MODIFIED FIBRONECTIN FRAGMENTS OR VARIANTS AND USES THEREOF

FIELD OF THE INVENTION

[001] The present invention generally relates to cell biology and, in particular, the function and interaction of extracellular matrix proteins with integrins. More specifically, the present invention relates to human fibronectin fragments and/or variants thereof as specific antagonists for integrins, in particular integrin α5β1 and integrin αvβ3. The sequence txt file submitted herewith is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[002] Integrins are a family of glycoprotein membrane receptors that mediate cell-matrix and cell-cell interactions. Integrins are heterodimers, consisting of α and β subunits. To date at least 24 distinct integrin heterodimers have been described, including 18 α and 8 β subunits. Integrins mediate anchorage and migration of cells via specific interaction with different extracellular matrix (ECM) proteins. In addition, cell survival, division and differentiation also rely on effective cell-ECM associations (Morgan *et al.* 2009, *IUBMB Life*, 61:731-38).

[003] Integrins α5β1 and αvβ3 are localized in the adhesion contacts of cultured cells. The integrin-ECM complex not only serves to sustain cell-cell and cell-matrix interactions needed for anchorage and migration, the formation of cell-ECM complex also triggers integrin-mediated intra-cellular signaling by recruiting enzymes and adaptors into dynamic complexes inside a cell. The intracellular signals downstream of integrin can influence gene expression, cell survival, differentiation and proliferation. Integrins have been implicated in many pathological conditions such as angiogenesis and tumor progression.

[004] Several integrins were known to interact with fibronectin via the Arg-Gly-Asp (RGD) motif present in fibronectin. These integrins include 5 αv integrins (αvβ1, αvβ3, αvβ5, αvβ6, and αvβ8) and two β1 integrins (α5β1 and α8β1) (Smith, W., 2008, *J. Allergy Clin. Immunol.* 121:S375-S379). Fibronectin is a high-molecular weight (about 440 kDa) glycoprotein of the extracellular matrix that binds to integrins as well as other extracellular matrix proteins. Fibronectin exists as a dimer of two monomers linked by disulfide bonds at the C-terminus. Each fibronectin monomer has a molecular weight of 230–250 kDa that contains three types of domains: type I, II, and III. Type I and II domains are stabilized by intra-chain disulfide bonds, while type III domains do not contain any disulfide bonds. The absence of disulfide bonds can result in flexibility in the structure of FN type III domain.

[005] Each domain contains a number of modules organized to form functional and protein-binding regions along the length of a fibronectin monomer. For example, modules in type I domains are required for initiation of fibronectin matrix assembly, and modules in both type I and type III domains are important for association with other fibronectin molecules. The RGD motif is located in module 10 of the type III domain (FNIII 10), and constitutes the binding site of fibronectin to integrins $\alpha5\beta1$ and $\alpha v\beta3$. The sequence in type III domain module 9 (FNIII 9), especially the PHSRN synergy loop, facilitates the binding of fibronectin to integrin $\alpha5\beta1$. Integrin $\alpha v\beta3$ binding of fibronectin does not require the synergistic effect of module 9.

[006] Because integrins' roles in regulating a variety of cellular functions, the feasibility of using integrin antagonists as treatments of diseases has been studied. For example, antagonists for integrin $\alpha IIb\beta3$, the integrin that activates platelet aggregation, were experimented as an anti-coagulant for treating thrombosis-related ischemic vascular diseases (Coller *et al.*, 2008, *Blood*, 112:3011-25). Disintegrin, such as Rhodostomin, is a family of small protein integrin antagonists naturally found in snake venom that inhibits integrin-mediated platelet aggregation and cell adhesion. Disintegrin, however, is non-specific and highly immunogenic. It competes with fibronectin for binding to $\beta1$- and $\beta3$-containing integrins on the cell surface and non-discriminatively inhibits the activities of integrins $\alpha5\beta1$, $\alpha v\beta3$ and integrin $\alpha IIb\beta3$. Thus, the use of disintegrin as an antagonist for integrins $\alpha5\beta1$ and $\alpha v\beta3$ posts a high risk of hemorrhage due to its $\alpha IIb\beta3$ antagonist activity that prevents platelet aggregation and blood clotting.

[007] Similarly, the *Yersinia pseudotuberculosis* protein invasin is an integrin-binding protein. The bacterial invasin protein facilitates bacteria entry into cells by binding to integrins. The use of invasin as an integrin antagonist is problematic because the bacterial protein is likely highly immunogenic and because the specificity of the invasin protein is not defined.

[008] At high concentrations, FNIII 9-10 to some extent mimics the biological activity of the full-length fibronectin molecule (van der Walle *et al.*, 2002, *Protein Engineering* 15:1021-24). FNIII9-10 competes with other ECM proteins for binding to integrins. Such truncated fibronectin molecule or fragment comprising the binding domain for integrin, *e.g.*, FNIII 10 or FNIII 9-10, is less immunogenic in human and has higher specificity, as compared with distintegrins, and thus does not cause hemorrhage. However, difficulties exist when using truncated fibronectin as integrin antagonists. One of the difficulties is stability and solubility. Human FNIII 9 or FNIII 9-10 alone is structurally unstable (see van der Walle, *supra*). Further, FNIII 9-10 at high concentration is insoluble, which presents great challenges

to its large scale preparation and production. Therefore, there is a need for a better designed integrin antagonist with low immunogenicity, high specificity, and enhanced stability and solubility.

SUMMARY OF THE INVENTION

[009] The invention provides, *inter alia*, integrin antagonists and uses thereof that are not hampered by the limitations found in the prior art.

[0010] It was unexpectedly discovered by the instant inventors that mutant or modified human fibronectin (FN) fragments disclosed herein exhibited integrin antagonist activity. In addition, the FNIII 10 or FNIII 9-10 mutants or variants disclosed herein showed increased solubility and stability as compared to FN fragments with wild type sequences.

[0011] In human FN, the RGD motif is located in a loop of type III domain 10 that is largely disordered and mobile, the flexibility presumably being important for its function. The instant inventors unexpectedly discovered that, increased intradomain rigidity by introducing an engineered di-sulfide bond within FNIII 10 conferred improved solubility and stability and/or maintained or improved antagonist activity for integrin $\alpha5\beta1$ and/or integrin $\alpha v\beta3$. In certain particular embodiments, the FNIII fragments of the invention demonstrate a solubility of at least from about 20 to about 24 mg/ml in a solution at pH 7.0. In certain other particular embodiments, the FNIII fragments of the invention demonstrate a solubility of at least from about 7 to about 27 mg/ml. In certain particular embodiments, the solubility is achieved in the absence of free amino acids Arg and Glu. In certain other embodiments, the FNIII fragments of the invention demonstrate an increased solubility by from about 10% to about 300%, in particular from about 20% to about 280%, 25% to about 250%, 30% to about 200%, 20% to about 150%, as compared to FNIII fragments having the wild type human sequences.

[0012] While not required for binding to integrin $\alpha v\beta3$, module 9 is believed to provide synergistic enhancement of binding to integrin $\alpha5\beta1$. The instant inventors surprisingly discovered that, in the presence of FNIII 9, a di-sulfide bond introduced in module 10 via two Cys substitutions flanking the RGD motif, for example comprising the formula Cys-X_8-Cys, further for example comprising the formula $Cys^{1490}X_2RGDX_3Cys^{1499}$, can improve the solubility and stability of the FNIII 9-10 variants and increase their integrin $\alpha5\beta1$ antagonist activity. Further, the present inventors unexpectedly discovered that an engineered di-sulfide bond in FNIII module 10 flanking the RGD motif, for example comprising the formula Cys-X_7-Cys, further for example comprising the formula $Cys^{1491}XRGDX_3Cys^{1499}$, can improve the solubility and stability of the FNIII 10 variants and their antagonist activity for integrin $\alpha v\beta3$. Further, the instant inventors surprisingly discovered that, in the context of FNIII 9-10, variants with the Cys

substitutions comprising the formula for example Cys-X7-Cys, and further for example $Cys^{1491}XRGDX_3Cys^{1499}$ exhibited binding specificity for integrin αvβ3 instead of integrin α5β1.

[0013] Thus, in one aspect, the invention provides isolated polypeptides comprising a modified human fibronectin fragment that comprises human fibronectin type III domain module 10 (FNIII 10), wherein the FNIII 10 comprises an Arg-Gly-Asp (RGD) motif and two Cys substitutions to form a di-sulfide bond, wherein one Cys substitution is N-terminal to the RGD motif and the other Cys substitution is C-terminal to the RGD motif, and wherein the FNIII 10 comprises an amino acid sequence that is at least 85%, at least 90%, at least 95% or at least 98% homologous to SEQ ID NO:2. In certain embodiments, the polypeptide inhibits or is capable of inhibiting integrin α5β1 or integrin αvβ3 activity and does not inhibit integrin αIIbβ3 activity. Throughout the instant application, the modified human fibronectin fragment can optionally further comprise other modules and/or domains of human fibronectin. In certain embodiments, the modified human fibronectin further comprises type III domain module 9, and the human fibronectin type III domain module 9 and 10 (FNIII 9-10) comprises an amino acid sequence that is at least 85%, at least 90%, at least 95% or at least 98% homologous to SEQ ID NO:4. In certain other embodiments, the FNIII 9-10 optionally further comprises the Leu to Pro substitution at amino acid position 1408 in module 9.

[0014] In certain embodiments, the two Cys substitutions are separated by about 6 to about 9 amino acid residues, flanking the RGD motif. In certain other embodiments, the two Cys substitutions are separated by 7 or 8 amino acid residues. In certain embodiments, the two Cys substitutions are located within amino acid positions 1487-1501. In certain other embodiments, the FNIII 10 further comprises at least one amino acid substitution at amino acid position 1491, 1492, 1496, 1497 or 1498, and wherein the amino acid substitution at position 1491 is Arg or Ile, the amino acid substitution at position 1492 is Ala or Pro, the amino acid substitution at position 1496 is Met, Asn or Trp, the amino acid substitution at position 1497 is Asn, and the amino acid substitution at position 1498 is Asp or Glu. The amino acid numbering used throughout the application is based on the amino acid numbering of the full length human fibronectin protein (SEQ ID NO:74). For instance, the Thr residue at amino acid position 1491 based on the sequence of SEQ ID NO:74 refers to the Thr residue at amino acid position 76 of FNIII 10 as shown in SEQ ID NO:2.

[0015] In certain particular embodiments, the Cys substitutions are Thr to Cys substitution at amino acid position 1491 (T1491C) and Ser to Cys substitution at amino acid position 1499 (S1499C). In certain embodiments, the FNIII 10 comprises the formula $C^{1491}X_{1(n)}RGDX_{2(n)}C^{1499}$ wherein said n is 1, 2 or 3, wherein X_1 and X_2 can represent the same or different amino acid residues. In certain particular

embodiments, the FNIII 10 comprises the formula $C^{1491}X_{1(1)}RGDX_{2(3)}C^{1499}$. In certain particular embodiments, the polypeptide inhibits integrin αvβ3 activity.

[0016] In yet other embodiments, the FNIII 10 comprises the formula Cys^{1491}-X_1-Arg-Gly-Asp-X_2-X_3-X_4-Cys^{1499}, wherein X_1 is Gly, Ala or Pro; X_2 is Ser, Met, Asn or Trp; X_3 is Pro or Asn; and X_4 is Ala, Asp or Glu. In certain particular embodiments, X_1 is Pro, X_2 is Met, X_3 is Pro, and X_4 is Asp. In certain other particular embodiments, X_1 is Pro, X_2 is Trp, X_3 is Asn, and X_4 is Glu. In yet other particular embodiments, X_1 is Ala, X_2 is Asn, X_3 is Pro, and X_4 is Asp. In certain particular embodiments, X_1 is Gly, X_2 is Ser, X_3 is Pro, and X_4 is Ala. In certain other embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10 or SEQ ID NO:12. In certain particular embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:6. In certain other particular embodiments, the polypeptide selectively inhibits or is capable of selectively inhibiting integrin αvβ3 activity.

