly Tyr Gln Trp Val Ser Glu Glu His Glu Glu Ala His His Thr Ala
        435                 440                 445
Tyr Leu Val Phe Ser Pro Ser Lys Ser Phe Val His Leu Glu Pro Met
    450                 455                 460
Ser His Glu Leu Pro Cys Gly His Thr Gln Thr Val Gln Ala His Tyr
465                 470                 475                 480
Ile Leu Asn Gly Gly Thr Leu Leu Gly Leu Lys Lys Leu Ser Phe Tyr
                485                 490                 495
Tyr Leu Ile Met Ala Lys Gly Gly Ile Val Arg Thr Gly Thr His Gly
            500                 505                 510
Leu Leu Val Lys Gln Glu Asp Met Lys Gly His Phe Ser Ile Ser Ile
        515                 520                 525
Pro Val Lys Ser Asp Ile Ala Pro Val Ala Arg Leu Leu Ile Tyr Ala
    530                 535                 540
Val Leu Pro Thr Gly Asp Val Ile Gly Asp Ser Ala Lys Tyr Asp Val
545                 550                 555                 560
Glu Asn Cys Leu Ala Asn Lys Val Asp Leu Ser Phe Ser Pro Ser Gln
                565                 570                 575
Ser Leu Pro Ala Ser His Ala His Leu Arg Val Thr Ala Ala Pro Gln
            580                 585                 590
Ser Val Cys Ala Leu Arg Ala Val Asp Gln Ser Val Leu Leu Met Lys
        595                 600                 605
Pro Asp Ala Glu Leu Ser Ala Ser Ser Val Tyr Asn Leu Leu Pro Glu
    610                 615                 620
Lys Asp Leu Thr Gly Phe Pro Gly Pro Leu Asn Asp Gln Asp Asp Glu
625                 630                 635                 640
Asp Cys Ile Asn Arg His Asn Val Tyr Ile Asn Gly Ile Thr Tyr Thr
                645                 650                 655
Pro Val Ser Ser Thr Asn Glu Lys Asp Met Tyr Ser Phe Leu Glu Asp
            660                 665                 670
Met Gly Leu Lys Ala Phe Thr Asn Ser Lys Ile Arg Lys Pro Lys Met
        675                 680                 685
Cys Pro Gln Leu Gln Gln Tyr Glu Met His Gly Pro Glu Gly Leu Arg
    690                 695                 700
Val Gly Phe Tyr Glu Ser Asp Val Met Gly Arg Gly His Ala Arg Leu
705                 710                 715                 720
Val His Val Glu Glu Pro His Thr Glu Thr Val Arg Lys Tyr Phe Pro
                725                 730                 735
Glu Thr Trp Ile Trp Asp Leu Val Val Val Asn Ser Ala Gly Val Ala
            740                 745                 750
Glu Val Gly Val Thr Val Pro Asp Thr Ile Thr Glu Trp Lys Ala Gly
        755                 760                 765
Ala Phe Cys Leu Ser Glu Asp Ala Gly Leu Gly Ile Ser Ser Thr Ala
    770                 775                 780
Ser Leu Arg Ala Phe Gln Pro Phe Phe Val Glu Leu Thr Met Pro Tyr
```

785 790 795 800
Ser Val Ile Arg Gly Glu Ala Phe Thr Leu Lys Ala Thr Val Leu Asn
805 810 815
Tyr Leu Pro Lys Cys Ile Arg Val Ser Val Gln Leu Glu Ala Ser Pro
820 825 830
Ala Phe Leu Ala Val Pro Val Glu Lys Glu Gln Ala Pro His Cys Ile
835 840 845
Cys Ala Asn Gly Arg Gln Thr Val Ser Trp Ala Val Thr Pro Lys Ser
850 855 860
Leu Gly Asn Val Asn Phe Thr Val Ser Ala Glu Ala Leu Glu Ser Gln
865 870 875 880
Glu Leu Cys Gly Thr Glu Val Pro Ser Val Pro Glu His Gly Arg Lys
885 890 895
Asp Thr Val Ile Lys Pro Leu Leu Val Glu Pro Glu Gly Leu Glu Lys
900 905 910
Glu Thr Thr Phe Asn Ser Leu Leu Cys Pro Ser Gly Gly Glu Val Ser
915 920 925
Glu Glu Leu Ser Leu Lys Leu Pro Pro Asn Val Val Glu Glu Ser Ala
930 935 940
Arg Ala Ser Val Ser Val Leu Gly Asp Ile Leu Gly Ser Ala Met Gln
945 950 955 960
Asn Thr Gln Asn Leu Leu Gln Met Pro Tyr Gly Cys Gly Glu Gln Asn
965 970 975
Met Val Leu Phe Ala Pro Asn Ile Tyr Val Leu Asp Tyr Leu Asn Glu
980 985 990
Thr Gln Gln Leu Thr Pro Glu Val Lys Ser Lys Ala Ile Gly Tyr Leu
995 1000 1005
Asn Thr Gly Tyr Gln Arg Gln Leu Asn Tyr Lys His Tyr Asp Gly Ser
1010 1015 1020
Tyr Ser Thr Phe Gly Glu Arg Tyr Gly Arg Asn Gln Gly Asn Thr Trp
1025 1030 1035 1040
Leu Thr Ala Phe Val Leu Lys Thr Phe Ala Gln Ala Arg Ala Tyr Ile
1045 1050 1055
Phe Ile Asp Glu Ala His Ile Thr Gln Ala Leu Ile Trp Leu Ser Gln
1060 1065 1070
Arg Gln Lys Asp Asn Gly Cys Phe Arg Ser Ser Gly Ser Leu Leu Asn
1075 1080 1085
Asn Ala Ile Lys Gly Gly Val Glu Asp Glu Val Thr Leu Ser Ala Tyr
1090 1095 1100
Ile Thr Ile Ala Leu Leu Glu Ile Pro Leu Thr Val Thr His Pro Val
1105 1110 1115 1120
Val Arg Asn Ala Leu Phe Cys Leu Glu Ser Ala Trp Lys Thr Ala Gln
1125 1130 1135
Glu Gly Asp His Gly Ser His Val Tyr Thr Lys Ala Leu Leu Ala Tyr
1140 1145 1150
Ala Phe Ala Leu Ala Gly Asn Gln Asp Lys Arg Lys Glu Val Leu Lys
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Ser Leu Asn Glu Glu Ala Val Lys Lys Asp Asn Ser Val His Trp Glu
1170 1175 1180
Arg Pro Gln Lys Pro Lys Ala Pro Val Gly His Phe Tyr Glu Pro Gln
1185 1190 1195 1200
Ala Pro Ser Ala Glu Val Glu Met Thr Ser Tyr Val Leu Leu Ala Tyr
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Leu Thr Ala Gln Pro Ala Pro Thr Ser Glu Asp Leu Thr Ser Ala Thr
1220 1225 1230
Asn Ile Val Lys Trp Ile Thr Lys Gln Gln Asn Ala Gln Gly Gly Phe

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        1235                1240                1245

Ser Ser Thr Gln Asp Thr Val Val Ala Leu His Ala Leu Ser Lys Tyr
    1250                1255                1260
Gly Ala Ala Thr Phe Thr Arg Thr Gly Lys Ala Ala Gln Val Thr Ile
1265                1270                1275                1280
Gln Ser Ser Gly Thr Phe Ser Ser Lys Phe Gln Val Asp Asn Asn Asn
                1285                1290                1295
Arg Leu Leu Leu Gln Gln Val Ser Leu Pro Glu Leu Pro Gly Glu Tyr
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Ser Met Lys Val Thr Gly Glu Gly Cys Val Tyr Leu Gln Thr Ser Leu
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Lys Tyr Asn Ile Leu Pro Glu Lys Glu Glu Phe Pro Phe Ala Leu Gly
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Val Gln Thr Leu Pro Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser
1345                1350                1355                1360
Phe Gln Ile Ser Leu Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser
                1365                1370                1375
Asn Met Ala Ile Val Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu
            1380                1385                1390
Lys Pro Thr Val Lys Met Leu Glu Arg Ser Asn His Val Ser Arg Thr
        1395                1400                1405
Glu Val Ser Ser Asn His Val Leu Ile Tyr Leu Asp Lys Val Ser Asn
    1410                1415                1420
Gln Thr Leu Ser Leu Phe Phe Thr Val Leu Gln Asp Val Pro Val Arg
1425                1430                1435                1440
Asp Leu Lys Pro Ala Ile Val Lys Val Tyr Asp Tyr Tyr Glu Thr Asp
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Glu Phe Ala Ile Ala Glu Tyr Asn Ala Pro Cys Ser Lys Asp Leu Gly
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Asn Ala
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<210> 491
<211> 439
<212> PRT
<213> Spodoptera litura nucleopolyhedrovirus

<400> 491

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Asp Cys Ala Asn Leu Ser Asp Ser Ser Leu Arg Asp Leu Ile Tyr Val
            20                  25                  30
Asn Asn Val Ala Val Ser Lys Thr Gly Asn Tyr Ile Asn Arg Ser Val
        35                  40                  45
Ile Met Ala Leu Asn Ile Ser Gly Pro Val Val Ser Val Asn Arg Val
    50                  55                  60
Ser Met His Ile Val His Met Tyr Arg Ser His Ile Asp Arg Ile Phe
65                  70                  75                  80
Asp Arg Phe Asn Arg Leu Thr Tyr Ser Ala Thr Val Thr Asp Gly Gly
                85                  90                  95
Asp Ile Asp Arg Val Leu Lys Ser Asp Asp Tyr Thr Val Val Cys Met
            100                 105                 110
Ser Arg Ser Glu Leu Leu Asp Asn Tyr Lys Lys Cys Leu Ile Asn Glu
        115                 120                 125
Met Gly Ala Thr Gln Asp Asp Val Glu Lys Phe Arg Lys Tyr Cys Leu
    130                 135                 140
Lys Pro Leu Val Glu Thr Glu Asn Asp Gly Gly Val Glu Asp Arg Lys
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145                 150                 155                 160
Lys Pro Tyr Val Val Ile Cys Ser Leu Lys Pro Lys Leu Leu Asn Lys
                165                 170                 175
Asn Lys Thr Leu Cys Phe Thr Tyr Lys Pro Gln Thr Gly Gln Val Ile
            180                 185                 190
Val Pro Leu Met His Glu Ile Asn Glu Asn Gly Ser Asp Val Tyr Ser
        195                 200                 205
Tyr Glu Val Met Ala Met Ile Lys Asp Val Arg Leu Ser Asn Lys Pro
    210                 215                 220
Leu Ser Met Leu Glu Arg Leu Lys Arg Ser Met Asp Gln Ile Val Leu
225                 230                 235                 240
Asn His Asn Glu Asn Lys Tyr Met Met Thr Asn Gln Leu Glu Ser Leu
                245                 250                 255
Lys Tyr Tyr Leu Lys Ser Ile Asn Ser Asn Glu Asp Asp Asp Leu Asn
            260                 265                 270
Lys Leu Met Asn Val Leu Asn Asn Leu Ile Asp Gln Leu Glu Lys Val
        275                 280                 285
Leu His Lys Lys Ser Ile Cys Asp Phe Ser Asp Asp Asp Glu Asp Asp
    290                 295                 300
Asp Gly Leu Ile Asp Met Lys Tyr Tyr Asn Ser Ile Ile Glu Asp Asn
305                 310                 315                 320
Met Arg Ile Leu Leu Met Lys Ile Gln Gln Tyr Ile Asp Asp Arg His
                325                 330                 335
Met Phe Leu Ser Pro Pro Leu Ser Val Glu Lys Ser Thr Lys Ile Arg
            340                 345                 350
Leu Phe Glu Asn Val Met Ser Phe Met Lys Arg Phe Asn Leu Gly Glu
        355                 360                 365
Leu Tyr Ser Tyr Leu Lys Lys Ile Ile Asp Trp Lys Thr His Glu Asn
    370                 375                 380
Asn Gln Lys Leu Ala Trp Pro Glu Ile Val Asp Asp Lys Tyr Ala Phe
385                 390                 395                 400
Leu Lys Tyr Asp Tyr Phe Gly Thr Pro His Gly Phe Val Tyr Asp Gln
                405                 410                 415
Lys Asp Arg Thr Met Tyr Val Lys Leu His Cys Gly Ile Ala Ala Asn
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Arg Asn Ile Tyr Ile Asp Ile
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<210> 492