[0017] In certain other embodiments, wherein the modified human fibronectin fragment further comprises human fibronectin type III domain module 9 (FNIII 9) that optionally comprises Leu to Pro substitution at amino acid position 1408, and wherein the FNIII 9 and FNIII 10 (FNIII 9-10) comprises an amino acid sequence that is at least 85%, at least 90%, at least 95% or at least 98% homologous to the amino acid sequence of SEQ ID NO:4. In certain embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, or SEQ ID NO:26. In certain particular embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:20.

[0018] In certain other embodiments, the Cys substitutions are Val to Cys substitution at amino acid position 1490 (V1490C) and Ser to Cys substitution at amino acid position 1499 (S1499C), wherein the modified human fibronectin fragment optionally further comprises human fibronectin type III domain module 9 that optionally further comprises the Leu to Pro substitution at amino acid position 1408. In certain embodiments, the FNIII 10 comprises the formula Cys^{1490}-X_1-X_2-Arg-Gly-Asp-X_3-Pro-X_4-Cys^{1499}, wherein, X_1 is Thr, Arg or Ile; X_2 is Gly, Ala or Pro; X_3 is Phe, Arg, Asp, Ser, Met or Asn; and X_4 is Ala or Asp. In certain particular embodiments, X_1 is Arg, X_2 is Ala, X_3 is Asn, and X_4 is Asp. In certain other embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:108, SEQ ID NO:109 or SEQ ID NO:110. In certain particular embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:32, SEQ ID NO:108, SEQ ID NO:109 or SEQ ID NO:110. In certain particular embodiments, the polypeptide selectively inhibits or is capable of selectively inhibiting integrin α5β1 activity. In certain embodiment, the Cys substitutions are Val to Cys substitution at amino acid position 1490 (V1490C) and Ser to Cys substitution at amino acid

position 1499 (S1499C), wherein the modified human fibronectin fragment optionally further comprises human fibronectin type III domain module 9 that optionally further comprises the Leu to Pro substitution at amino acid position 1408 and optional the Asn to Ala substitution at amino acid position 1341, the His to Pro substitution at amino acid position 1377, the Pro to Lys substitution at amino acid 1376, or the Pro to Asp substitution at amino acid position 1376. In certain particular embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113 or SEQ ID NO:114.In certain particular embodiments, the polypeptide selectively inhibits or is capable of selectively inhibiting integrin $\alpha 5\beta 1$ activity.

[0019] Flexibility of the FNIII 9-10 interdomain linkage was thought to allow large scale conformational changes in the human FN protein. Partial structural uncoupling of FNIII 9 and FNIII 10 by the extension of the linker at the FNIII 9-10 interface led to loss of the synergistic binding of module 9 (Altroff *et al.*, 2004, *J. Biological Chemistry*, 279:55995-56003). Previous results showed that interdomain rigidity introduced by a di-sulfide bond across the junction of modules 9 and 10 abolished the synergistic cell adhesion activity of FNIII 9-10 via binding to integrin $\alpha 5\beta 1$, and reduced its affinity to FNIII 9-independent integrin $\alpha v\beta 3$ binding (Altroff *et al.*, *supra*).

[0020] The instant inventors, however, surprisingly discovered that an interdomain linkage between modules 9 and 10 created by a non-covalent linkage maintained its binding affinity to integrins $\alpha 5\beta 1$. The non-covalent linkage can provide proper orientation for FNIII 9 and FNIII10 and facilitate binding to integrin $\alpha 5\beta 1$.

[0021] Thus, in another aspect, the invention provides isolated polypeptides comprising a modified human fibronectin fragment that comprises human fibronectin type III domain module 9 and human fibronectin type III domain module 10 (FNIII 9-10), wherein FNIII 9 optionally comprises Leu to Pro substitution at amino acid position 1408, wherein FNIII 9 and/or FNIII 10 comprises at least one amino acid substitution, wherein the amino acid residues in FNIII 9 and FNIII 10 form a non-covalent bond, and wherein FNIII 9 and FNIII 10 comprises an amino acid sequence that is at least 85%, at least 90%, at least 95% or at least 98% homologous to the amino acid sequence of SEQ ID NO:4 and that is not SEQ ID NO NO:64. In certain particular embodiments, the polypeptide inhibits or is capable of inhibiting integrin $\alpha 5\beta 1$ activity.

[0022] In accordance with this aspect of the invention, in certain embodiments, the amino acid substitutions in FNIII 9 and FNIII 10 form an interdomain di-sulfide bond. In certain other embodiments, the amino acid substitutions in FNIII 9 and FNIII 10 form an interdomain hydrogen bond. In certain particular embodiments, the amino acid substitution in FNIII 9 is Ala to Asp substitution at amino acid

position 1340 (A1340D) and the amino acid substitution in FNIII 10 is Val to Lys substitution at amino acid position 1442 (V1442K) (Figure 4). In certain further embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:40. In certain other embodiments, the amino acid substitution in FNIII 10 is Thr to Arg substitution at amino acid position 1491 (T1491R). In certain particular embodiments, the non-covalent interdomain linkage is formed between Asn at amino acid position 1341 and the amino acid residue at position 1491. In certain further embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:72.

[0023] In a further aspect, the invention provides isolated polypeptide comprising a modified human fibronectin fragment that comprises human fibronectin type III domain module 10 (FNIII 10) comprising the formula Val^{1490}-X_1-X_2-Arg-Gly-Asp-X_3-X_4-X_5-X_6-Ser^{1500}, wherein X_1 is Thr or Arg; X_2 is Ala or Pro; X_3 is Met, Trp or Asn; X_4 is Pro or Asn; X_5 is Asp or Glu; and X_6 is Ser or Gly, wherein the modified fibronectin fragment comprises an amino acid sequence that is at least 85%, at least 90%, at least 95% or at least 98% homologous to SEQ ID NO:2 and is not SEQ ID NO:50. In certain particular embodiment, X_1 is Thr; X_2 is Pro; X_3 is Met; X_4 is Pro; X_5 is Asp; and X_6 is Ser. In certain other particular embodiment, X_1 is Thr; X_2 is Ala; X_3 is Asn; X_4 is Pro; X_5 is Asp; and X_6 is Ser. In further embodiments, X_1 is Arg; X_2 is Ala; X_3 is Asn; X_4 is Pro; X_5 is Asp; and X_6 is Ser. In certain particular embodiments, the polypeptide inhibits or is capable of inhibiting integrin $\alpha5\beta1$ activity and/or integrin $\alpha v\beta3$ activity. In certain other embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:48, SEQ ID NO:52 or SEQ ID NO:54. In certain particular embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:48.

[0024] In accordance with this aspect of the invention, in certain embodiments, the modified fibronectin fragment further comprises human fibronectin type III domain module 9 (FNIII 9) that optionally comprises Leu to Pro substitution at amino acid position 1408, and wherein the FNIII 9 and FNIII 10 (FNIII 9-10) comoprises an amino acid sequence that is at least 85%, at least 90%, at least 95% or at least 98% homologous to the amino acid sequence of SEQ ID NO:4. In certain particular embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60 or SEQ ID NO:62. In certain particular embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:60 or SEQ ID NO:62.

[0025] All embodiments described herein can be combined with other embodiments unless it is clear from the context that they cannot. For example, a modified fibronectin fragment comprising FNIII 9-10 that comprises an intradomain disulfide bond can further comprise an engineered interdomain linkage

between FNIII 9 and FNIII 10. Other combinations are also understood to be encompassed by the instant invention.

[0026] In a further aspect, compositions are provided comprising the polypeptides described herein. In yet another aspect, the invention provides pharmaceutical compositions comprising the polypeptides of the invention and a pharmaceutical acceptable excipient, diluent or carrier. In certain particular embodiments, the pharmaceutical compositions comprise a therapeutically effective amount of the polypeptides described in various aspects described above.

[0027] In a further aspect, the invention provides methods of inhibiting integrin-mediated cell adhesion, growth, migration or differentiation, comprising the step of contacting a cell with an effective amount of the polypeptide of the instant invention, wherein the integrin comprises αvβ3 and/or α5β1 integrin. In accordance with these aspects of the invention, in certain embodiments the integrin is integrin αvβ3. In certain further embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:44 or SEQ ID NO:56. In certain particular embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:6. In certain other further embodiments, the integrin is integrin α5β1, and the polypeptide has the amino acid sequence of SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56 or SEQ ID NO:58. In certain particular embodiments, the polypeptide has the amino acid sequence of SEQ ID NO:32.

[0028] In yet another aspect, the invention provides methods of inhibiting integrin-mediated cell adhesion, growth, migration or differentiation in a mammal, comprising the step of administering to a mammal in need thereof a pharmaceutical composition comprising the inventive polypeptides described herein, wherein the integrin is αvβ3 or α5β1. In further aspects, the invention provides methods of inhibiting or treating tumor growth, tumor progression or tumor metastasis in a mammal, comprising the step of administering to a mammal a pharmaceutical composition comprising the inventive polypeptides described herein, wherein the tumor expresses αvβ3 or α5β1. In certain embodiments, the pharmaceutical composition comprises a therapeutic effective amount of the inventive polypeptides described herein. In accordance with these aspects, in certain embodiments, the integrin is integrin αvβ3, and the polypeptide has the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:48 or SEQ ID NO:56. In certain other embodiments, the integrin is integrin α5β1, and the polypeptide has the amino acid sequence of SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:72. In certain particular embodiments, the mammal is a human.

[0029] In yet a further aspect, the invention provides methods of inhibiting an angiogenesis-related disease in a mammal comprising administering to a mammal in need thereof pharmaceutical compositions comprising the inventive polypeptides described herein, wherein the angiogenesis-related disease is cancer, macular degeneration, edema or arthritis. In accordance with this aspect, in certain particular embodiments, the angiogenesis-related disease comprises an disease mediated by integrin $\alpha v\beta 3$ and/or $\alpha 5\beta 1$; in certain other embodiments, the pharmaceutical composition comprises a polypeptide comprising the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:48, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:72.

[0030] In yet another aspect, the invention provides isolated polynucleotides comprising a nucleotide sequence that encodes the inventive polypeptide described herein. In certain embodiments, the polynucleotides comprise a nucleotide sequence of SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, or SEQ ID NO:61. In certain particular embodiments, the polynucleotides comprise a nucleotide sequence of SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:19, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:47, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59 or SEQ ID NO:61.

[0031] In further aspects, the invention provides expression vectors comprising the inventive polynucleotides described herein, or host cells comprising the expression vectors. In a further aspect, the invention provides methods of preparing a polypeptide comprising the steps of (a) culturing the host cell provided herein under conditions effective to allow expression of the polypeptide encoded from the expression vector; and (b) recovering the polypeptide from the culture. In certain particular embodiments, the isolated polypeptides are recovered in a buffer without free Arg and/or Glu.

[0032] Specific embodiments of the present invention will become evident from the following more detailed description of certain preferred embodiments and the claims.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[0033] **Figure 1** is an illustration of an exemplary modified human FNIII 10 with an engineered intradomain disulfide bond formed in the RGD loop region between the T1491C and S1499C substitutions.

[0034] **Figure 2** shows amino acid sequence alignment of wild type human FNIII 9-10 (SEQ ID NO:4) with orthologs from different mammalian species: Chimpanzee (GenBank Accession Number: XP_003309506) (SEQ ID NO:66); Cow (DAA32456)(SEQ ID NO:67); Boar (XP_003133691)(SEQ ID NO:68); Mouse (BAE28040) (SEQ ID NO:69); and Rat (EDL75262) (SEQ ID NO:70). Key: "*" identical; ":" conserved substitution; "." semi-conservative substitution.