<211> 341
<212> PRT
<213> Cowpox virus

<400> 492

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Phe Ile Ser Pro Pro Ser Ile Ser Ser Val Leu Thr Ile Leu Tyr Tyr
            20                  25                  30
Gly Ala Asn Gly Ser Thr Ala Glu Gln Leu Ser Lys Tyr Val Glu Lys
        35                  40                  45
Glu Ala Asp Lys Asn Lys Asp Asp Ile Ser Phe Lys Ser Met Asn Lys
    50                  55                  60
Val Tyr Gly Arg Tyr Ser Ala Val Phe Lys Asp Ser Phe Leu Arg Lys
65                  70                  75                  80
Ile Gly Asp Asn Phe Gln Thr Val Asp Phe Thr Asp Cys Arg Thr Val
                85                  90                  95
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Asp Ala Ile Asn Lys Cys Val Asp Ile Phe Thr Glu Gly Lys Ile Asn
            100                 105                 110
Pro Leu Leu Asp Glu Pro Leu Ser Pro Asp Thr Cys Leu Leu Ala Ile
        115                 120                 125
Ser Ala Val Tyr Phe Lys Ala Lys Trp Leu Met Pro Phe Glu Lys Glu
    130                 135                 140
Phe Thr Ser Asp Tyr Pro Phe Tyr Val Ser Pro Thr Glu Met Val Asp
145                 150                 155                 160
Val Ser Met Met Ser Met Tyr Gly Glu Ala Phe Asn His Ala Ser Val
                165                 170                 175
Lys Glu Ser Phe Gly Asn Phe Ser Ile Ile Glu Leu Pro Tyr Val Gly
            180                 185                 190
Asp Thr Ser Met Val Val Ile Leu Pro Asp Asn Ile Asp Gly Leu Glu
        195                 200                 205
Ser Ile Glu Gln Asn Leu Thr Asp Thr Asn Phe Lys Lys Trp Cys Asp
    210                 215                 220
Ser Met Asp Ala Met Phe Ile Asp Val His Ile Pro Lys Phe Lys Val
225                 230                 235                 240
Thr Gly Ser Tyr Asn Leu Val Asp Ala Leu Val Lys Leu Gly Leu Thr
                245                 250                 255
Glu Val Phe Gly Ser Thr Gly Asp Tyr Ser Asn Met Cys Asn Ser Asp
            260                 265                 270
Val Ser Val Asp Ala Met Ile His Lys Thr Tyr Ile Asp Val Asn Glu
        275                 280                 285
Glu Tyr Thr Glu Ala Ala Ala Ala Thr Cys Ala Leu Val Ala Asp Cys
    290                 295                 300
Ala Ser Thr Val Thr Asn Glu Phe Cys Ala Asp His Pro Phe Ile Tyr
305                 310                 315                 320
Val Ile Arg His Val Asp Gly Lys Ile Leu Phe Val Gly Arg Tyr Cys
                325                 330                 335
Ser Pro Thr Thr Asn
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<210> 493
<211> 432
<212> PRT
<213> Homo sapiens

<220>
<223> antithrombin III mature

<400> 493

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            20                  25                  30
Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
        35                  40                  45
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
    50                  55                  60
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65                  70                  75                  80
Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
                85                  90                  95
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
            100                 105                 110
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Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys
        115                 120                 125
Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn
    130                 135                 140
Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp
145                 150                 155                 160
Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys
                165                 170                 175
Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn
            180                 185                 190
Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn
        195                 200                 205
Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu
    210                 215                 220
Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr
225                 230                 235                 240
Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
                245                 250                 255
Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
            260                 265                 270
Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
        275                 280                 285
Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
    290                 295                 300
Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
305                 310                 315                 320
Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
                325                 330                 335
Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
            340                 345                 350
Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
        355                 360                 365
His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
    370                 375                 380
Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val
385                 390                 395                 400
Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
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Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
            420                 425                 430
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<210> 494
<211> 9765
<212> DNA
<213> Artificial Sequence

<220>

<223> pAcGP67b vector

<400> 494
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ctcactgact cgctgcgctc ggtcgttcgg ctgcggcgag cggtatcagc tcactcaaag 7440
gcggtaatac ggttatccac agaatcaggg gataacgcag gaaagaacat gtgagcaaaa 7500
ggccagcaaa aggccaggaa ccgtaaaaag gccgcgttgc tggcgttttt ccataggctc 7560
cgccccccctg acgagcatca caaaaatcga cgctcaagtc agaggtggcg aaacccgaca 7620
ggactataaa gataccaggc gtttcccccct ggaagctccc tcgtgcgctc tcctgttccg 7680
accctgccgc ttaccggata cctgtccgcc tttctccctt cgggaagcgt ggcgctttct 7740
catagctcac gctgtaggta tctcagttcg gtgtaggtcg ttcgctccaa gctgggctgt 7800
gtgcacgaac cccccgttca gcccgaccgc tgcgccttat ccggtaacta tcgtcttgag 7860
tccaacccgg taagacacga cttatcgcca ctggcagcag ccactggtaa caggattagc 7920
agagcgaggt atgtaggcgg tgctacagag ttcttgaagt ggtggcctaa ctacggctac 7980
actagaagga cagtatttgg tatctgcgct ctgctgaagc cagttacctt cggaaaaaga 8040
gttggtagct cttgatccgg caaacaaacc accgctggta gcggtggttt ttttgtttgc 8100
aagcagcaga ttacgcgcag aaaaaaagga tctcaagaag atcctttgat cttttctacg 8160
gggtctgacg ctcagtggaa cgaaaactca cgttaaggga ttttggtcat gagattatca 8220
aaaaggatct tcacctagat ccttttaaat taaaaatgaa gttttaaatc aatctaaagt 8280
atatatgagt aaacttggtc tgacagttac caatgcttaa tcagtgaggc acctatctca 8340
gcgatctgtc tatttcgttc atccatagtt gcctgactcc ccgtcgtgta gataactacg 8400
atacgggagg gcttaccatc tggccccagt gctgcaatga taccgcgaga cccacgctca 8460
ccggctccag atttatcagc aataaaccag ccagccggaa gggccgagcg cagaagtggt 8520
cctgcaactt tatccgcctc catccagtct attaattgtt gccgggaagc tagagtaagt 8580
agttcgccag ttaatagttt gcgcaacgtt gttgccattg ctacaggcat cgtggtgtca 8640
cgctcgtcgt ttggtatggc ttcattcagc tccggttccc aacgatcaag gcgagttaca 8700
tgatccccca tgttgtgcaa aaaagcggtt agctccttcg gtcctccgat cgttgtcaga 8760
agtaagttgg ccgcagtgtt atcactcatg gttatggcag cactgcataa ttctcttact 8820
gtcatgccat ccgtaagatg cttttctgtg actggtgagt actcaaccaa gtcattctga 8880
gaatagtgta tgcggcgacc gagttgctct tgcccggcgt caatacggga taataccgcg 8940
ccacatagca gaactttaaa agtgctcatc attggaaaac gttcttcggg gcgaaaactc 9000
tcaaggatct taccgctgtt gagatccagt tcgatgtaac ccactcgtgc acccaactga 9060
tcttcagcat cttttacttt caccagcgtt tctgggtgag caaaaacagg aaggcaaaat 9120
gccgcaaaaa agggaataag ggcgacacgg aaatgttgaa tactcatact cttccttttt 9180
caatattatt gaagcattta tcagggttat tgtctcatga gcggatacat atttgaatgt 9240
atttagaaaa ataaacaaat aggggttccg cgcacatttc cccgaaaagt gccacctgac 9300
gtctaagaaa ccattattat catgacatta acctataaaa ataggcgtat cacgaggccc 9360
tttcgtctcg cgcgtttcgg tgatgacggt gaaaacctct gacacatgca gctcccggag 9420
acggtcacag cttgtctgta agcggatgcc gggagcagac aagcccgtca gggcgcgtca 9480
gcgggtgttg gcgggtgtcg gggctggctt aactatgcgg catcagagca gattgtactg 9540
agagtgcacc atatgcggtg tgaaataccg cacagatgcg taaggagaaa ataccgcatc 9600
aggcgccatt cgccattcag gctgcgcaac tgttgggaag ggcgatcggt gcgggcctct 9660
tcgctattac gccagctggc gaaaggggga tgtgctgcaa ggcgattaag ttgggtaacg 9720
ccagggtttt cccagtcacg acgttgtaaa acgacggcca gtgcc 9765

<210> 495
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> FLAG tag

<400> 495
Asp Tyr Lys Asp Asp Asp Asp Lys
1 5

<210> 496
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 6xHis tag

<400> 496
His His His His His His
 1   5

<210> 497
<211> 432
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant AT3 sequence

<223> AT3/RRVRKE

<400> 497
His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
 1   5   10   15
Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
            20   25   30
Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
        35   40   45
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
    50   55   60
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65   70   75   80
Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
                85   90   95
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
            100   105   110
Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys
        115   120   125
Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn
    130   135   140
Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp
145   150   155   160
Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys
                165   170   175
Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn
            180   185   190
Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn
        195   200   205
Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu
    210   215   220
Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr
225   230   235   240
Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly

```
                245                 250                 255
Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
            260                 265                 270
Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
        275                 280                 285
Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
    290                 295                 300
Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
305                 310                 315                 320
Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
                325                 330                 335
Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
            340                 345                 350
Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
        355                 360                 365
His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
    370                 375                 380
Ser Thr Ala Val Val Arg Arg Val Arg Lys Glu Asn Pro Asn Arg Val
385                 390                 395                 400
Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
                405                 410                 415
Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
            420                 425                 430


<210> 498
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> replacement cleavage site RRVRKE


<400> 498
Arg Arg Val Arg Lys Glu
 1               5


<210> 499
<211> 432
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant AT3 sequence

<223> AT3/SLGRKI

<400> 499
His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
 1               5                  10                  15
Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
            20                  25                  30
Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
        35                  40                  45
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
```

```
    50                  55                  60
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65                  70                  75                  80
Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
                85                  90                  95
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
            100                 105                 110
Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys
        115                 120                 125
Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn
    130                 135                 140
Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp
145                 150                 155                 160
Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys
                165                 170                 175
Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn
            180                 185                 190
Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn
        195                 200                 205
Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu
    210                 215                 220
Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr
225                 230                 235                 240
Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
                245                 250                 255
Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
            260                 265                 270
Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
        275                 280                 285
Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
    290                 295                 300
Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
305                 310                 315                 320
Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
                325                 330                 335
Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
            340                 345                 350
Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
        355                 360                 365
His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
    370                 375                 380
Ser Thr Ala Val Val Ser Leu Gly Arg Lys Ile Asn Pro Asn Arg Val
385                 390                 395                 400
Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
                405                 410                 415
Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
            420                 425                 430
```

<210> 500
<211> 432
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant AT3 sequence

<223> SKGRSL

<400> 500
His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
1 5 10 15
Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
20 25 30
Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
50 55 60
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80
Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
100 105 110
Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys
115 120 125
Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn
130 135 140
Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp
145 150 155 160
Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys
165 170 175

Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn
180 185 190
Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn
195 200 205
Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu
210 215 220
Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr
225 230 235 240
Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
245 250 255
Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
260 265 270
Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
275 280 285
Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
290 295 300
Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
305 310 315 320
Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
325 330 335
Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
340 345 350
Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
355 360 365
His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
370 375 380
Ser Thr Ala Val Val Ser Lys Gly Arg Ser Leu Asn Pro Asn Arg Val
385 390 395 400
Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
405 410 415
Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys

420 425 430

<210> 501
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> replacement cleavage site SKGRSL

<400> 501
Ser Lys Gly Arg Ser Leu
1 5

<210> 502
<211> 432
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant AT3 sequence

<223> AT3/PRFKII

<400> 502
His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
1 5 10 15
Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
20 25 30
Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
50 55 60
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80
Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
100 105 110
Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys
115 120 125
Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn
130 135 140
Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp
145 150 155 160
Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys
165 170 175
Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn
180 185 190
Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn
195 200 205
Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu
210 215 220
Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr

```
225                 230                 235                 240
Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
                245                 250                 255
Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
            260                 265                 270
Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
        275                 280                 285
Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
    290                 295                 300
Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
305                 310                 315                 320
Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
                325                 330                 335
Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
            340                 345                 350
Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
        355                 360                 365
His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
    370                 375                 380
Ser Thr Ala Val Val Pro Arg Phe Lys Ile Ile Asn Pro Asn Arg Val
385                 390                 395                 400
Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
                405                 410                 415
Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
            420                 425                 430
```

<210> 503
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> replacement cleavage site PRFKII

<400> 503
```
Pro Arg Phe Lys Ile Ile
 1               5
```

<210> 504
<211> 723
<212> DNA
<213> Homo sapiens

<220>
<223> MT-SP1 protease domain

<400> 504
```
gttgttgggg gcacggatgc ggatgagggc gagtggccct ggcaggtaag cctgcatgct 60
ctgggccagg gccacatctg cggtgcttcc ctcatctctc ccaactggct ggtctctgcc 120
gcacactgct acatcgatga cagaggattc aggtactcag accccacgca gtggacggcc 180
ttcctgggct tgcacgacca gagccagcgc agcgcccctg gggtgcagga gcgcaggctc 240
aagcgcatca tctcccaccc cttcttcaat gacttcacct tcgactatga catcgcgctg 300
ctggagctgg agaaaccggc agagtacagc tccatggtgc ggcccatctg cctgccggac 360
gcctcccatg tcttccctgc cggcaaggcc atctgggtca cgggctgggg acacacccag 420
```

tatggaggca ctggcgcgct gatcctgcaa aagggtgaga tccgcgtcat caaccagacc 480
acctgcgaga acctcctgcc gcagcagatc acgccgcgca tgatgtgcgt gggcttcctc 540
agcggcggcg tggactcctg ccagggtgat tccgggggac ccctgtccag cgtggaggcg 600
gatgggcgga tcttccaggc cggtgtggtg agctggggag acggctgcgc tcagaggaac 660
aagccaggcg tgtacacaag gctccctctg tttcgggact ggatcaaaga gaacactggg 720
gta 723

<210> 505
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> MT-SP1 protease domain

<400> 505
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1   5   10   15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20   25   30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35   40   45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50   55   60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65   70   75   80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85   90   95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100   105   110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115   120   125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130   135   140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145   150   155   160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165   170   175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180   185   190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195   200   205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210   215   220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225   230   235   240
Val

<210> 506
<211> 444
<212> PRT
<213> Homo sapiens

<220>
<223> MT-SP1 protease domain fusion

<223> STII/MT-SP1/GeneII

<400> 506

```
Met Lys Lys Asn Ile Ala Phe Leu Leu Ala Ser Met Phe Val Phe Ser
 1               5                  10                  15
Ile Ala Thr Asn Ala Tyr Ala Val Val Gly Gly Thr Asp Ala Asp Glu
            20                  25                  30
Gly Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His
        35                  40                  45
Ile Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala
    50                  55                  60
His Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln
65                  70                  75                  80
Trp Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro
                85                  90                  95
Gly Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe
            100                 105                 110
Asn Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys
        115                 120                 125
Pro Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala
    130                 135                 140
Ser His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly
145                 150                 155                 160
His Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu
                165                 170                 175
Ile Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln
            180                 185                 190
Ile Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp
        195                 200                 205
Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp
    210                 215                 220
Gly Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala
225                 230                 235                 240
Gln Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp
                245                 250                 255
Trp Ile Lys Glu Asn Thr Gly Val Ser Gly Ser Ser Gly Gly Gly Ser
            260                 265                 270
Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Gly
        275                 280                 285
Gly Gly Ser Gly Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala
    290                 295                 300
Asn Lys Gly Ala Met Thr Glu Asn Ala Asp Glu Asn Ala Leu Gln Ser
305                 310                 315                 320
Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr Asp Tyr Gly Ala Ala
                325                 330                 335
Ile Asp Gly Phe Ile Gly Asp Val Ser Gly Leu Ala Asn Gly Asn Gly
            340                 345                 350

Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly
        355                 360                 365
Asp Gly Asp Asn Ser Pro Leu Met Asn Asn Phe Arg Gln Tyr Leu Pro
    370                 375                 380
Ser Leu Pro Gln Ser Val Glu Cys Arg Pro Phe Val Phe Ser Ala Gly
385                 390                 395                 400
```