[0035] **Figures 3A-C** show thermostabiltiy and solubility of wild-type and mutant FN fragments as shown by NMR (Fig. 3A), differential scanning caliometry and ammonium sulfate precipitation (Fig. 3B, 3C). In Fig. 3B: FNIII 9-10 L1408P- middle peak, square; FNIII 9-10 L1408P (RARGDNPD)- left peak, triangle; and FNIII 9-10 L1408P (CRARGDNPDC)- right peak, circle. In Fig. 3C: FNIII 10- middle peak, circle; FNIII 10 (PRGDMPD) protein (SEQ ID NO:48)- left peak, square; and FNIII 10 (CPRGDMPDC) protein (SEQ ID NO: 6)- right peak, triangle.

[0036] **Figure 4** shows an illustration of an exemplary modified FNIII 9-10 with an engineered interdomain hydrogen bond formed between the A1340D substitution in module 9 and the V1422K substitution in module 10.

[0037] **Figure 5A** presents computer-based models showing the interacting surface between FNIII 9 with integrin $\alpha 5$ subunit (right panel). Possible points of interaction are indicated. **Figure 5B** shows computer docking models of FNIII 9-10 L1408P-CRA (SEQ ID NO:32)-integrin binding complexes and integrin binding selectivity based on the calculated docking energy.

[0038] **Figures 6A-C** show results of purification of different FNIII 9-10 variants by Ni^{2+}- chelating chromatography. The elution profile analyzed by measuring A280 (Absorbance) (left) and images of Coomassie blue staining of SDS gel electrophoresis (right) of FNIII 9-10 variants in the form of monomers or dimers formed by intermolecular S-S bond in the presence or absence of the reducing agent 2- mercaptoethanol.

[0039] **Figures 7A-D** show results of the effects of various FNIII fragments on cell migration, cell survival and cell growth. **Figure 7A-** the left panel presents a bar graph summarizing the inhibitory effect of FNIII 9-10 L1408P (CRARGDNPDC) (SEQ ID NO:32) on A549 cells migration and the right panel presents a bar graph summarizing the inhibitory effect of FNIII 10 (CPRGDMPDC) protein (SEQ ID NO:6) on A375 cells. **Figure 7B** presents a bar graph showing that various FNIII variants induced G1

arrest in A375 melanoma cells. **Figures 7C** and 7**D** present bar graphs showing that various FNIII fragments induced apoptosis in A375 cells and A549 cells, repectively.

[0040] **Figure 8A-B** present thermostability (A) and solubility (B) of ^{9} FNIII 9-10 variants.

[0041] **Figure 9A-B** present thermostability (A) and solubility (B) of FNIII 10 variants.

[0042] **Figures 10A-B** present inhibition of VEGF-induced tube formation (A) by FNIII 9-10 variant, an integrin $\alpha5\beta1$-specific antagonist and no inhibition of bFGF-induced tube formation by ^{9,10}Fn3 variant (B).

[0043] **Figure 11** presents the inhibition of VEGF-induced angiogenesis by FNIII 9-10 (CRARGDNPDC) variant (SEQ ID NO:32), an integrin $\alpha5\beta1$-specific antagonist. .

[0044] **Figure 12** presents the inhibition of bFGF-induced angiogenesis by FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6), an integrin $\alpha v\beta3$-specific antagonist.

[0045] **Figure 13** presents the inhibition of tumor growth in A375-bearing NOD-SCID mice by FNIII 9-10 (CRARGDNPDC) variant (SEQ ID NO:32) in a dose-dependent manner.

[0046] **Figure 14A-C** presents the inhibition of tumor growth in A549-bearing NOD-SCID mice by FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6) in a dose-dependent manner

DETAILED DESCRIPTION OF THE INVENTION

[0047] All publications, patents and patent applications cited herein are hereby expressly incorporated by reference for all purposes.

[0048] Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press) and *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA). Unless specific definitions are provided, the nomenclature utilized in connection with, and the laboratory procedures and techniques of molecular biology, genetic engineering, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0049] Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. For example, reference to a "polypeptide" means one or more polypeptides.

[0050] As described below, the invention provides isolated polypeptides comprising a modified human fibronectin fragment that comprises human fibronectin type III domain module 10 (FNIII 10), wherein the FNIII 10 comprises an Arg-Gly-Asp (RGD) motif, wherein the modified human fibronectin fragment comprises at least one amino acid substitution, and wherein the modified human fibronectin fragment comprises an amino acid sequence that is at least 85%, at least 90%, at least 95%, or at least 98% homologous to SEQ ID NO:2. In certain embodiments, the modified human fibronectin fragment further comprises FNIII 9, optionally further comprising Leu to Pro substitution at amino acid position 1408, and wherein the modified human fibronectin fragment comprises an amino acid sequence that is at least 85%, at least 90%, at least 95% or at least 98% homologous to SEQ ID NO:4. The amino acid numbering used throughout this application follows the amino acid numbering of full-length mature human fibronectin (SEQ ID NO:74). The full-length human fibronectin cDNA and protein sequences are based on GenBank Accession Numbers NM_212476 (SEQ ID NO:73) and NP_997641 (SEQ ID NO:74), respectively.

[0051] Also encompassed within the instant invention are isolated polypeptides that comprise modified fibronectin fragments comprising, in addition to the inventive modified FNIII 10 or modified FNIII 9-10, additional modules and domains of fibronectin, including without limitation module 6, module 7 and/or module 8 of fibronectin type III domain. Full-length FN polypeptides with the one or more inventive mutations described herein are also encompassed within the scope of the invention.

[0052] Human fibronectin binds integrin $\alpha5\beta1$ and integrin $\alpha v\beta3$ via the RGD motif, which resides in FNIII 10. See Figure 1. FNIII 10 alone, however, shows only low affinity for integrin $\alpha v\beta3$. The instant inventors unexpectedly discovered that introducing into the RGD loop an intrachain di-sulfide bond formed between two Cys substitutions within FNIII 10 improved integrin binding and/or antagonist activity of FNIII 10. Further, it was unexpectedly discovered that Cys substitutions comprising the formula Cys^{1491}-X_1-RGD-X_2-X_3-X_4-Cys^{1499} improved integrin $\alpha v\beta3$ antagonist activity in the context of either FNIII 10 or FNIII 9-10. On the other hand, modified FNIII 9-10 comprising the formula Cys^{1490}-X_1-X_2-Arg-Gly-Asp-X_3-Pro-X_4-Cys^{1499} exhibited equal or superior integrin $\alpha5\beta1$ antagonist activity as compared to FNIII 9-10 with the wild type sequence. In certain other embodiments, further mutations including conservative amino acid substitutions can be introduced in the modified inventive fibronectin fragment described herein without affecting the desirable activity of the modified fibronectin fragment.

[0053] It was believed that at high concentration, FNIII 9-10 at some extent mimics full-length FN biological activity. FNIII 9-10 or FNIII 10 was known to be structurally unstable in solution. It was previously reported that a Leu to Pro substitution at amino acid position 1408 (L1408P) improved stability of FNIII 9. *See* van der Walle *et al.*, *supra*. It was also previously reported that an Asp to Asn

substitution at amino acid position 1422 (D1422N) within FNIII 10 improved the stability of FNIII 10 (Koide A., et al. *Biochemistry* 2001, 40:10326-10333). The instant inventors, however, unexpectedly discovered that an engineered di-sulfide bond formed within the RGD loop, for example comprising the formula $Cys^{1491}XRGDX_3Cys^{1499}$ increased the stability and solubility of the FN fragment FNIII 9-10 and FNIII 10, irrespective of the presence of the L1408P and/or the D1422N substitution. It was also discovered by the instant inventors that an engineered di-sulfide bond formed within the RGD loop comprising the formula $Cys^{1490}X_2RGDX_3Cys^{1499}$ increased the stability and solubility of the FN fragment FNIII 9-10.

[0054] Unlike certain other naturally occurring integrin β1 binding protein such as invasin of *Yersinia pseudotuberculosi*, the α5β1 integrin interacting surface of FNIII 9-10 is less flexible due to minimal interaction between the two modules. See Hamburger *et al.*, *Science*, 1999, 286:291. Structural flexibility between FN module 9 and module 10 has been suggested to be important in maintaining FN biological function. See Altroff *et al.*, *supra*; Van Nhieu *et al.* 1996, *J. Biol. Chem.* 271:7665-72; and *Biochemistry* 37:10945 (1998). It was surprisingly discovered by the instant inventors, however, that restricted interdomain movement between FNIII 9 and FNIII 10 did not affect the integrin α5β1antagonistic activity of FNIII 9-10.

[0055] In accordance with this aspect of the invention, in certain embodiments, the invention provides isolated polypeptides comprising a modified human fibronectin fragment that comprises human fibronectin type III domain module 9 and human fibronectin type III domain module 10 (FNIII 9-10), wherein the FNIII 9 optionally comprises Leu to Pro substitution at amino acid position 1408, wherein the FNIII 9 and the FNIII 10 each comprises at least one amino acid substitution, wherein the amino acid substitutions in the FNIII 9 and the FNIII 10 form a non-covalent bond, and wherein the FNIII 9 and FNIII 10 comprises an amino acid sequence that is at least 85%, at least 90%, at least 95% or at least 98% homologous to the amino acid sequence of SEQ ID NO:4 and that is not SEQ ID NO NO:64. In certain particular embodiments, the polypeptide inhibits integrin α5β1 activity.

[0056] By using computer-aided three-dimensional docking model, the instant inventors identified amino acid residues of FNIII 9 that are involved in interaction with integrin α5 subunit (Figure 5A, right panel). The docking model also shows that FNIII 9 does not interact with the αIIb or αV subunit. Computer-generated docking model of FNIII 9-10 L1408P CRARGDNPDC (SEQ ID NO:32) demonstrates that this FNIII variant shows selectiveity for integrin α5β1 binding as evidenced by favorable docking energy (Figure 5B, lower panel).

[0057] In addition to the various embodiments described herein, polypeptides comprising modified FN fragment that comprises additional amino acid substitutions that do not affect the desirable antagonist activity and wherein the modified FN fragment is at least 85%, at least 90%, at least 95% or at least 98% homologous to the corresponding wild type FN sequence are also encompassed within the instant invention. The amino acid sequence of FN is highly conserved among different mammalian species. As an example, Figure 2 shows amino acid sequence alignment of FNIII 9-10 from human and FNIII 9-10 from other indicated mammalian species, the sequences of which are available from the NCBI (National Center for Biotechnology Information) database. The sequences of full-length FN are also publicly available. Thus, it is within the ability of an ordinarily skilled artisan to determine whether FN variants of the invention with additional mutations, including without limitation insertion(s), deletion(s), and substitution(s), that are at least 85%, at least 90%, at least 95% or at least 98% homologous to SEQ ID NO:2 (or SEQ ID NO:4), and that would have maintained the desired activity of the FN fragments based on the conservation of the sequences among different mammalian species.

[0058] The term "isolated protein" or "isolated polypeptide" as used herein refers to a protein encoded by a nucleic acid including, *inter alia*, genomic DNA, cDNA, recombinant DNA, recombinant RNA, or nucleic acid of synthetic origin or some combination thereof, which (1) is free of at least some proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, *e.g.*, from the same cell or species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is naturally found when isolated from the source cell, (5) is not linked (by covalent or noncovalent interaction) to all or a portion of a polypeptide to which the "isolated protein" is linked in nature, (6) is operatively linked (by covalent or noncovalent interaction) to a polypeptide with which it is not linked in nature, or (7) does not occur in nature. Preferably, the isolated protein is substantially free from other contaminating proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic or research use.

[0059] As used herein, the terms "polynucleotide," "nucleotide," "oligonucleotide," and "nucleic acid" may be used interchangeably to refer to nucleic acid comprising DNA, RNA, derivative thereof, or combination thereof.