```
Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys Ile Asn Leu Phe Arg
                405                 410                 415
Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val Phe
            420                 425                 430
Ser Thr Phe Ala Asn Ile Leu Arg Asn Lys Glu Ser
        435                 440
```

<210> 507
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutated MT-SP1 protease domain

<223> CB496

<400> 507

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 508
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> MT-SP1 forward primer

<400> 508
gcgcagatat cgtaccgcat atgaaaaaga atatcgcatt tctt 44

<210> 509
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> MT-SP1 reverse primer

<400> 509
gtgcatgctg actgactgag ctcccgctta ccccagtgtt ctc 43

<210> 510
<211> 1335
<212> DNA
<213> Homo sapiens

<220>
<223> MT-SP1 protease domain fusion

<223> STII/MT-SP1/GeneIII

<400> 510
atgaaaaaga atatcgcatt tcttcttgca tctatgttcg ttttttctat tgctacaaat 60
gcctatgcag ttgttggggg cacggatgcg gatgagggcg agtggccctg gcaggtaagc 120
ctgcatgctc tgggccaggg ccacatctgc ggtgcttccc tcatctctcc caactggctg 180
gtctctgccg cacactgcta catcgatgac agaggattca ggtactcaga ccccacgcag 240
tggacggcct tcctgggctt gcacgaccag agccagcgca gcgcccctgg ggtgcaggag 300
cgcaggctca agcgcatcat ctcccacccc ttcttcaatg acttcacctt cgactatgac 360
atcgcgctgc tggagctgga gaaaccggca gagtacagct ccatggtgcg gcccatctgc 420
ctgccggacg cctcccatgt cttccctgcc ggcaaggcca tctgggtcac gggctgggga 480
cacacccagt atggaggcac tggcgcgctg atcctgcaaa agggtgagat ccgcgtcatc 540
aaccagacca cctgcgagaa cctcctgccg cagcagatca cgccgcgcat gatgtgcgtg 600
ggcttcctca gcggcggcgt ggactcctgc cagggtgatt ccgggggacc cctgtccagc 660
gtggaggcgg atgggcggat cttccaggcc ggtgtggtga gctggggaga cggctgcgct 720
cagaggaaca agccaggcgt gtacacaagg ctccctctgt ttcgggactg gatcaaagag 780
aacactgggg taagcgggag ctccggtggt ggctctgagg gtggcggttc tgagggtggc 840
ggctctgagg gaggcggttc cggtggtggc tctggttccg gtgattttga ttatgaaaag 900
atggcaaacg ctaataaggg ggctatgacc gaaaatgccg atgaaaacgc gctacagtct 960
gacgctaaag gcaaacttga ttctgtcgct actgattacg gtgctgctat cgatggtttc 1020
attggtgacg tttccggcct tgctaatggt aatggtgcta ctggtgattt tgctggctct 1080
aattcccaaa tggctcaagt cggtgacggt gataattcac ctttaatgaa taatttccgt 1140
caatatttac cttccctccc tcaatcggtt gaatgtcgcc cttttgtctt tagcgctggt 1200
aaaccatatg aattttctat tgattgtgac aaaataaact tattccgtgg tgtctttgcg 1260
tttcttttat atgttgccac ctttatgtat gtattttcta cgtttgctaa catactgcgt 1320
aataaggagt cttaa 1335

<210> 511
<211> 23
<212> PRT
<213> Escherichia coli

<220>
<223> STII leader sequence

<400> 511
Met Lys Lys Asn Ile Ala Phe Leu Leu Ala Ser Met Phe Val Phe Ser
 1   5   10   15
Ile Ala Thr Asn Ala Tyr Ala
            20

<210> 512
<211> 180
<212> PRT
<213> M13 phage

<220>
<223> GeneIII

<400> 512
Ser Gly Ser Ser Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly
 1   5   10   15
Gly Ser Glu Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Asp Phe
            20   25   30
Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu Asn
        35   40   45
Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser
    50   55   60
Val Ala Thr Asp Tyr Gly Ala Ala Ile Asp Gly Phe Ile Gly Asp Val
65   70   75   80
Ser Gly Leu Ala Asn Gly Asn Gly Ala Thr Gly Asp Phe Ala Gly Ser
                85   90   95
Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp Asn Ser Pro Leu Met
            100   105   110
Asn Asn Phe Arg Gln Tyr Leu Pro Ser Leu Pro Gln Ser Val Glu Cys
        115   120   125
Arg Pro Phe Val Phe Ser Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp
    130   135   140
Cys Asp Lys Ile Asn Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr
145   150   155   160
Val Ala Thr Phe Met Tyr Val Phe Ser Thr Phe Ala Asn Ile Leu Arg
                165   170   175
Asn Lys Glu Ser
            180

<210> 513
<211> 4
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthesized protease cleavage site RQAR

<400> 513
Arg Gln Ala Arg
1

<210> 514
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthesized protease cleavage site SLGR

<400> 514
Ser Leu Gly Arg
1

<210> 515
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CB469

<400> 515
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
1 5 10 15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
20 25 30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
35 40 45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
85 90 95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
100 105 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
115 120 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
130 135 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145 150 155 160

```
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
```

```
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 516
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP-1 protease domain

<223> CPC-0019595

<400> 516
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
```

```
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Thr Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asp Gln Ala
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Leu Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 517
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0023085

<400> 517

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr

                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
```

```
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 518
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0024153

<400> 518

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Thr Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Gly
```

<210> 519

<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0025366

<400> 519
Val Val Gly Gly Thr Asp Ala Glu Glu Gly Glu Trp Pro Trp Gln Val
 1   5   10   15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20   25   30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35   40   45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50   55   60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65   70   75   80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Pro Phe Asp Tyr
                85   90   95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100   105   110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115   120   125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Ile Gln Tyr Gly Gly Thr
    130   135   140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145   150   155   160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165   170   175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180   185   190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195   200   205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210   215   220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225   230   235   240
Val

<210> 520
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0025387

<400> 520
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1   5   10   15

```
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 521
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0025582

```
<400> 521
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
```

```
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Phe Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Gly
```

<210> 522
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP-1 protease domain

<223> CPC-0025720

<400> 522

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly Arg Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
```

```
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 523
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0025876

<400> 523

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Phe Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 524
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0025974

<400> 524
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1   5   10   15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20   25   30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35   40   45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50   55   60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65   70   75   80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85   90   95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100   105   110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115   120   125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130   135   140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145   150   155   160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165   170   175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180   185   190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195   200   205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210   215   220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225   230   235   240
Val

<210> 525
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0026100

<400> 525
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1   5   10   15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20   25   30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg

```
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Val Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Gly
```

<210> 526
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0026323

<400> 526

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Met Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Asp Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
```

```
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Leu Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 527
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0027399

<400> 527

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
```

225 230 235 240
Val

<210> 528
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0027706

<400> 528
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Tyr Thr Phe Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Val Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ile Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 529
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0027797

<400> 529
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1   5   10   15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20   25   30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35   40   45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50   55   60
Arg Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65   70   75   80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85   90   95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100   105   110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Ser Ala Gly
        115   120   125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130   135   140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145   150   155   160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165   170   175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180   185   190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195   200   205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210   215   220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225   230   235   240
Val

<210> 530
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0028017

<400> 530
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1   5   10   15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20   25   30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35   40   45

```
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly

        195                 200                 205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 531
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0028333

```
<400> 531
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Lys Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Leu Phe Asn Asp Tyr Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
```

```
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 532
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0028341

<400> 532

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Thr Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Ser Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Leu Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
```

```
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 533
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0033634

<400> 533

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Leu Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Leu Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 534
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0028791

<400> 534
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 535
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0027484

<400> 535
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15

```
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Lys Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 536
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 protease domain

<223> CPC-0028993

```
<400> 536
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Ser Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
```

```
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Ser Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 537
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0019595

<400> 537

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
```

```
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
```

```
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Thr Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asp Gln Ala Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Leu Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 538
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0023085

```
<400> 538
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15

Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
```

```
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
```

```
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
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<210> 539
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0024153

<400> 539

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Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
```

Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
85 90 95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
100 105 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
115 120 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
130 135 140

Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145 150 155 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
165 170 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
180 185 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
195 200 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
210 215 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225 230 235 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
245 250 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
260 265 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
275 280 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
290 295 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305 310 315 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
325 330 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
340 345 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
355 360 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
370 375 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385 390 395 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
405 410 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
420 425 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
435 440 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
450 455 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465 470 475 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys

```
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Thr Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Gly
    850                 855
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<210> 540
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0025366

<400> 540

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Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270

Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
```

```
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Glu Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Pro Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Ile Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 541
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0025387

<400> 541
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1   5   10   15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20   25   30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35   40   45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50   55   60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65   70   75   80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85   90   95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100   105   110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115   120   125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130   135   140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145   150   155   160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165   170   175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180   185   190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195   200   205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210   215   220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225   230   235   240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245   250   255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260   265   270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275   280   285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290   295   300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305   310   315   320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325   330   335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn

```
                340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
            355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400

Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His

            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
```

```
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 542
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length


<223> CPC-0025582

<400> 542
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
```

```
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525

Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
```

705 710 715 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
725 730 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
740 745 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
755 760 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Phe Leu Pro Gln Gln Ile
770 775 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785 790 795 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
805 810 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
820 825 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
835 840 845
Ile Lys Glu Asn Thr Gly Gly
850 855

<210> 543
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0025720

<400> 543
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
1 5 10 15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
20 25 30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
35 40 45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
85 90 95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
100 105 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
115 120 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
130 135 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145 150 155 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
165 170 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
180 185 190

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Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
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                645                 650                 655

Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly Arg
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 544
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length


<223> CPC-0025876

<400> 544
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
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        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
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```
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Phe Leu Pro Gln Gln Ile
    770                 775                 780

Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 545
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length


<223> CPC-0025974

<400> 545
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
```

```
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
```

```
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 546
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0026100

<400> 546
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
1 5 10 15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
20 25 30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
35 40 45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
85 90 95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
100 105 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
115 120 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
130 135 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145 150 155 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
165 170 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
180 185 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
195 200 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
210 215 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225 230 235 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
245 250 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
260 265 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
275 280 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
290 295 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305 310 315 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
325 330 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
340 345 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
355 360 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
370 375 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385 390 395 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
405 410 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
420 425 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp

```
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Val Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Gly
    850                 855
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<210> 547
<211> 855

<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0026323

<400> 547
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1   5   10   15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20   25   30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35   40   45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50   55   60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65   70   75   80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85   90   95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100   105   110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115   120   125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130   135   140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145   150   155   160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165   170   175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180   185   190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195   200   205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210   215   220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225   230   235   240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245   250   255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260   265   270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275   280   285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290   295   300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305   310   315   320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325   330   335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340   345   350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355   360   365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe

370 375 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385 390 395 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
405 410 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
420 425 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
435 440 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
450 455 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465 470 475 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
485 490 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
500 505 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
515 520 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
530 535 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545 550 555 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
565 570 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
580 585 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
595 600 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
610 615 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625 630 635 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Met Val Ser Ala Ala His
645 650 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
660 665 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
675 680 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
690 695 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705 710 715 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
725 730 735
His Asp Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
740 745 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
755 760 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
770 775 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785 790 795 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
805 810 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Leu
820 825 830