[0060] As used herein, the terms "polypeptide" and "protein" may be used interchangeably to refer to proteins produced by naturally-occurring and non-recombinant cells, by genetically-engineered or recombinant cells, or by chemical synthesis, and comprise molecules having the amino acid sequence of the native protein, or sequences that have deletions, additions, and/or substitutions of one or more amino

acids of the native sequence. In accordance with the instant invention, the polypeptide or protein specifically encompasses modified human fibronectin or fragments thereof or variants thereof. In certain particular embodiments, the polypeptide or protein encompasses human fibronectin fragments or variants thereof that inhibit integrin activity. In certain particular embodiments, the integrin is integrin α5β1 or αvβ3. In certain other particular embodiments, the integrin is not αIIbβ3.

[0061] The term "integrin antagonist" or "antagonist for integrin" as used herein refers to a molecule capable of inhibiting, blocking, neutralizing, reducing, abrogating or interfering with integrin activities. In certain embodiments, the antagonist inhibits integrin activities by binding to integrin and sequestering integrin from binding to other molecules, for example other ECM proteins. In certain other embodiments, the antagonist inhibits integrin activities by binding to integrin and preventing integrin from triggering downstream signaling events in the cells.

[0062] The term "inhibition" or "inhibit" in the context of integrin activity as used herein refers to a property of an integrin antagonist that reduces the activity of integrin as analyzed by various functional assays, including without limitation, binding assays, migration assays, apoptosis assays and cell adhesion assays. In certain embodiments of the invention, the polypeptide comprising a modified fibronectin fragment inhibit integrin activity, in certain particular embodiments, the integrin is integrin α5β1. In certain other particular embodiments, the integrin is integrin αvβ3. In certain further embodiments, the polypeptide inhibits integrin activity by from about 0 % to about 100 % as compared to the control in the absence of the polypeptide antagonist.

[0063] The term "selectively inhibit," "selective inhibition," "differentially inhibit" or "differential inhibition" as used herein refers to the property of an antagonist that shows differential specificity for a particular target molecule. For example, a polypeptide comprising a modified FN fragment that inhibits integrin αvβ3 activity but does not inhibit integrin α5β1 activity selectively inhibits integrin αvβ3. In certain embodiments, the polypeptide comprising a modified fibronectin fragment comprising FNIII 10, optimally further comprising FNIII 9, selectively inhibits integrin αvβ3 activities; in certain other embodiments, the polypeptide comprising a modified fibronectin fragment comprising FNIII 9-10 selectively inhibits integrin α5β1 activities. In certain alternative embodiments, the polypeptide comprising a modified fibronectin fragment comprising FNIII 9-10 specifically inhibits both integrin αvβ3 and integrin α5β1 activities.

[0064] The term "naturally-occurring" as used herein refers to an object that can be found in nature, for example, a polypeptide or polynucleotide sequence that is present in an organism (including a virus) that can be isolated from a source in nature and which has not been intentionally modified by man. The term

"naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to materials which are found in nature and are not manipulated by man. Similarly, "recombinant," "non-naturally occurring" or "non-native" as used herein refers to a material that is not found in nature or that has been structurally modified or synthesized by man.

[0065] The term "wild type" in the context of nucleic acid sequence or polypeptide sequence as used herein refers to native or naturally-occurring sequences that have not been intentionally modified by man. The wild type human fibronectin amino acid sequences are set forth in SEQ ID NO: 74. It is understood that naturally occurring allelic variants may exist that have amino acid sequences variation from the wild type sequence. The wild type human FN amino acid sequence is set forth in SEQ ID NO:74 as a reference to the numbering of amino acid residues used throughout the application.

[0066] The term "protein fragment" or "polypeptide fragment" as used herein refers to a polypeptide or protein that has an amino acid sequence less than the full length amino acid sequence of the corresponding wild type protein. A fragment of a protein can contain truncation(s) of the full-length protein from the N' terminus and/or from the C' terminus, or truncation(s) from the internal portion of the full-length protein. In certain embodiments, the fragment of a polypeptide retains the desirable activity of the full-length polypeptide. In certain other embodiments, the fragment of a polypeptide acquires desirable additional or altered activity as compared to the full-length protein. In certain particular embodiments, the protein fragment is a human fibronectin fragment, comprising a modified human fibronectin domain III module 10 (FNIII 10) or modules 9 and 10 (FNIII 9-10) that comprises one or more of the inventive modifications described herein. In certain other embodiments, polypeptides comprising the modified human fibronectin further comprising additional insertion(s), deletion(s), or substitution(s) and retaining the desirable activities are also encompassed by the instant invention.

[0067] The term "variant," "mutant" of "modified" as used herein refers to a sequence, either polynucleotide or polypeptide sequence, that contains at least one substitution or variation different from a wild type sequence. In certain embodiments, the variant comprises a modified human fibronectin fragment that comprises human fibronectin type III domain module 10 (FNIII 10) that contains at least one amino acid substitution. Modified FN variants further comprising post translational modifications are also contemplated and encompassed within the scope of the invention. Full length human FN comprises the corresponding inventive amino acid substitution(s) described herein is also contemplated and encompassed by the instant invention.

[0068] The term "homology" or "homologous" as used herein refers to the level of overall sequence similarity and/or identity between corresponding fibronectin fragments. High sequence homology

suggests conservation of protein activity. A number of publicly available algorithms or software programs can be used to determine sequence homology. It is within the ability of one skilled in the art to determine the suitability of additional conservative or non-conservative amino acid substitutions and the level of sequence homology.

[0069] The phrase "N-terminal to" or "C-terminal to" is understood by an ordinarily skilled in the art to refer to the relative locations of two or more amino acid residues in a protein or fragment thereof. For example, an amino acid residue in a peptide sequence N-terminal to a reference amino acid residue is understood to reside in a position of the peptide sequence that is closer to the N-terminus of the peptide sequence than the reference amino acid residue is to the N-terminus. Similarly, an amino acid residue C-terminal to a reference amino acid residue is understood to reside in a position of the peptide sequence closer to the C-terminus of the peptide sequence than the reference amino acid residue is to the C-terminus.

[0070] The human FNIII 10 and FNIII 9-10 variants are summarized in Table 1 below:

[0071] Table 1

Description	Sequence
Wild type FNIII 10	V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V **T G R G D S P A S** S K P I S I N Y R T (SEQ ID NO:2)
FNIII 10 (CX_7C)	V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V **C P R G D M P D C** S K P I S I N Y R T (SEQ ID NO:6)
	V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V **C P R G D W N E C** S K P I S I N Y R T (SEQ ID NO:8)
	V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V **C A R G D N P D C** S K P I S I N Y R T (SEQ ID NO:10)
	V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y

	YRITYGETGGNSPVQEFTVPGSKSTATISGLK PGVDYTITVYAV**CGRGDSPAC**SKPISINYRT (SEQ ID NO:12)
FNIII 10 (CX_8C)	VSDVPRDLEVVAATPTSLLISWDAPAVTVRY YRITYGETGGNSPVQEFTVPGSKSTATISGLK PGVDYTITVYA**CIPRGDMPDC**SKPISINYRT (SEQ ID NO:14)
	VSDVPRDLEVVAATPTSLLISWDAPAVTVRY YRITYGETGGNSPVQEFTVPGSKSTATISGLK PGVDYTITVYA**CRARGDNPDC**SKPISINYRT (SEQ ID NO:16)
	VSDVPRDLEVVAATPTSLLISWDAPAVTVRY YRITYGETGGNSPVQEFTVPGSKSTATISGLK PGVDYTITVYA**CTGRGDSPAC**SKPISINYRT (SEQ ID NO:18)
Wild type FN III 9-10	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESPLLIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAV**TGRGDSPAS**SKPISINYRT (SEQ ID NO:4)
FN III 9-10 (L1408P)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESP**P**LIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAV**TGRGDSPAS**SKPISINYRT (SEQ ID NO:63)
FN III 9-10 (CX_7C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESPLLIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG

	ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAV**CPRGDMPDC**SKPISINYRT (SEQ ID NO:20)
FN III 9-10 (L1408P) (CX_7C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESP**P**LIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAV**CARGDNPDC**SKPISINYRT (SEQ ID NO:22)
FN III 9-10 (L1408P) (CX_7C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESP**P**LIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAV**CGRGDSPAC**SKPISINYRT (SEQ ID NO:24)
FN III 9-10 (CX_7C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESPLLIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAV**CGRGDSPAC**SKPISINYRT (SEQ ID NO:26)
FN III 9-10 (L1408P) (CX_8C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESP**P**LIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYA**CTGRGDSPAC**SKPISINYRT (SEQ ID NO:28)
FN III 9-10 (L1408P) (CX_8C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP

	G T E Y V V S I V A L N G R E E S P **P** L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A **C I P R G D M P D C** S K P I S I N Y R T (SEQ ID NO:30)
FN III 9-10 (L1408P) (CX_8C)	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E D R V P H S R N S I T L T N L T P G T E Y V V S I V A L N G R E E S P **P** L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A **C R A R G D N P D C** S K P I S I N Y R T (SEQ ID NO:32)
FN III 9-10 (L1408P) (CX_8C)	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E D R V P H S R N S I T L T N L T P G T E Y V V S I V A L N G R E E S P P L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V **C R A R G D F P D C** S K P I S I N Y R T (SEQ ID NO:108)
FN III 9-10 (L1408P) (CX_8C)	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E D R V P H S R N S I T L T N L T P G T E Y V V S I V A L N G R E E S P P L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V **C R A R G D R P D C** S K P I S I N Y R T (SEQ ID NO:109)
FN III 9-10 (L1408P) (CX_8C)	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E D R V P H S R N S I T L T N L T P G T E Y V V S I V A L N G R E E S P P L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V **C R A R G D D P D C** S K P I S I N Y R T (SEQ ID NO:110)

FNIII 9-10 (L1408P, N1341A) (CX_8C)	GLDSPTGIDFSDITAASFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESPPLIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYA**CRARGDNPDC**SKPISINYRT (SEQ ID NO:111)
FNIII 9-10 (L1408P, PPSRN) (CX_8C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVP**P**SRNSITLTNLTP GTEYVVSIVALNGREESPPLIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYA**CRARGDNPDC**SKPISINYRT (SEQ ID NO:112)
FNIII 9-10 (L1408P, KHSRN) (CX_8C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRV**K**HSRNSITLTNLTP GTEYVVSIVALNGREESPPLIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYA**CRARGDNPDC**SKPISINYRT (SEQ ID NO:113)
FNIII 9-10 (L1408P, DHSRN) (CX_8C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRV**D**HSRNSITLTNLTP GTEYVVSIVALNGREESPPLIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYA**CRARGDNPDC**SKPISINYRT (SEQ ID NO:114)
FN III 9-10 (CX_8C)	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESPLLIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY

	TITVYA**C**T**G**R**G**D**S**P**A**C**S**KPISINYRT (SEQ ID NO:34)
FNIII 9-10 L1408P, A1340D	GLDSPTGIDFSDIT**D**NSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESP**P**LIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAVTG**R**G**D**SPASSKPISINYRT (SEQ ID NO:36)
FNIII 9-10 L1408P, V1442K	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESP**P**LIGQQSTVSDVPR DLEVVAATPTSLLISWDAPA**K**TVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAVTG**R**G**D**SPASSKPISINYRT (SEQ ID NO:38)
FNIII 9-10 L1408P, A1340D, V1442K	GLDSPTGIDFSDIT**D**NSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESP**P**LIGQQSTVSDVPR DLEVVAATPTSLLISWDAPA**K**TVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAVTG**R**G**D**SPASSKPISINYRT (SEQ ID NO:40)
FNIII 9-10 L1408P, T1491R	GLDSPTGIDFSDITANSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESP**P**LIGQQSTVSDVPR DLEVVAATPTSLLISWDAPAVTVRYYRITYG ETGGNSPVQEFTVPGSKSTATISGLKPGVDY TITVYAV**R**G**R**G**D**SPASSKPISINYRT (SEQ ID NO:72)
FNIII 9-10 L1408P, A1340C, V1442C	GLDSPTGIDFSDIT**C**NSFTVHWIAPRATITGY RIRHHPEHFSGRPREDRVPHSRNSITLTNLTP GTEYVVSIVALNGREESP**P**LIGQQSTVSDVPR