```
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 548
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length


<223> CPC-002739

<400> 548
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
```

305 310 315 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
325 330 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
340 345 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
355 360 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
370 375 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385 390 395 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
405 410 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
420 425 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
435 440 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
450 455 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465 470 475 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
485 490 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
500 505 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
515 520 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
530 535 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545 550 555 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
565 570 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
580 585 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
595 600 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
610 615 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625 630 635 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
645 650 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
660 665 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
675 680 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
690 695 700
Asp Phe Thr Leu Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705 710 715 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
725 730 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
740 745 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
755 760 765

```
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 549
<211> 855

<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length


<223> CPC-0027706

<400> 549
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
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His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
```

690 695 700
Asp Tyr Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705 710 715 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
725 730 735
His Val Phe Pro Ala Gly Lys Ala Val Trp Val Thr Gly Trp Gly His
740 745 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
755 760 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
770 775 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785 790 795 800
Cys His Gly Asp Ser Gly Gly Pro Leu Ser Ile Val Glu Ala Asp Gly
805 810 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
820 825 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
835 840 845
Ile Lys Glu Asn Thr Gly Val
850 855

<210> 550
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0027797

<400> 550
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
1 5 10 15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
20 25 30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
35 40 45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
85 90 95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
100 105 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
115 120 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
130 135 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145 150 155 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
165 170 175

Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
180 185 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
195 200 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
210 215 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225 230 235 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
245 250 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
260 265 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
275 280 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
290 295 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305 310 315 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
325 330 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
340 345 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
355 360 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
370 375 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385 390 395 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
405 410 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
420 425 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
435 440 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
450 455 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465 470 475 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
485 490 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
500 505 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
515 520 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
530 535 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545 550 555 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
565 570 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
580 585 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
595 600 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
610 615 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile

625 630 635 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
645 650 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
660 665 670
Thr Ala Phe Leu Gly Leu Arg Asp Gln Ser Gln Arg Ser Ala Pro Gly
675 680 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
690 695 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705 710 715 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
725 730 735
His Val Phe Ser Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
740 745 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
755 760 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
770 775 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785 790 795 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
805 810 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln
820 825 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
835 840 845
Ile Lys Glu Asn Thr Gly Val
850 855

<210> 551
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0028017

<400> 551
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
1 5 10 15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
20 25 30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
35 40 45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
85 90 95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
100 105 110

```
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
```

```
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 552
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length


<223> CPC-0028333

<400> 552
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
```

```
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
```

```
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Lys Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Leu Phe Asn
    690                 695                 700
Asp Tyr Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 553
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0028341

<400> 553
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
1 5 10 15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
20 25 30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
35 40 45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
85 90 95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
100 105 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
115 120 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
130 135 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145 150 155 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
165 170 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
180 185 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
195 200 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
210 215 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225 230 235 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
245 250 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
260 265 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
275 280 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
290 295 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305 310 315 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
325 330 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
340 345 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
355 360 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
370 375 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385 390 395 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
405 410 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
420 425 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp

```
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Thr
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Ser Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Leu Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
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<210> 554
<211> 855

<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0033634

<400> 554
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1   5   10   15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20   25   30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35   40   45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50   55   60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65   70   75   80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85   90   95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100   105   110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115   120   125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130   135   140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145   150   155   160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165   170   175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180   185   190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195   200   205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210   215   220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225   230   235   240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245   250   255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260   265   270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275   280   285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290   295   300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305   310   315   320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325   330   335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340   345   350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355   360   365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe

```
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Leu Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
```

Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Leu Arg Asp Trp
835 840 845
Ile Lys Glu Asn Thr Gly Val
850 855

<210> 555
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0028791

<400> 555
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
1 5 10 15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
20 25 30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
35 40 45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
85 90 95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
100 105 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
115 120 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
130 135 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145 150 155 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
165 170 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
180 185 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
195 200 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
210 215 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225 230 235 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
245 250 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
260 265 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
275 280 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
290 295 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr

305 310 315 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
325 330 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
340 345 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
355 360 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
370 375 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385 390 395 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
405 410 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
420 425 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
435 440 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
450 455 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465 470 475 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
485 490 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
500 505 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
515 520 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
530 535 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545 550 555 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
565 570 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
580 585 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
595 600 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
610 615 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625 630 635 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
645 650 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
660 665 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
675 680 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
690 695 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705 710 715 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
725 730 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
740 745 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
755 760 765

```
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 556
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length


<223> CPC-0027484

<400> 556
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
```

```
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Lys
    690                 695                 700
```

```
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
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<210> 557
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MT-SP1 full length

<223> CPC-0028993

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<400> 557
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
```

```
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
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Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Ser Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Ser Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
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Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
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<210> 558
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> N-terminal sequence of pIVEX 2.3d MTSP

<400> 558
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Met Glu Lys Thr Arg His His His His His His Ser Gly Ser Asp Cys
 1               5                  10                  15
Gly Leu Arg Ser Phe Thr Arg Gln Ala Arg
            20                  25
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<210> 559
<211> 3560
<212> DNA
<213> Artificial Sequence

<220>
<223> pIVEX 2.3d vector

<400> 559
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cagcttgtct gtaagcggat gccgggagca gacaagcccg tcagggcgcg tcagcgggtg 120
ttggcgggtg tcggggctgg cttaactatg cggcatcaga gcagattgta ctgagagtgc 180
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accatatatg cggtgtgaaa taccgcacag atgcgtaagg agaaaatacc gcatcaggcg 240
ccattcgcca ttcaggctgc gcaactgttg ggaagggcga tcggtgcggg cctcttcgct 300
attacgccag ctggcgaaag ggggatgtgc tgcaaggcga ttaagttggg taacgccagg 360
gttttcccag tcacgacgtt gtaaaacgac ggccagtgcc aagcttgcat gcaaggagat 420
ggcgcccaac agtcccccgg ccacggggcc tgccaccata cccacgccga aacaagcgct 480
catgagcccg aagtggcgag cccgatcttc cccatcggtg atgtcggcga tataggcgcc 540
agcaaccgca cctgtggcgc cggtgatgcc ggccacgatg cgtccggcgt agaggatcga 600
gatctcgatc ccgcgaaatt aatacgactc actataggga gaccacaacg gtttccctct 660
agaaataatt ttgtttaact ttaagaagga gatataccat ggcacatatg agcggccgcg 720
tcgactcgag cgagctcccg gggggggttc tcatcatcat catcatcatt aataaaaggg 780
cgaattccag cacactggcg gccgttacta gtggatccgg ctgctaacaa agcccgaaag 840
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aaacgggtct tgaggggttt tttgctgaaa ggaggaacta tatccggata tccacaggac 960
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<210> 560
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> pQE-Insert-F2 forward primer

<400> 560
ttcacgagac aggctcgtgt tgttgggggc acggat 36

<210> 561
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> pQE-Insert-R3 reverse primer

<400> 561
cagctaatta agcttattat accccagtgt tctcttt 37

<210> 562
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> pQE-Linear-F2 primer

<400> 562
acgagcctgt ctcgtgaatg accgcagccc 30

<210> 563
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> pQE-Linear-R1 primer

<400> 563
taataagctt aattagctga gcttggactc c 31

<210> 564
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> forward primer: MTSP-5F

<400> 564
ggagaaaccg gcagagtac 19

<210> 565
<211> 19
<212> DNA
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<220>
<223> reverse primer MTSP-5R

<400> 565
ggttctcgca ggtggtctg 19

<210> 566
<211> 5443
<212> DNA
<213> Artificial Sequence

<220>
<223> pET21a vector

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<210> 567

<211> 379
<212> PRT
<213> Homo sapiens

<220>
<223> PAI-1 stable

<400> 567
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1 5 10 15
Val Arg Val Phe Gln Gln Val Ala Gln Ala Ser Lys Asp Arg Asn Val
20 25 30
Val Phe Ser Pro Tyr Gly Val Ala Ser Val Leu Ala Met Leu Gln Leu
35 40 45
Thr Thr Gly Gly Glu Thr Gln Gln Gln Ile Gln Ala Ala Met Gly Phe
50 55 60
Lys Ile Asp Asp Lys Gly Met Ala Pro Ala Leu Arg His Leu Tyr Lys
65 70 75 80
Glu Leu Met Gly Pro Trp Asn Lys Asp Glu Ile Ser Thr Thr Asp Ala
85 90 95
Ile Phe Val Gln Arg Asp Leu Lys Leu Val Gln Gly Phe Met Pro His
100 105 110
Phe Phe Arg Leu Phe Arg Ser Thr Val Lys Gln Val Asp Phe Ser Glu
115 120 125
Val Glu Arg Ala Arg Phe Ile Ile Asn Asp Trp Val Lys Thr His Thr
130 135 140
Lys Gly Met Ile Ser His Leu Leu Gly Thr Gly Ala Val Asp Gln Leu
145 150 155 160
Thr Arg Leu Val Leu Val Asn Ala Leu Tyr Phe Asn Gly Gln Trp Lys
165 170 175
Thr Pro Phe Pro Asp Ser Ser Thr His Arg Arg Leu Phe His Lys Ser
180 185 190
Asp Gly Ser Thr Val Ser Val Pro Met Met Ala Gln Thr Asn Lys Phe
195 200 205
Asn Tyr Thr Glu Phe Thr Thr Pro Asp Gly His Tyr Tyr Asp Ile Leu
210 215 220
Glu Leu Pro Tyr His Gly Asp Thr Leu Ser Met Phe Ile Ala Ala Pro
225 230 235 240
Tyr Glu Lys Glu Val Pro Leu Ser Ala Leu Thr Asn Ile Leu Ser Ala
245 250 255
Gln Leu Ile Ser His Trp Lys Gly Asn Met Thr Arg Leu Pro Arg Leu
260 265 270
Leu Val Leu Pro Lys Phe Ser Leu Glu Thr Glu Val Asp Leu Arg Lys
275 280 285
Pro Leu Glu Asn Leu Gly Met Thr Asp Met Phe Arg Gln Phe Gln Ala
290 295 300
Asp Phe Thr Ser Leu Ser Asp Gln Glu Pro Leu His Val Ala Leu Ala
305 310 315 320
Leu Gln Lys Val Lys Ile Glu Val Asn Glu Ser Gly Thr Val Ala Ser
325 330 335
Ser Ser Thr Ala Val Ile Val Ser Ala Arg Met Ala Pro Glu Glu Ile
340 345 350
Ile Ile Asp Arg Pro Phe Leu Phe Val Val Arg His Asn Pro Thr Gly
355 360 365
Thr Val Leu Phe Met Gly Gln Val Met Glu Pro
370 375

<210> 568
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> I136T/N164D/T166A/F184(A)L/D217V

<400> 568
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
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Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Thr Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asp Gln Ala
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Leu Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 569
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> I41F

<400> 569
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            20   25   30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35   40   45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50   55   60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65   70   75   80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85   90   95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100   105   110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115   120   125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130   135   140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145   150   155   160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165   170   175

Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180   185   190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195   200   205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210   215   220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225   230   235   240
Val

<210> 570
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> I41F/A126T/V244G

<400> 570
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1   5   10   15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20   25   30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35   40   45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50   55   60

```
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met

            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Thr Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Gly
```

<210> 571
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> D23E/I41F/T98P/T144I

<400> 571

```
Val Val Gly Gly Thr Asp Ala Glu Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Pro Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Ile Gln Tyr Gly Gly Thr
```

```
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 572
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> I41F

<400> 572

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
```

```
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 573
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> I41F/L171F/V244G

<400> 573

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Phe Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Gly
```

<210> 574
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> H143R/Q175R

<400> 574
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly Arg Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 575
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> I41F/L171F

<400> 575
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile

```
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Phe Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 576
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> R230W

```
<400> 576
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
```

Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115   120   125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130   135   140

Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145   150   155   160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165   170   175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180   185   190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195   200   205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210   215   220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225   230   235   240
Val

<210> 577
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> I41F/I154V/V244G

<400> 577
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1   5   10   15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20   25   30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35   40   45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50   55   60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu

65   70   75   80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85   90   95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100   105   110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115   120   125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130   135   140
Gly Ala Leu Val Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145   150   155   160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165   170   175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly

```
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Gly
```

<210> 578
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> I141F/L52M/V129D/Q221(A)L

<400> 578

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Phe Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Met Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Asp Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Leu Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 579
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> F99L

<400> 579
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Leu Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 580
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> F97Y/I136V/Q192H/S201I

<400> 580
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Tyr Thr Phe Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Val Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys His Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ile Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 581
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> H71R/P131S/D217V

<400> 581
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60

```
Arg Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Ser Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 582
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> D217V

<400> 582

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
```

```
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 583
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> T65K/F93L/F97Y/D217V

<400> 583

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Lys Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Leu Phe Asn Asp Tyr Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Val Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
```

Val

<210> 584
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> I41T/P173S/Q209L

<400> 584
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Thr Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Ser Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Leu Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 585
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> F97L//F234L

<400> 585
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
50 55 60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65 70 75 80
Lys Arg Ile Ile Ser His Pro Leu Phe Asn Asp Phe Thr Phe Asp Tyr
85 90 95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
100 105 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
115 120 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
130 135 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145 150 155 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
165 170 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
180 185 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
195 200 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
210 215 220
Tyr Thr Arg Leu Pro Leu Leu Arg Asp Trp Ile Lys Glu Asn Thr Gly
225 230 235 240
Val

<210> 586
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> Q175R

<400> 586
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
1 5 10 15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
20 25 30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
35 40 45

```
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 587
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> N95K

<400> 587

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Lys Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
```

```
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 588
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 protease domain

<223> Y60(G)S

<400> 588

```
Val Val Gly Gly Thr Asp Ala Asp Glu Gly Glu Trp Pro Trp Gln Val
 1               5                  10                  15
Ser Leu His Ala Leu Gly Gln Gly His Ile Cys Gly Ala Ser Leu Ile
            20                  25                  30
Ser Pro Asn Trp Leu Val Ser Ala Ala His Cys Tyr Ile Asp Asp Arg
        35                  40                  45
Gly Phe Arg Ser Ser Asp Pro Thr Gln Trp Thr Ala Phe Leu Gly Leu
    50                  55                  60
His Asp Gln Ser Gln Arg Ser Ala Pro Gly Val Gln Glu Arg Arg Leu
65                  70                  75                  80
Lys Arg Ile Ile Ser His Pro Phe Phe Asn Asp Phe Thr Phe Asp Tyr
                85                  90                  95
Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro Ala Glu Tyr Ser Ser Met
            100                 105                 110
Val Arg Pro Ile Cys Leu Pro Asp Ala Ser His Val Phe Pro Ala Gly
        115                 120                 125
Lys Ala Ile Trp Val Thr Gly Trp Gly His Thr Gln Tyr Gly Gly Thr
    130                 135                 140
Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile Arg Val Ile Asn Gln Thr
145                 150                 155                 160
Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile Thr Pro Arg Met Met Cys
                165                 170                 175
Val Gly Phe Leu Ser Gly Gly Val Asp Ser Cys Gln Gly Asp Ser Gly
            180                 185                 190
Gly Pro Leu Ser Ser Val Glu Ala Asp Gly Arg Ile Phe Gln Ala Gly
        195                 200                 205
Val Val Ser Trp Gly Asp Gly Cys Ala Gln Arg Asn Lys Pro Gly Val
    210                 215                 220
```

```
Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp Ile Lys Glu Asn Thr Gly
225                 230                 235                 240
Val
```

<210> 589
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> I136T/N164D/T166A/F184(A)L/D217V

<400> 589

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
```

```
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335

Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly

        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Thr Trp Val Thr Gly Trp Gly His
            740                 745                 750
```

```
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asp Gln Ala Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Leu Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 590
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> I41F

<400> 590

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
```

```
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
```

```
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 591
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> I41F/A126T/V244G

```
<400> 591
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
```

```
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
```

```
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Thr Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Gly
    850                 855
```

<210> 592
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> D23E/I41F/T98P/T144I

<400> 592

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
```

```
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
                100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
```

```
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Glu Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Pro Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Ile Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 593
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> I41F

<400> 593

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
```

```
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
```

```
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 594
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> I41F/L171F/V244G

<400> 594

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
```

```
                420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Phe Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Gly
    850                 855
```

<210> 595
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> H143R/Q175R

<400> 595
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
1 5 10 15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
20 25 30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
35 40 45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
85 90 95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
100 105 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
115 120 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
130 135 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145 150 155 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
165 170 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
180 185 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
195 200 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
210 215 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225 230 235 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
245 250 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
260 265 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
275 280 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
290 295 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305 310 315 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
325 330 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
340 345 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp

```
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly Arg
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
```

```
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 596
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> I41F/L171F

<400> 596

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
```

```
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
```

```
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Phe Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 597

<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> R230W

<400> 597

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
```

```
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
```

```
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 598
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> I41F/I154V/V244G

<400> 598

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
```

```
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
```

610 615 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625 630 635 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
645 650 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
660 665 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
675 680 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
690 695 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705 710 715 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
725 730 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
740 745 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Val Leu Gln Lys Gly Glu Ile
755 760 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
770 775 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785 790 795 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
805 810 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
820 825 830

Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
835 840 845
Ile Lys Glu Asn Thr Gly Gly
850 855

<210> 599
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> I141F/L52M/V129D/Q221(A)L

<400> 599
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
1 5 10 15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
20 25 30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
35 40 45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
50 55 60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65 70 75 80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile

```
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
```

```
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Phe
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Met Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Asp Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Leu
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 600
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length


<223> F99L

<400> 600
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
```

```
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
```

```
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Leu Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 601
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> F97Y/I136V/Q192H/S201I

<400> 601

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
```

```
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Tyr Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Val Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys His Gly Asp Ser Gly Gly Pro Leu Ser Ile Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 602
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> H71R/P131S/D217V

<400> 602
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1   5   10   15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20   25   30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35   40   45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50   55   60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65   70   75   80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85   90   95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100   105   110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115   120   125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130   135   140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145   150   155   160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165   170   175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180   185   190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195   200   205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210   215   220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225   230   235   240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245   250   255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260   265   270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275   280   285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290   295   300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305   310   315   320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325   330   335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn

```
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu Arg Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Ser Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
```

```
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 603
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length


<223> D217V

<400> 603
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
```

```
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720

Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
```

```
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 604
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length


<223> T65K/F93L/F97Y/D217V

<400> 604
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1                5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
```

```
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
```

```
            660                 665                 670
Lys Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Leu Phe Asn
    690                 695                 700
Asp Tyr Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Val Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 605
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length


<223> I41T/P173S/Q209L

<400> 605
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
```

```
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
```

```
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Thr
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Ser Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Leu Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 606
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length


<223> F97L//F234L

<400> 606
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
```

```
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
```

```
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Leu Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Leu Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 607
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length


<223>  Q175R

<400> 607
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
```

```
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
```

```
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
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<210> 608
<211> 855
<212> PRT
<213> Homo sapiens

<220>

<223> Mutant MTSP1 full length

<223> N95K

<400> 608

```
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1               5                  10                  15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20                  25                  30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35                  40                  45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50                  55                  60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65                  70                  75                  80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85                  90                  95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100                 105                 110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115                 120                 125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130                 135                 140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145                 150                 155                 160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165                 170                 175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180                 185                 190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195                 200                 205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210                 215                 220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225                 230                 235                 240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245                 250                 255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260                 265                 270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275                 280                 285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290                 295                 300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305                 310                 315                 320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325                 330                 335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
```