	D L E V V A A T P T S L L I S W D A P A **C** T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T G **R G D** S P A S S K P I S I N Y R T (SEQ ID NO:64)
FNIII 9-10, L1408P, D1373R	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E **R** R V P H S R N S I T L T N L T P G T E Y V V S I V A L N G R E E S P **P** L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T G **R G D** S P A S S K P I S I N Y R T (SEQ ID NO:42)
FNIII 9-10, L1408P, R1379D	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E D R V P H S **D** N S I T L T N L T P G T E Y V V S I V A L N G R E E S P **P** L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T G R G D S P A S S K P I S I N Y R T (SEQ ID NO:44)
FNIII 9-10, L1408P, D1373R, R1379D	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E **R** R V P H S **D** N S I T L T N L T P G T E Y V V S I V A L N G R E E S P **P** L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T G **R G D** S P A S S K P I S I N Y R T (SEQ ID NO:46)
FNIII 10 variant	V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T **P R G D M P D** S S K P I S I N Y R T (SEQ ID NO:48)
FNIII 10 variant	V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T **P R G D W N E G** S K P I S I N Y R T (SEQ ID NO:50)

FNIII 10 variant	V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T **A R G D N P D** S S K P I S I N Y R T (SEQ ID NO:52)
FNIII 10 variant	V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V **R A R G D N P D** S S K P I S I N Y R T (SEQ ID NO:54)
FNIII 10 variant, D1422N	V S D V P R **N** L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T G **R G D** S P A S S K P I S I N Y R T (SEQ ID NO:65)
FNIII 9-10 variant	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E D R V P H S R N S I T L T N L T P G T E Y V V S I V A L N G R E E S P L L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T **P R G D M P D** S S K P I S I N Y R T (SEQ ID NO:56)
FNIII 9-10 variant	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E D R V P H S R N S I T L T N L T P G T E Y V V S I V A L N G R E E S P L L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T **P R G D W N E G** S K P I S I N Y R T (SEQ ID NO:58)
FNIII 9-10 variant (L1408P)	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E D R V P H S R N S I T L T N L T P G T E Y V V S I V A L N G R E E S P **P** L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V T **A R G D N P D** S S K P I S I N Y R T (SEQ ID NO:60)

FNIII 9-10 variant (L1408P)	G L D S P T G I D F S D I T A N S F T V H W I A P R A T I T G Y R I R H H P E H F S G R P R E D R V P H S R N S I T L T N L T P G T E Y V V S I V A L N G R E E S P **P** L I G Q Q S T V S D V P R D L E V V A A T P T S L L I S W D A P A V T V R Y Y R I T Y G E T G G N S P V Q E F T V P G S K S T A T I S G L K P G V D Y T I T V Y A V **R A R G D N P D** S S K P I S I N Y R T (SEQ ID NO:62)

[0072] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. *See* IMMUNOLOGY--A SYNTHESIS, 2nd Edition, (E. S. Golub and D. R. Gren, Eds.), 1991, Sinauer Associates, Sunderland, Mass., which is incorporated herein by reference for any purpose. According to certain embodiments, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) may be made in the naturally-occurring sequence (in certain embodiments, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts or comprising functional domains). In certain embodiments, a conservative amino acid substitution does not substantially change the structural characteristics of the parent sequence (*e.g.*, a replacement amino acid should not disrupt secondary structure that characterizes the parent or native protein, such as a helix). Examples of art-recognized polypeptide secondary and tertiary structures are described in PROTEINS, STRUCTURES AND MOLECULAR PRINCIPLES (Creighton, Ed.), 1984, W. H. New York: Freeman and Company; INTRODUCTION TO PROTEIN STRUCTURE (Branden and Tooze, eds.), 1991, New York: Garland Publishing; and Thornton *et at.*, 1991, *Nature* 354: 105, which are each incorporated herein by reference.

[0073] Naturally occurring residues may be divided into classes based on common side chain properties: 1) hydrophobic: norleucine, Met, Ala, Val, Leu, Ile; 2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; 3) acidic: Asp, Glu; 4) basic: His, Lys, Arg; 5) residues that influence chain orientation: Gly, Pro; and 6) aromatic: Trp, Tyr, Phe.

[0074] Conservative amino acid substitutions may encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties.

[0075] In contrast, non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class. Such substituted residues may be introduced into homologous or non-homologous or non-conserved regions of the molecule.

[0076] In making such changes, according to certain embodiments, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5) (Kyte *et al.*, 1982, *J. Mol. Biol.* 157:105-131).

[0077] The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art (see, *for example*, Kyte *et al.*, 1982, *ibid.*). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ±2 is included. In certain embodiments, those that are within ±1 are included, and in certain embodiments, those within ±0.5 are included.

[0078] It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigen-binding or immunogenicity, *i.e.*, with a biological property of the protein.

[0079] As described in U.S. Patent No. 4,554,101, the following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 ± 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5) and tryptophan (-3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ±2 is included, in certain embodiments, those that are within ±1 are included, and in certain embodiments, those within ±0.5 are included. Exemplary amino acid substitutions are set forth in Table 2.

[0080] **Table 2**

Original Residues	Exemplary Substitutions	Preferred Substitutions
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, Gln, Asn, 1,4 Diamine-butyric Acid	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

[0081] A skilled artisan can determine suitable variants of the polypeptide as set forth herein using well-known techniques. In certain embodiments, one skilled in the art can identify suitable areas of the

molecule that can be changed without destroying activity by targeting regions not believed to be important for activity. In certain embodiments, one can identify residues and portions of the molecules that are conserved among similar polypeptides (by for example analysis of sequence alignment). In certain embodiments, even areas that are important for biological activity or for structure can be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

[0082] Additionally, one skilled in the art can identify amino acid residues in similar or related polypeptides that are important for activity or maintaining structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues important for activity or structure in similar proteins. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues. An amino acid sequence alignment of FNIII 9-10 from different mammalian species is shown in Figure 2.

[0083] One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of such information, one skilled in the art can predict the alignment of amino acid residues of a polypeptide with respect to its three dimensional structure. In certain embodiments, one skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art. Such variants can be used to gather information about suitable variants. For example, if it was discovered that a change to a particular amino acid residue resulted in destroyed, undesirably reduced, or unsuitable activity, variants with such a change can be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or in combination with other mutations.

[0084] Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, non-naturally occurring amino acids such as α-,α-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include but are not limited to: 4-hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the left-hand

direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0085] In certain other embodiments, the polypeptide comprising human fibronectin fragment further comprises a heterologous entity to form a fusion protein. The heterologous entity can facilitate detection and/or purification of the recombinantly synthesized human fibronectin fragment. Suitable heterologous entity includes without limitation a multi-histidine tag, GFP (green fluorescence protein) tag, GST (glutathione S-transferase) tag, and maltose binding protein tag, FLAG tag or HA tag. It is within the ability of one of skill in the art the selection of a suitable tag and construction of an expression vector that expresses the protein of interest with a heterologous tag (or epitope tag). The target protein linked to a desired epitope tag can be created by PCR, in which the sequence encoding the epitope tag is incorporated in the primer sequence. Expression vector designed for recombinant expression of a protein of interest conjugated to a heterologous tag is commercially available, for example, pGEX-2KS (GE Healthcare Life Sciences, Piscataway, NJ) and pET21a (Novagen). In certain embodiments, the heterologous entity or epitope tag is removed by for example protease cleavage at a built-in protease cleavage site after purification of the recombinantly synthesized polypeptide.

[0086] The term "expression vector" refers to a vector that is suitable for transformation of a host cell or a target cell and contains nucleic acid sequences that direct and/or control the expression of inserted heterologous nucleic acid sequences. Expression includes, but is not limited to, processes such as transcription, translation, and RNA splicing, if introns are present. In certain embodiments, an expression vector comprises a polynucleotide sequence that encodes a human fibronectin fragment or variant thereof. In certain particular embodiments, the expression vector comprises a polynucleotide sequence that encodes a hexa-histidine-conjugated human fibronectin fragment or variant thereof.

[0087] Typically, expression vectors used in any of the host cells or target cells contain sequences for vector maintenance and for cloning and expression of exogenous nucleotide sequences. Such sequences, collectively referred to as "flanking sequences" in certain embodiments will typically include one or more of the following nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation signal sequence, a polylinker region comprising one or a plurality of restriction endonuclease sites for inserting nucleic acid encoding the polypeptide to be expressed, and a selectable marker element.

[0088] The term "transduction" is used to refer to the transfer of genes from one bacterium to another, usually by a phage. "Transduction" also refers to the acquisition and transfer of eukaryotic cellular sequences by viruses such as retroviruses.

[0089] The term "transfection" is used to refer to the uptake of foreign or exogenous DNA by a cell, and a cell has been "transfected" when the exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are well known in the art and are disclosed herein. *See, e.g.*, Graham *et al.*, 1973, *Virology* 52: 456; Sambrook *et al.*, 2001, MOLECULAR CLONING: A LABORATORY MANUAL, 3d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Davis *et al.*, 1986, BASIC METHODS IN MOLECULAR BIOLOGY (Elsevier); and Chu *et al.*, 1981, *Gene* 13: 197. Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells.

[0090] The term "transformation" as used herein refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain a new DNA. For example, a cell is transformed where it is genetically modified from its native state. Following transfection or transduction, the transforming DNA may recombine with that of the cell by physically integrating into a chromosome of the cell, may be maintained transiently as an episomal element without being replicated, or may replicate independently as a plasmid. A cell is stably transformed when the DNA is replicated with the division of the cell.

[0091] The term "host cell" is used to refer to a cell into which has been introduced, or that is capable of having introduced, a nucleic acid sequence and then of expressing a gene of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent, so long as the gene is present. In preferred embodiments, the host cell is a eukaryotic cell, more preferably a mammalian cell and most preferably a rodent or human cell.

[0092] In another aspect, the invention provides methods of methods of inhibiting integrin-mediated cell adhesion, growth, migration or differentiation, comprising the step of contacting a cell with a therapeutically effective amount of the polypeptide of the instant invention, wherein the integrin is $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrin. In yet another aspect, the invention provides methods of inhibiting or treating tumor growth, tumor progression or tumor metastasis in a mammal, comprising the step of administering to a mammal a pharmaceutical composition comprising the inventive polypeptides described herein, wherein the tumor expresses $\alpha v\beta 3$ and/or $\alpha 5\beta 1$. Non-exhaustive examples of suitable tumors include lung carcinoma, breast tumor, colon tumor, osteosarcoma, pancreatic tumor, ovarian tumor, cervical tumor, glioblastoma, prostate tumor, liver tumor and melanoma. In certain embodiments, the tumor expresses integrin $\alpha 5\beta 1$, and the non-exhaustive examples of suitable tumors include lung, breast, colon,

melanoma, osteosarcoma and prostate tumor. In certain other embodiments, the tumor expresses integrin αvβ3, and the non-exhaustive examples of suitable tumors include breast, melanoma, pancreatic, ovarian, cervical glioblastoma and prostate tumor.

[0093] In a further aspect, the invention provides methods of inhibiting an angiogenesis-related disease in a mammal comprising administering to a mammal in need thereof pharmaceutical compositions comprising the inventive polypeptides described herein, wherein the angiogenesis-related disease is cancer, macular degeneration, edema, arthritis, multiple sclerosis, vascular malformations, obesity, psoriasis, warts, allergic dermatitis, Kaposi's sarcoma in AIDS, diabetic retinopathy, primary pulmonary hypertension, asthma, cystic fibrosis, inflammatory bowel disease, periodontal disease, liver cirrhosis, endometriosis, ovarian cysts, uterine bleeding, osteomyelitis or diabetic nephropathy. In accordance with this aspect, in certain particular embodiments, the angiogenesis-related disease comprises a disease mediated by integrin αvβ3 and/or α5β1.

[0094] As used herein, the term "effective amount" or a "therapeutically effective amount"of an isolated polypeptide refers to an amount sufficient to achieve the stated desired result, for example, inhibiting integrin-mediated cell adhesion, growth, migration or differentiation, or inhibiting or treating tumor growth, tumor progression or tumor metastasis. The amount of a polypeptide or compound which constitutes an "effective amount" or "therapeutically effective amount" will vary depending on the polypeptide or compound, the disorder and its severity, and the age of the subject to be treated, but can be determined routinely by one of ordinary skill in the art. In certain embodiments, the subject is a mammal. In certain particular embodiments, the mammal is a human.

[0095] "Treating" or "treatment" as used herein covers the treatment of a disease or disorder described herein, in a mammal, for example a human, and includes: (i) inhibiting a disease or disorder, *i.e.*, arresting its development; (ii) relieving a disease or disorder, *i.e.*, causing regression of the disorder; (iii) slowing progression of the disorder; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder.

[0096] Administration routes for the pharmaceutical compositions of the invention include orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, subcutaneous, intramuscular, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. The pharmaceutical compositions may be administered by bolus injection or continuously by infusion, or by implantation device. The pharmaceutical composition also can be administered locally *via* implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or

encapsulated. Where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of the desired molecule may be via diffusion, timed-release bolus, or continuous administration.

[0097] The polypeptides of the invention can be formulated according to known methods for preparing pharmaceutical compositions, in which the polypeptide to be delivered is combined with a pharmaceutically acceptable carrier, diluent or excipient. Suitable carrier, diluent and excipient and the preparation thereof are described, for example, in Genaro, A. O. "Remington: The Science and Practice of Pharmacy." Lippincott Williams & Wilkins (2005).

[0098] For aqueous pharmaceutical compositions used *in vivo*, sterile pyrogen-free water is preferred. Such formulations will contain an effective amount of the polypeptide together with a suitable amount of pharmaceutically acceptable carrier, diluent or excipient in order to prepare pharmaceutically acceptable compositions suitable for administration to a mammal, especially human. It is within the knowledge of one ordinarily skilled artisan or physician, and further taught in the instant application, the effective amount of the composition to be administered to a mammal, preferably a human to achieve the desirable therapeutic effect.

[0099] In certain embodiments, the composition comprising modified FN fragments of the invention can further comprise other anti-cancer, anti-angiogenesis and chemotherapy drugs to provide therapeutic effects.

[00100]The modified FN fragments of the invention can be chemically modified to prevent or reduce proteolytic degradation. Methods for chemcial modification or optimization of protein or fragments thereof are well known in the art, including without limitation substitution of natural amino acid residues with unnatural amino acid residues, amino acid bond replacement, blocking N or C-terminal ends by N-acylation, N-pyroglutamate, and/or C-amidation, and N-terminal esterification or pegylation modifications. See for example Vlieghe et al., 2010, Drug Discovery Today, 15:40-56.

[00101]In a further aspect, kits are provided that comprise the inventive polypeptides, composition or pharmaceutical composition described herein. The pharmaceutical compositions of the present invention may be in the form of an emulsion, gel, solution, suspension, etc. The compositions of the present invention can also be lyophilized to produce a composition in a dried form for ease in transportation and storage. The compositions of the present invention may be stored in a sealed vial, container, ampule or the like. In the case where the composition is in a dried form, the composition is dissolved or resuspended (*e.g.*, in sterilized distilled water or a buffer) before administration. An inert carrier such as

saline or phosphate buffered saline or any such carrier, in which the composition has suitable solubility, may be used.

[00102]The Examples, which follow, are illustrative of specific embodiments of the invention, and various uses thereof. They are set forth for explanatory purposes only, and are not to be taken as limiting the invention.

EXAMPLES

Example 1 Construction of Expression Vectors Expressing Wild-type and Variants of FNIII Fragments

[00103]Wild-type human FN III 9-10 was cloned and expressed in the vector pET21a (Novagen). The DNA encoding FNIII variants was composed of codons preferentially used in *E. coli*. Wild-type FNIII 9-10 coding sequence was amplified by polymerase chain reaction (PCR) with the forward primer 5'-CATATGCATATGCACCACCACCACCACCACGGTCTTGATTCCCCAACT-3' (SEQ ID NO:75) that had the Nde I recognition site and six histidine residues for affinity purification. The reverse primer is 5'-AAGCTTAAGCTTTCATGTTCGGTAATTAATGGAAATTGG-3' (SEQ ID NO: 76) with the Hind III recognition site and a TCA (or TTA) stop codon. The PCR product was purified and then ligated into the Nde I and Hind III sites of the *E.coli* recombination vector, pET21a (Novagen). The recombinant plasmid was used to transform *E. coli* DH5α strain, and colonies were selected on agar plates with LB (1% tryptone, 0.5% yeast extract, 1.0% NaCI, 1.0% agar at pH 7.4) and 100 μg/ml antibiotic Ampicillin.

[00104] FNIII 9-10 variants were synthesized and amplified by PCR using an overlapping oligonucleotide strategy with primers containing Nde I and Hind III restriction sites. The nucleotide sequences of various primers used for synthesizing or confirming variants are listed in Table 3.

[00105]The polymerase chain reactions were performed according to the procedure described in US2008/0188413, which is incorporated by reference herein in its entirety. Briefly, the reaction was carried out at 95°C for 1 min, 55°C for 1 min, and 72°C for 1 min for 25 cycles. A mixture of primers was also used for generating multiple mutation sites. The PCR products were separated on 2% agarose gel electrophoresis and visualized by ethidium bromide staining. The desired PCR products were purified and then ligated into the Eco RI and Sac II sites of the yeast transfer vector pPICZ alpha A. The recombinant plasmid was used to transform an *Escherichia coli* XL1-blue strain and colonies were selected on agar plates containing antibiotic Zeocin. Plasmid DNA from Zeocin-positive colonies was amplified and isolated, and the FNIII sequences contained in the plasmids were confirmed by DNA sequencing.

[00106] Table 3

Primer	Sequence	SEQ ID NO:
NdeI--3FN9-10 (forward)	CATATGCATATGCACCACCACCACCACCACGGTCTTGATTCCCCAACT	75
HindIII--3FN9-10 (reverse)	AAGCTTAAGCTTTCATGTTCGGTAATTAATGGAAATTGG	76
NdeI--3FN10 (forward)	CATATGCATATGCACCACCACCACCACCACGTTTCTGATGTTCCGA	77
RGD loop PRGDMPD (F)	CGTGGTGATATGCCTGACAGCAGCAAG	78
RGD loop PRGDMPD (R)	AGGCATATCACCACGAGGAGTGACAGCATA	79
RGD loop ARGDNPD (F)	CGTGGTGATAATCCTGACAGCAGCAAG	80
RGD loop ARGDNPD (R)	AGGATTATCACCACGAGCAGTGACAGCATA	81
RGD loop PRGDWNEG (F)	GGAGACTGGAATGAAGGAAGCAAGCCA	82
RGD loop PRGDWNEG (R)	ATTCCAGTCTCCACGCGGAGTGACAGCATA	83
RGD loop RARGDNPD (F)	TATGCTGTCCGTGCTCGTGGTGAT	84
RGD loop RARGDNPD (R)	ACCACGAGCACGGACAGCATACAC	85
3FN9 L1408P (F)	AGTCCCCCGTTGATTGGC	86
3FN9 L1408P (R)	CAACGGGGGACTTTCCTC	87
3FN10 D1442N (F)	CCGAGGAATCTGGAAGTTG	88
3FN10 D1442N (R)	CAGATTCCTCGGAACATC	89
Interdomian linkage A1340D (F)	TCTGATATTACTGATAACTCTTTTACTGTG	90
Interdomian linkage	AGAGTTATCAGTAATATCAGAAAAGTCAAT	91

A1340D (R)		
Interdomain linkage V1422K (F)	GCTAAAACAGTGAGATATTACAGGATC	92
Interdomain linkage V1422K (R)	CACTGTTTTAGCAGGAGCATCCCA	93
D1373R (F)	GAACGTCGGGTGCCC	94
D1373R (R)	CCGACGTTCACGAGGTCT	95
R1379D (F)	GTGCCCCACTCTGATAATTCCATCACC	96
R1379D (R)	GGTGATGGAATTATCAGAGTGGGGCAC	97
CX_7C CARGDNPDC(F)	CGTGGTGATAATCCTGACTGTAGCAAGCCA	98
CARGDNPDC(R)	AGGATTATCACCACGAGCACAGACAGCATA	99
CPRGDMPDC(F)	CGTGGTGATATGCCTGACTGTAGCAAGCCA	100
CPRGDMPDC(R)	AGGCATATCACCACGAGGACAGACAGCATA	101
CPRGDWNEC(F)	GGAGACTGGAATGAATGTAGCAAGCCA	102
CPRGDWNEC(R)	ATTCCAGTCTCCACGCGGACAGACAGCATA	103
CX_8C CRARGDNPDC(F)	CGTGGTGATAATCCTGACTGTAGCAAGCCA	104
CRARGDNPDC(R)	AGGATTATCACCACGAGCACGACAAGCATACAC	105
CTGRGDSPAC(F)	GGTCGTGGAGACAGCCCCGCATGTAGCAAGCCA	106
CTGRGDSPAC(R)	GTCTCCACGACCAGTACAAGCATACAC	107

Example 2 Expression and Purification of FNIII 9-10 and FNIII 10 Variants

[00107] Protein expression of wild-type FNIII 9-10, FNIII 10 or variants thereof was carried out using the *Pichia* EASYCOMP™ Transformation Kit (Invitrogen) according to the manufacturer's recommendations with minor modifications. Briefly, a total of 10 µg plasmids containing DNA encoding FNIII 9-10, FNIII 10 or variants thereof were digested with Sac I to linearize the plasmids. *Pichia* strain X33 was transformed with the linearized constructs by a heat shock method, using the *Pichia* EASYCOMP™ Kit. The linearized construct was integrated at the 5' AOX1 locus by a single crossover. *Pichia* cells were lysed by Lyticase (Sigma) and analyzed by PCR to verify integration of the FNIII sequences into the *Pichia* genome. Colonies were selected on agar plates containing YPD (1% yeast extract, 2% peptone, 2% glucose, and 2% agar) and 100 µg/ml Zeocin. A number of colonies with

multiple copies of the FNIII insertions were selected for the highest FNIII 9-10 or FNIII 10 protein expression.

[00108] Recombinant FNIII 9-10, FNIII 10 and the variants were produced as follows: selected colonies were grown in the YPD medium (1% yeast extract, 2% peptone, and 2% dextrose) containing 100 μg/ml Zeocin at 30° C. After 48 hours, cells were collected by centrifugation and grown in 1 liter of minimal methanol medium (containing 1.34% yeast nitrogen base with ammonium sulfate without amino acids and 4 x 10^{-5} % biotin). A total of 1% methanol was added once every 24 hours to induce expression of FNIII or variants thereof for 2 days. The supernatant was collected by centrifugation and dialyzed twice against 5 liter buffer A (5 mM EDTA, 8M urea and 10 mM Na-phosphate buffer, pH 7.7). The final solution was loaded into a nickel-chelating column and eluted with a gradient of 200 mM imidazole. The recombinant FNIII 9-10, FNIII 10 and variants thereof were further purified by HPLC (reverse phase C18 HPLC). The purified recombinant FNIII had a purity of greater than 95% as judged by tricine-SDS-PAGE. Expression and purity of several FNIII variants is shown in Figure 6. Representative HPLC profile and the purity of the FNIII 9-10 variants having the sequence of CPRGDMPDC (SEQ ID NO:20, L1408P (CARGDNPDC) protein (SEQ ID NO:22 and L1408P, V1442K substitution (SEQ ID NO:28) are shown in Figures 6A-C, respectively.