```
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Tyr Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Lys
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Gln Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855
```

<210> 609
<211> 855
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant MTSP1 full length

<223> Y60(G)S

<400> 609
Met Gly Ser Asp Arg Ala Arg Lys Gly Gly Gly Gly Pro Lys Asp Phe
 1   5   10   15
Gly Ala Gly Leu Lys Tyr Asn Ser Arg His Glu Lys Val Asn Gly Leu
            20   25   30
Glu Glu Gly Val Glu Phe Leu Pro Val Asn Asn Val Lys Lys Val Glu
        35   40   45
Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
    50   55   60
Leu Leu Leu Val Leu Leu Gly Ile Gly Phe Leu Val Trp His Leu Gln
65   70   75   80
Tyr Arg Asp Val Arg Val Gln Lys Val Phe Asn Gly Tyr Met Arg Ile
                85   90   95
Thr Asn Glu Asn Phe Val Asp Ala Tyr Glu Asn Ser Asn Ser Thr Glu
            100   105   110
Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
        115   120   125
Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
    130   135   140
Ala Phe Ser Glu Gly Ser Val Ile Ala Tyr Tyr Trp Ser Glu Phe Ser
145   150   155   160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
                165   170   175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
            180   185   190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
        195   200   205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
    210   215   220
Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225   230   235   240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu
                245   250   255
Ser Leu Thr Phe Arg Ser Phe Asp Leu Ala Ser Cys Asp Glu Arg Gly
            260   265   270
Ser Asp Leu Val Thr Val Tyr Asn Thr Leu Ser Pro Met Glu Pro His
        275   280   285
Ala Leu Val Gln Leu Cys Gly Thr Tyr Pro Pro Ser Tyr Asn Leu Thr
    290   295   300
Phe His Ser Ser Gln Asn Val Leu Leu Ile Thr Leu Ile Thr Asn Thr
305   310   315   320
Glu Arg Arg His Pro Gly Phe Glu Ala Thr Phe Phe Gln Leu Pro Arg
                325   330   335
Met Ser Ser Cys Gly Gly Arg Leu Arg Lys Ala Gln Gly Thr Phe Asn

```
            340                 345                 350
Ser Pro Tyr Tyr Pro Gly His Tyr Pro Pro Asn Ile Asp Cys Thr Trp
        355                 360                 365
Asn Ile Glu Val Pro Asn Asn Gln His Val Lys Val Arg Phe Lys Phe
    370                 375                 380
Phe Tyr Leu Leu Glu Pro Gly Val Pro Ala Gly Thr Cys Pro Lys Asp
385                 390                 395                 400
Tyr Val Glu Ile Asn Gly Glu Lys Tyr Cys Gly Glu Arg Ser Gln Phe
                405                 410                 415
Val Val Thr Ser Asn Ser Asn Lys Ile Thr Val Arg Phe His Ser Asp
            420                 425                 430
Gln Ser Tyr Thr Asp Thr Gly Phe Leu Ala Glu Tyr Leu Ser Tyr Asp
        435                 440                 445
Ser Ser Asp Pro Cys Pro Gly Gln Phe Thr Cys Arg Thr Gly Arg Cys
    450                 455                 460
Ile Arg Lys Glu Leu Arg Cys Asp Gly Trp Ala Asp Cys Thr Asp His
465                 470                 475                 480
Ser Asp Glu Leu Asn Cys Ser Cys Asp Ala Gly His Gln Phe Thr Cys
                485                 490                 495
Lys Asn Lys Phe Cys Lys Pro Leu Phe Trp Val Cys Asp Ser Val Asn
            500                 505                 510
Asp Cys Gly Asp Asn Ser Asp Glu Gln Gly Cys Ser Cys Pro Ala Gln
        515                 520                 525
Thr Phe Arg Cys Ser Asn Gly Lys Cys Leu Ser Lys Ser Gln Gln Cys
    530                 535                 540
Asn Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ser Cys Pro
545                 550                 555                 560
Lys Val Asn Val Val Thr Cys Thr Lys His Thr Tyr Arg Cys Leu Asn
                565                 570                 575
Gly Leu Cys Leu Ser Lys Gly Asn Pro Glu Cys Asp Gly Lys Glu Asp
            580                 585                 590
Cys Ser Asp Gly Ser Asp Glu Lys Asp Cys Asp Cys Gly Leu Arg Ser
        595                 600                 605
Phe Thr Arg Gln Ala Arg Val Val Gly Gly Thr Asp Ala Asp Glu Gly
    610                 615                 620
Glu Trp Pro Trp Gln Val Ser Leu His Ala Leu Gly Gln Gly His Ile
625                 630                 635                 640
Cys Gly Ala Ser Leu Ile Ser Pro Asn Trp Leu Val Ser Ala Ala His
                645                 650                 655
Cys Tyr Ile Asp Asp Arg Gly Phe Arg Ser Ser Asp Pro Thr Gln Trp
            660                 665                 670
Thr Ala Phe Leu Gly Leu His Asp Gln Ser Gln Arg Ser Ala Pro Gly
        675                 680                 685
Val Gln Glu Arg Arg Leu Lys Arg Ile Ile Ser His Pro Phe Phe Asn
    690                 695                 700
Asp Phe Thr Phe Asp Tyr Asp Ile Ala Leu Leu Glu Leu Glu Lys Pro
705                 710                 715                 720
Ala Glu Tyr Ser Ser Met Val Arg Pro Ile Cys Leu Pro Asp Ala Ser
                725                 730                 735
His Val Phe Pro Ala Gly Lys Ala Ile Trp Val Thr Gly Trp Gly His
            740                 745                 750
Thr Gln Tyr Gly Gly Thr Gly Ala Leu Ile Leu Gln Lys Gly Glu Ile
        755                 760                 765
Arg Val Ile Asn Gln Thr Thr Cys Glu Asn Leu Leu Pro Gln Arg Ile
    770                 775                 780
Thr Pro Arg Met Met Cys Val Gly Phe Leu Ser Gly Gly Val Asp Ser
785                 790                 795                 800
```

```
Cys Gln Gly Asp Ser Gly Gly Pro Leu Ser Ser Val Glu Ala Asp Gly
                805                 810                 815
Arg Ile Phe Gln Ala Gly Val Val Ser Trp Gly Asp Gly Cys Ala Gln
            820                 825                 830
Arg Asn Lys Pro Gly Val Tyr Thr Arg Leu Pro Leu Phe Arg Asp Trp
        835                 840                 845
Ile Lys Glu Asn Thr Gly Val
    850                 855


<210> 610
<211> 380
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant mature PAI-1

<223> PAI-1/RRAR

<400> 610
Met Val His His Pro Pro Ser Tyr Val Ala His Leu Ala Ser Asp Phe
 1               5                  10                  15
Gly Val Arg Val Phe Gln Gln Val Ala Gln Ala Ser Lys Asp Arg Asn
            20                  25                  30
Val Val Phe Ser Pro Tyr Gly Val Ala Ser Val Leu Ala Met Leu Gln
        35                  40                  45
Leu Thr Thr Gly Gly Glu Thr Gln Gln Gln Ile Gln Ala Ala Met Gly
    50                  55                  60
Phe Lys Ile Asp Asp Lys Gly Met Ala Pro Ala Leu Arg His Leu Tyr
65                  70                  75                  80
Lys Glu Leu Met Gly Pro Trp Asn Lys Asp Glu Ile Ser Thr Thr Asp
                85                  90                  95
Ala Ile Phe Val Gln Arg Asp Leu Lys Leu Val Gln Gly Phe Met Pro
            100                 105                 110
His Phe Phe Arg Leu Phe Arg Ser Thr Val Lys Gln Val Asp Phe Ser
        115                 120                 125
Glu Val Glu Arg Ala Arg Phe Ile Ile Asn Asp Trp Val Lys Thr His
    130                 135                 140
Thr Lys Gly Met Ile Ser Asn Leu Leu Gly Lys Gly Ala Val Asp Gln
145                 150                 155                 160
Leu Thr Arg Leu Val Leu Val Asn Ala Leu Tyr Phe Asn Gly Gln Trp
                165                 170                 175
Lys Thr Pro Phe Pro Asp Ser Ser Thr His Arg Arg Leu Phe His Lys
            180                 185                 190
Ser Asp Gly Ser Thr Val Ser Val Pro Met Met Ala Gln Thr Asn Lys
        195                 200                 205
Phe Asn Tyr Thr Glu Phe Thr Thr Pro Asp Gly His Tyr Tyr Asp Ile
    210                 215                 220
Leu Glu Leu Pro Tyr His Gly Asp Thr Leu Ser Met Phe Ile Ala Ala
225                 230                 235                 240
Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala Leu Thr Asn Ile Leu Ser
                245                 250                 255
Ala Gln Leu Ile Ser His Trp Lys Gly Asn Met Thr Arg Leu Pro Arg
            260                 265                 270
Leu Leu Val Leu Pro Lys Phe Ser Leu Glu Thr Glu Val Asp Leu Arg
        275                 280                 285
```

```
Lys Pro Leu Glu Asn Leu Gly Met Thr Asp Met Phe Arg Gln Phe Gln
    290                 295                 300
Ala Asp Phe Thr Ser Leu Ser Asp Gln Glu Pro Leu His Val Ala Gln
305                 310                 315                 320
Ala Leu Gln Lys Val Lys Ile Glu Val Asn Glu Ser Gly Thr Val Ala
                325                 330                 335
Ser Ser Ser Thr Ala Val Ile Arg Arg Ala Arg Met Ala Pro Glu Glu
            340                 345                 350
Ile Ile Met Asp Arg Pro Phe Leu Phe Val Val Arg His Asn Pro Thr
        355                 360                 365
Gly Thr Val Leu Phe Met Gly Gln Val Met Glu Pro
    370                 375                 380


<210> 611
<211> 380
<212> PRT
<213> Homo sapiens

<220>
<223> Mutant mature PAI-1

<223> PAI-1/69 (containing PFGRS)