Example 3 FNIII 10 Intradomain Disulfide Bond Improved Stability and Solubility of FNIII 9-10 and FNIII 10

[00109] It was previously shown that a Leu to Pro substitution at amino acid position 1408 improved the stability of FNIII 9-10 (van der Walle *et al.*, 2002, *Protein Engineering* 15:1021-24). The stability of intra-domain disulfide bond mutations in module 10 was tested by one-dimensional NMR spectrum analysis in buffer at different pH values. The presence of the L1408P mutation improved the stability of FNIII 9-10 at pH 5.0 as compared to wild type FNIII 9-10 in a solution containing 50 mM free arginine and glutamine. Free arginine and glutamine were added for the purpose of increasing maximal achievable protein concentration and imporiving long-term sample stability against precipitation and degradation (see Golovanov A.P., et al. J. Am. Chem. Soc. 126 (2004) 8933–8939). However, the stability of L1408P mutant decreased at higher pH, *e.g.*, pH 6.0 (Fig. 3A, lower right panel), or lower pH, *e.g.*, pH 3.5, in the absence of free arginine and glutamine. On the other hand, intradomain disulfide bond stabilized FNIII 9-10 in phosphate buffer even at pH 7.5 without the need for the L1408P mutation and without the need for free arginine and glutamine. As shown in Figure 3A, upper right panel, FNIII 9-10 (CPRGDMPDC, SEQ ID NO:20) with the intradomain disulfide bond and without the L1408P mutation remained stable at

pH 7.5, in a solution without arginine and glutamine. The intradomain disulfide bond also increased stability and solubility of FNIII 9-10 variants (Fig. 3B).

[00110]It has also been shown that substitution from Asp to Asn in module 10 at position 1422 (SEQ ID NO:65) improved stability of FNIII 10 in the presence of 50 mM free arginine and glutamine at pH 5. The stability of the D1422N mutant, however, decreased when the pH was increased to 5.4 and 6. See Figure 3A, lower left panel. As shown in Figure 3C, the intradomain disulfide bond present in FNIII 10 (CPRGDMPDC) protein (SEQ ID NO:6) improved stability and solubility of FNIII 10 without the need for the D1422N mutation (Fig. 3C).

Example 4 FNIII 9-10 or FNIII 10 Variants Inhibited Integrin α5β1- or αvβ3-mediated Cell Attachment

[00111]The integrin antagonist activity of FNIII variants were evaluated by cell adhesion inhibition assays as described previously (Zhang, *et al.*, 1998 *J Biol Chem* 273:7345-7350). Briefly, 96-well Immulon-2 microtiter plates (Costar, Corning, NY) were coated with 100 µl of phosphate-buffered saline (PBS: 10 mM phosphate buffer, 0.15M NaCl, pH 7.4) containing substrates at a concentration of 50-500 nM, and incubated overnight at 4 °C. The substrates for coating included: fibrinogen (FG) 50 µg/ml for α5β1, vitronectin (VN) 10 µg/ml for αvβ3, and fibronectin (FN) 25 µg/ml for αIIbβ3. Non-specific protein binding sites were blocked by incubating each well with 200 µl of heat-denatured 1% bovine serum albumin (BSA, Calbiochem) at room temperature (25 °C) for 1.5 hr. Afterwards, the blocking heat-denatured BSA was discarded and each well was washed twice with 200 µl of PBS.

[00112]Chinese hamster ovary (CHO) cells expressing αvβ3 (CHO-αvβ3) and α5β1 (CHO-α5β1) integrins were maintained in 100 µl of Dulbecco's Modified Eagle's Medium (DMEM) medium. Both CHO-αvβ3 and CHO-α5β1 were kind gifts of Dr. Y. Takada (Scripps Research Institute) established by stable transfection with a neomycin-resistant gene. CHO cells growing in log phase were detached by trypsinization and used in the assay at 3 x 10^5 cells/ml. FNIII 9-10, FNIII 10 and variants thereof were added to the cultured cells at the concentrations of 0.001-500 µM and incubated at 37 °C in 5% CO_2 for 15 minutes. The treated cells were then added into the coated plate and incubated at 37 °C in 5% CO_2 for 1 hour. The incubation solution was then discarded and non-adhered cells were removed by washing twice with 200 µl PBS.

[00113]Bound cells were quantified by crystal violet staining. Briefly, the well was fixed with 100 µl of 10% formalin for 10 minutes and dried. Fifty microliters of 0.05% crystal violet were then added into the well at room temperature for 20 minutes. Each well was washed with 200 µl of distilled water four times

and dried. Colorization was carried out by adding 150 µl of colorizing solution (50% alcohol and 0.1% acetic acid). The resulting absorbance was read at 600 nm and the readings were correlated with the number of adhering cells. Inhibition was defined as % inhibition=100-[OD_{600} (FNIII wild type or variant-treated sample)/ OD_{600} (untreated sample)] x 100. IC_{50} was defined as the concentration (nM) required for 50% inhibition of cell adhesion. Therefore, lower IC_{50} indicates grater specificity or potency of the variant in inhibiting the cell adhesion activity of respective integrin. The results are summarized in Tables 4 and 5 below.

[00114] Wild type FNIII 10 did not effectively compete with FN for binding to integrin αvβ3 and thus did not show integrin αvβ3 antagonist activity in the cell adhesion assay. FNIII 10 with the sequence PRGDWNEGSK at amino acid positions 1492-1451 (SEQ ID NO:50) showed integrin αvβ3 binding activity, and competed with full length FN for binding to integrin αvβ3. See Table 4 and Richards et al., J Mol Biol. 2003, 326(5):1475-88.

[00115] It was unexpectedly discovered that introducing into the RGD loop a di-sulfide bond between two Cys substitutions flanking the RGD motif in a sequence comprising the formula of Cys-X7-Cys, for example between the T1491C and S1499C substitutions, greatly enhanced integrin αvβ3 antagonist activity (*see e.g.*, Table 4, SEQ ID NO:6, 8 and 10 as compared to SEQ ID NO:2). In addition, the engineered di-sulfide bond further enhanced integrin αvβ3 antagonist activity of an FNIII 10 variant that already exhibited integrin αvβ3 antagonist activity. For example, two cysteine substitutions flanking the RGD motif in the background of FNIII 10 PRGDMPD (i.e., SEQ ID NO:6 with CPRGDMPDC) increased integrin αvβ3 binding affinity as compared to the variant without the Cys substitutions (SEQ ID NO:48) by 7 fold, and thus decreased the concentration required to inhibit 50% of cell adhesion (compare results of SEQ ID NO:6 with SEQ ID NO:48).

[00116] In summary, introduction of a di-sulfide bond within the loosely structured RGD loop substantially increased the binding affinity of FNIII variants for integrin αvβ3, and thus increased integrin αvβ3 antagonist activity as measured by the cell adhesion assay.

Table 4

FIII Fragment	IC_{50}, nM			
	α5β1 (cell adhesion assay)	**αvβ3 (cell adhesion assay)**	**αIIbβ3 (cell adhesion assay)**	**Platelet Aggregation (Inhibition of**

				ADP-induced platelet aggregation)
Wild type FNIII 10 (SEQ ID NO:2, VTG RGDSPASSK) (Control)	> 4590 (39%)*	4579	> 9180 (0%)	~ 45000
Control FNIII 10 mutant (SEQ ID NO:50, VTPRGDWN EGSK) (Control)	> 4513 (32.5%)	908	> 9027 (0%)	> 6454 (14%)
FNIII 10 C-X_7-C (SEQ ID NO:6, VCPRGDMPD CSK)	> 73218 (42%)	93	> 62124 (19%)	~ 62000
FNIII 10 C-X_7-C (SEQ ID NO:8, VCPRGDWNE CSK)	> 4494 (48%)	418	> 4494 (0%)	~ 10000
FNIII 10 C-X_7-C (SEQ ID NO:10, VCARGDN PDCSK)	> 4546 (0%)	432	> 4546 (0%)	> 25463 (2%)
FNIII 10 variant (SEQ ID NO:48, VTPRGDMP DSSK)	> 6805 (31.7%)	645	> 9073 (0%)	> 22155 (4%)
FNIII 9-10 C-X_7-C (SEQ ID NO:20, VCPRGDMP DCSK)	~ 4765	112	> 2382 (26%)	> 5003 (12%)

* percentages in parentheses represent percentage of inhibition compared with control in the absence of the FN fragments

[00117] Wild type FNIII 9-10 binds to integrin α5β1 but not integrin αvβ3. See results of wild type FNIII 9-10 (SEQ ID NO:4) in Table 5. Interestingly, FNIII 9-10 variants having an engineered di-sulfide bond flanking the RGD motif in the formula C-X_7-C exhibited altered binding specificity. For example, FNIII 9-10 having the amino acid sequence VCPRGDMPDCSK at amino acid positions 1490-1501 (SEQ ID NO:20) showed, instead of integrin α5β1, integrin αvβ3 antagonist activity, even though FNIII 9-10 has been considered an integrin α5β1 binder. See Table 4, comparing results of SEQ ID NOs:6 and 20 with those of Table 5, results of SEQ ID NO:4.

[00118] On the other hand, an intradomain di-sulfide bond formed by Cys substitutions in a sequence comprising the formula C-X_8-C did not alter the binding specificity of FNIII 9-10, and in some instances improved the binding affinity to integrin α5β1 (*see e.g.*, Table 5, results of SEQ ID NO:32 as compared with results of SEQ ID NO:4 or SEQ ID NO:63).

[00119] It was previously shown that an interdomain di-sulfide bond between modules 9 and 10 (in the background of the L1408P substitution), although stabilized the FNIII 9-10 fragment, decreased the synergistic effect of module 9 to bind integrin α5β1 (Altroff *et al.*, *supra*). The instant inventors, however, unexpectedly discovered that FNIII 9-10 (in the background of the L1408P substitution) with an interdomain linkage formed between an engineered Asp and Lys at positions 1340 and 1442 (A1340D and V1442K substitutions) maintained the binding affinity as compared to integrin α5β1 (see Table 5, results of SEQ ID NO:40 as compared to results of SEQ ID NO:4 or SEQ ID NO:63).

[00120] In additon, some of the FNIII 9-10 variants also acquired binding affinity to integrin αvβ3 (see Table 4, results of SEQ ID NO:60 as compared to results of SEQ ID NO:4 or SEQ ID NO:63).