<400> 611
Met Val His His Pro Pro Ser Tyr Val Ala His Leu Ala Ser Asp Phe
 1               5                  10                  15
Gly Val Arg Val Phe Gln Gln Val Ala Gln Ala Ser Lys Asp Arg Asn
            20                  25                  30
Val Val Phe Ser Pro Tyr Gly Val Ala Ser Val Leu Ala Met Leu Gln
        35                  40                  45
Leu Thr Thr Gly Gly Glu Thr Gln Gln Gln Ile Gln Ala Ala Met Gly
    50                  55                  60
Phe Lys Ile Asp Asp Lys Gly Met Ala Pro Ala Leu Arg His Leu Tyr
65                  70                  75                  80
Lys Glu Leu Met Gly Pro Trp Asn Lys Asp Glu Ile Ser Thr Thr Asp
                85                  90                  95
Ala Ile Phe Val Gln Arg Asp Leu Lys Leu Val Gln Gly Phe Met Pro
            100                 105                 110
His Phe Phe Arg Leu Phe Arg Ser Thr Val Lys Gln Val Asp Phe Ser
        115                 120                 125
Glu Val Glu Arg Ala Arg Phe Ile Ile Asn Asp Trp Val Lys Thr His
    130                 135                 140
Thr Lys Gly Met Ile Ser Asn Leu Leu Gly Lys Gly Ala Val Asp Gln
145                 150                 155                 160
Leu Thr Arg Leu Val Leu Val Asn Ala Leu Tyr Phe Asn Gly Gln Trp
                165                 170                 175
Lys Thr Pro Phe Pro Asp Ser Ser Thr His Arg Arg Leu Phe His Lys
            180                 185                 190
Ser Asp Gly Ser Thr Val Ser Val Pro Met Met Ala Gln Thr Asn Lys
        195                 200                 205
Phe Asn Tyr Thr Glu Phe Thr Thr Pro Asp Gly His Tyr Tyr Asp Ile
    210                 215                 220
Leu Glu Leu Pro Tyr His Gly Asp Thr Leu Ser Met Phe Ile Ala Ala
225                 230                 235                 240
Pro Tyr Glu Lys Glu Val Pro Leu Ser Ala Leu Thr Asn Ile Leu Ser
                245                 250                 255
```

```
Ala Gln Leu Ile Ser His Trp Lys Gly Asn Met Thr Arg Leu Pro Arg
            260                 265                 270
Leu Leu Val Leu Pro Lys Phe Ser Leu Glu Thr Glu Val Asp Leu Arg
        275                 280                 285
Lys Pro Leu Glu Asn Leu Gly Met Thr Asp Met Phe Arg Gln Phe Gln
    290                 295                 300
Ala Asp Phe Thr Ser Leu Ser Asp Gln Glu Pro Leu His Val Ala Gln
305                 310                 315                 320
Ala Leu Gln Lys Val Lys Ile Glu Val Asn Glu Ser Gly Thr Val Ala
                325                 330                 335
Ser Ser Ser Thr Ala Val Ile Pro Phe Gly Arg Ser Ala Pro Glu Glu
            340                 345                 350
Ile Ile Met Asp Arg Pro Phe Leu Phe Val Val Arg His Asn Pro Thr
        355                 360                 365
Gly Thr Val Leu Phe Met Gly Gln Val Met Glu Pro
    370                 375                 380
```

<210> 612
<211> 1395
<212> DNA
<213> Homo sapiens

<220>
<223> ATIII

<400> 612

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atgtattcca atgtgatagg aactgtaacc tctggaaaaa ggaaggttta tcttttgtcc 60
ttgctgctca ttggcttctg ggactgcgtg acctgtcacg ggagccctgt ggacatctgc 120
acagccaagc cgcgggacat tcccatgaat cccatgtgca tttaccgctc cccggagaag 180
aaggcaactg aggatgaggg ctcagaacag aagatcccgg aggccaccaa ccggcgtgtc 240
tgggaactgt ccaaggccaa ttcccgcttt gctaccactt tctatcagca cctggcagat 300
tccaagaatg acaatgataa cattttcctg tcacccctga gtatctccac ggcttttgct 360
atgaccaagc tgggtgcctg taatgacacc ctccagcaac tgatggaggt atttaagttt 420
gacaccatat ctgagaaaac atctgatcag atccacttct tctttgccaa actgaactgc 480
cgactctatc gaaaagccaa caaatcctcc aagttagtat cagccaatcg ccttttgga 540
gacaaatccc ttaccttcaa tgagacctac caggacatca gtgagttggt atatggagcc 600
aagctccagc ccctggactt caaggaaaat gcagagcaat ccagagcggc catcaacaaa 660
tgggtgtcca ataagaccga aggccgaatc accgatgtca ttccctcgga agccatcaat 720
gagctcactg ttctggtgct ggttaacacc atttacttca agggcctgtg gaagtcaaag 780
ttcagccctg agaacacaag gaaggaactg ttctacaagg ctgatggaga gtcgtgttca 840
gcatctatga tgtaccagga aggcaagttc cgttatcggc gcgtggctga aggcacccag 900
gtgcttgagt tgcccttcaa aggtgatgac atcaccatgg tcctcatctt gcccaagcct 960
gagaagagcc tggccaaggt ggagaaggaa ctcaccccag aggtgctgca ggagtggctg 1020
gatgaattgg aggagatgat gctggtggtc cacatgcccc gcttccgcat tgaggacggc 1080
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65   70   75   80
Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val Trp Glu Leu Ser Lys
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Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln His Leu Ala Asp Ser
            100   105   110
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Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp Ile Ser Glu Leu Val
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225                 230                 235                 240
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<223> OptiPAI-1stab

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Val Ala Gln Ala Ser Lys Asp Arg Asn Val Val Phe Ser Pro Tyr Gly
    50   55   60
Val Ala Ser Val Leu Ala Met Leu Gln Leu Thr Thr Gly Gly Glu Thr
65   70   75   80
Gln Gln Gln Ile Gln Ala Ala Met Gly Phe Lys Ile Asp Asp Lys Gly
                85   90   95
Met Ala Pro Ala Leu Arg His Leu Tyr Lys Glu Leu Met Gly Pro Trp
            100   105   110
Asn Lys Asp Glu Ile Ser Thr Thr Asp Ala Ile Phe Val Gln Arg Asp
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Leu Lys Leu Val Gln Gly Phe Met Pro His Phe Phe Arg Leu Phe Arg
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Ser Thr Val Lys Gln Val Asp Phe Ser Glu Val Glu Arg Ala Arg Phe
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Ile Ile Asn Asp Trp Val Lys Thr His Thr Lys Gly Met Ile Ser His
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Leu Leu Gly Thr Gly Ala Val Asp Gln Leu Thr Arg Leu Val Leu Val
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Asn Ala Leu Tyr Phe Asn Gly Gln Trp Lys Thr Pro Phe Pro Asp Ser
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Ser Thr His Arg Arg Leu Phe His Lys Ser Asp Gly Ser Thr Val Ser
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Val Pro Met Met Ala Gln Thr Asn Lys Phe Asn Tyr Thr Glu Phe Thr
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Thr Pro Asp Gly His Tyr Tyr Asp Ile Leu Glu Leu Pro Tyr His Gly
                245   250   255
Asp Thr Leu Ser Met Phe Ile Ala Ala Pro Tyr Glu Lys Glu Val Pro
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Leu Ser Ala Leu Thr Asn Ile Leu Ser Ala Gln Leu Ile Ser His Trp

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Glu Val Asn Glu Ser Gly Thr Val Ala Ser Ser Ser Thr Ala Val Ile
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Arg Arg Ala Arg Met Ala Pro Glu Glu Ile Ile Ile Asp Arg Pro Phe
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Gln Leu Thr Thr Gly Gly Glu Thr Gln Gln Gln Ile Gln Ala Ala Met
    50                  55                  60
Gly Phe Lys Ile Asp Asp Lys Gly Met Ala Pro Ala Leu Arg His Leu
65                  70                  75                  80
Tyr Lys Glu Leu Met Gly Pro Trp Asn Lys Asp Glu Ile Ser Thr Thr
                85                  90                  95
Asp Ala Ile Phe Val Gln Arg Asp Leu Lys Leu Val Gln Gly Phe Met
            100                 105                 110
Pro His Phe Phe Arg Leu Phe Arg Ser Thr Val Lys Gln Val Asp Phe
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Ser Glu Val Glu Arg Ala Arg Phe Ile Ile Asn Asp Trp Val Lys Thr
    130                 135                 140
His Thr Lys Gly Met Ile Ser His Leu Leu Gly Thr Gly Ala Val Asp
145                 150                 155                 160
Gln Leu Thr Arg Leu Val Leu Val Asn Ala Leu Tyr Phe Asn Gly Gln
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Trp Lys Thr Pro Phe Pro Asp Ser Ser Thr His Arg Arg Leu Phe His
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Lys Ser Asp Gly Ser Thr Val Ser Val Pro Met Met Ala Gln Thr Asn
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Lys Phe Asn Tyr Thr Glu Phe Thr Thr Pro Asp Gly His Tyr Tyr Asp
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Ser Ala Gln Leu Ile Ser His Trp Lys Gly Asn Met Thr Arg Leu Pro
            260                 265                 270
Arg Leu Leu Val Leu Pro Lys Phe Ser Leu Glu Thr Glu Val Asp Leu
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Arg Lys Pro Leu Glu Asn Leu Gly Met Thr Asp Met Phe Arg Gln Phe
    290                 295                 300
Gln Ala Asp Phe Thr Ser Leu Ser Asp Gln Glu Pro Leu His Val Ala
305                 310                 315                 320
Leu Ala Leu Gln Lys Val Lys Ile Glu Val Asn Glu Ser Gly Thr Val
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Ala Ser Ser Ser Thr Ala Val Ile Arg Arg Ala Arg Met Ala Pro Glu
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Glu Ile Ile Ile Asp Arg Pro Phe Leu Phe Val Val Arg His Asn Pro
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