Table 5

FIII Fragment	**IC_{50}, nM**			
	α5β1	**αvβ3**	**αIIbβ3**	**Platelet Aggregation**
Wild type FNIII 9-10 (SEQ ID NO:4) (Control)	245	> 3119 (33.2%)	> 4798 (0%)	~ 20000
Control FNIII 9-10	200	> 4802 (43.1%)	> 4802 (0%)	~ 30000

mutant, L1408P (SEQ ID NO:63)				
FNIII 9-10, L1408P, C-X_8-C (SEQ ID NO:32, CRARGDNPDCSK)	67	~ 4766	> 19064 (39%)	> 24781 (1.3%)
FNIII 9-10, L1408P, C-X_8-C (SEQ ID NO:34, CTGRGDSPACSK)	250	2092	> 4797 (0%)	> 23508 (24%)
FNIII 9-10, L1408P, A1340D, V1442K (SEQ ID NO:40)	214	4240	> 4779 (2%)	> 8602 (35.8%)
FNIII 9-10, L1408P, D1373R (SEQ ID NO:42)	224	3845	> 4791 (9%)	> 12410 (40%)
FNIII 9-10 variant (SEQ ID NO:56, VTPRGDMPDSSK)	284	1728	> 4250 (0%)	> 11446 (0%)
FNIII 9-10 variant (SEQ ID NO:58, VTPRGDWNEGSK)	270	1289	> 1250 (0%)	> 4919 (28.5%)
FNIII 9-10 variant, L1408P (SEQ ID NO:60, VTARGDNPDSSK)	165	423	> 4782 (0%)	> 66959 (14.2%)
FNIII 9-10 variant, L1408P (SEQ ID NO:62,	149	~ 3714	> 1250 (0%)	> 21466 (7.8%)

VRARGDNPDSSK)				
FNIII 9-10, L1408P, C-X_8-C (SEQ ID NO:108, CRARGDFPDC)	45			
FNIII 9-10, L1408P, C-X_8-C (SEQ ID NO:109, CRARGDRPDC)	53			
FNIII 9-10, L1408P, C-X_8-C (SEQ ID NO:110, CRARGDDPDC)	82			
FNIII 9-10, L1408P, N1341A, C-X_8-C (SEQ ID NO:111, CRARGDNPDC)	111			
FNIII 9-10, L1408P, PPSRN, C-X_8-C (SEQ ID NO:112, CRARGDNPDC)	66			
FNIII 9-10, L1408P, KHSRN, C-X_8-C (SEQ ID NO:113, CRARGDNPDC)	175			
FNIII 9-10, L1408P, DHSRN, C-X_8-C (SEQ ID NO:114,	562			

CRARGDNPDC)				

[00121] In summary, a di-sulfide bond introduced in the RGD loop of FNIII 9-10 in a sequence comprising the formula C-X_8-C can improve integrin $\alpha5\beta1$ antagonist activity (Table 5, comparing results of SEQ ID NO:32 with SEQ ID NO:4, SEQ ID NO:63 and SEQ ID NO:62).

Example 5 FNIII 10 and FNIII 9-10 Variants Did Not Bind to Integrin αIIbβ3 and Did Not Induce Platelet Aggregation

[00122] Venous blood (9 parts) samples from healthy donors who had not received any medication for at least two weeks were collected in 3.8% sodium citrate (1 part). Blood samples were centrifuged at 150 x g for 10 min to obtain platelet-rich plasma (PRP) and allowed to stand for 5 min, and PRP was collected. The platelet-poor plasma (PPP) was prepared from the remaining blood by centrifuging at 2000 x g for 25 min. The PPP platelet count was measured on a hematology analyzer and diluted to 250,000 platelets/μl. A solution of 190 μl of PRP and 10 μl of FNIII 10 or FNIII 9-10 variants at different concentrations or PBS buffer were incubated for 5 min in a Hema Tracer 601 aggregometer at 37°C. Ten microliters of 200 μM adenosine diphosphate (ADP) were further added to monitor the response of platelet aggregation by light transmission. As shown in Tables 4 and 5, none of the wild type or variants tested bound to integrin αIIbβ3 or promoted platelet aggregation.

Example 6 The Effects of FNIII 10 or FNIII 9-10 Variants on Integrin-Mediated Cell Migration, Cell Survival and Cell Growth

[00123] The effects of FNIII 10 or FNIII 9-10 variants on integrin-mediated biological process were analyzed. Human melanoma cells A375 or A549 stably expressing $\alpha v\beta3$ or $\alpha5\beta1$ as confirmed by flow cytometry were incubated with FNIII 10 CPRGDMPDC (SEQ ID NO:6 with CPRGDMPDC) or FNIII 9-10 L1408P CRARGDNPDCSK (SEQ ID NO:32) and the effects on cell migration was examined by transwell assay. Cell migration (Haptotaxis) assays were performed as described previously (Bisanz *et al.*, 2005, *Model. Mol. Ther.* 12:4 634-643). Inserts (Falcon) with 8-μm pore polycarbonate were coated with 200μl of Fibronectin (50μg/ml) on the underside of the porous membrane at room temperature for 2 h and then subjected to washing and blocking with 1% (w/v) heat-denatured BSA at room temperature for 2 h followed by two washes with PBS. Chambers were assembled with serum-free DMEM and then 1x 10^5 cells were placed on the upper chamber. Each experiment was accompanied by a control consisting of a polycarbonate filter coated on the underside with PBS/1% (w/v) BSA, and this consistently demonstrated no migration. After 6-h incubation, cells were fixed with 3.7% formaldehyde and stained with crystal

violet. Cells remaining in the upper chamber were removed with a cotton swab and migrating cells were photographed and quantified. Inhibition of migration by FN-III variants were performed as above with the exception of adding different dosages of FN-III variants to the upper chambers at the time of plating. The results are summarized in Figure 7A, which show that FN III variants inhibited cell migration.

[00124] In addition, the effects of the FNIII 10 or FNIII 9-10 variants on cell cycle arrest were examined. Cell cycle analyses were done as described previously (Brooks et al., 1994, Cell 79:1157-1164) with some modifications. Briefly, FN-III variants were added 24 hours after seeding, when the cells were well spread. 48 hours after treatment, floating and attached cells were washed and collected in PBS. Cells were centrifuged at 1,000 rpm for 10 min and resuspended in 3 ml of cold 70% PBS before stored at -80℃ overnight. After incubation at 4°C for 45 min, cells were harvested and centrifuged at 1,300 rpm for 10 min at 4°C. Subsequently cells were resuspended in 1 ml PI staining solution (200 µl of 1 mg/ml propidium iodide, 200 µl RNase A and 200 µl 5% Triton X-100 in 9.4 ml PBS) at 37°C for 15 min. Cell fluorescence was measured using a FACScan flow cytometer(Becton-Dickinson) as described above. The results are summarized in Figure 7B. In summary, treatment of FNIII wild type fragments caused increased percentage of G1 cells as compared to control (PBS), and treatment of FN III variants further induced cell cyle arrest.

[00125] Further, the abiltiy of FNIII or FNIII 9-10 variants to induce apoptosis was analyzed. Cell apoptosis experiments were done as described previously (Maubant *et al.*, 2006, *Blood* 108: 3035-3044) with some modification. Briefly, FN-III variants were added 24 hours after seeding, when the cells were well spread. 48 hours after treatment, floating and attached cells were collected and subjected to 100 µlannexin V/propidium iodide (PI) staining using annexin V–Alexa Fluor 488 (Molecular Probes) and PI (Sigma) at 37°C for 15 min. The resultant fluorescence was measured by flow cytometry. Staining cells with a combination of annexin V and PI revealed nonapoptotic cells (annexin V^-/PI^-), early apoptotic cells (annexin V^+/PI^-), late apoptotic cells (annexin V^+/PI^+), and necrotic cells (annexin V^-/PI^+). The results are summarized in Figures 7C-7D. In summary, FNIII and variants thereof induced apoptosis in integrin-expressin cells.

[00126] Having described the invention in detail and by reference to specific embodiments thereof, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims. More specifically, although some aspects of the present invention are identified herein as particularly advantageous, it is contemplated that the present invention is not necessarily limited to these particular aspects of the invention.

Example 6 Thermostability and Solubility of the Variants of the Invention

Thermostability Measured by Differential Scanning Calorimetry (DSC)

[00127] It is important for a biotherapeutic to remain stable throughout manufacturing, storage, and delivery to the patients. Differential scanning calorimetry (DSC) allows for the accurate, rapid and easy measurement of T*m*, the thermal transition midpoint of a protein, which has been shown to be a good indicator of the relative stability of biotherapeutics in solution (Demarest et al., 2004; Sanchez-Ruiz et al., 1988; Vermeer and Norde, 2000). Consequently, DSC was applied to: (1) screen buffers and excipients for formulation; (2) screen therapeutic candidates with reasonable stability in addition to activity; and (3) predict protein aggregation tendency. For the above reasons, we characterized the stability of our designed proteins, *Tm* of ^{9,10}Fn3 variants and ^{10}Fn3 variants by DSC.

[00128] DSC analysis was performed using a VP-DSC microcalorimeter (MicroCal). Samples were dialyzed into prepared buffer using a 3-kDa molecular mass cutoff membrane, and the final concentration of sample were adjusted to ~0.7mg/ml. All experiments were heated from 20 to 110℃ at a scan rate of 60℃/ hr. Buffer-buffer baselines were obtained under the same experimental conditions and subtracted from sample traces. Data analysis was performed in Origin 7.0 (OriginLab Corp, Northampton, MA) equipped with the DSC analysis add-on (MicroCal). Each protein excess heat capacity curve was corrected by reference subtraction of a matching buffer scan followed by concentration normalization of the data. The transition midpoint or melting temperature (apparent T*m*) was determined by calculating the apex of the thermal denaturation curve from the normalized data.

[00129] Differential scattering calorimetry (DSC) experiment has been used to study thermally induced transitions of biological macromolecules by monitoring the excess heat capacity of a solution (*Cp*) of the molecule of interest as a function of temperature (Bruylants et al., 2005; Spink, 2008). We carried out DSC experiments of a series of our engineered proteins for thermal stability comparison in PBS buffer. Since thermal denaturation process for our proteins was irreversible, the melting temperature (*Tm*) instead of transition enthalpy ($\Delta H°m$) was used to reflect the stability for our proteins. The heat-induced unfolding of these proteins produced a DSC profile consisting of one endothermic transition. Deconvolution of the DSC trace using a non-two-state transition model yielded one endotherm with a *T*m. The fitness of the model was confirmed by comparison of the experimental and calculated traces. A denaturation

curve with only one peak is usually taken to indicate the presence in the protein molecule of more than one domain, with the various domains undergoing denaturation not independently of each other. DSC experiments on three representative proteins exhibited a *Tm* value of 62.4℃, 60.8℃ and 58.7℃ in FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32), FNIII 9-10 L1408P (SEQ ID NO:63) and FNIII 9-10 L1408P (RARGDNPD) variant (SEQ ID NO:62), respectively (see Table 6 and Figure 8A). Stability of FNIII 10 wild type (SEQ ID NO:2), FNIII 10, FNIII 10 PRGDMPD variant (SEQ ID NO:48) and FNIII 10 (CPRGDMPDC) variant (SEQ ID NO: 6) variants is 80.7℃, 74.3℃ and 85.0℃, respectively (see Table 7 and Figure 9A). The presence of only one predominant endotherm confirmed the lack of heterogeneity due to the product with or without a disulfide bond. In this study, the *T*m values of the DSC transitions were reproducible and therefore may be assumed to reflect the relative thermal stabilities of WT and its mutants.

Table 6: After the incorporation of a disulfide bond, FNIII 9-10 variant increased their thermostability (3.7 ^{o}C) and solubility (~6-fold).

Protein	**Thermostability (℃)**	**Solubility (mg/ml)**
FNIII 9-10 L1408P (SEQ ID NO:63)	60.8	19.9
FNIII 9-10 RARGDNPD (SEQ ID NO:62)	58.7	4.0
FNIII 9-10 CRARGDNPDC (SEQ ID NO:32)	62.4	24.4

Table 7: After the incorporation of a disulfide bond, FN-III10 variant increased their thermostability (10.7 ^{o}C) and solubility (~4-fold).

Protein	**Thermostability**	**Solubility (mg/ml)**

	(℃)	
FNIII 10 wild type (SEQ ID NO:2)	**80.7**	**7.3**
FNIII 10 variant (**T**PRGDMPD; SEQ ID NO:48)	**74.3**	**5.3**
FNIII 10 variant (**CPRGDMPDC,** SEQ ID NO:6)	**85.0**	**27.8**

Solubility Measured by Ammonium Sulfate Precipitation

[00130] Solubility is a concern of physicochemical properties studied during pharmaceutical preformulation. For liquid dosage form development, accurate solubility data are essential to ensure the robustness of the finished product. For solid dosage forms, solubility data are important in determining if an adequate amount of drug is available for absorption *in vivo*. If a compound has a low aqueous solubility, it may be subject to dissolution rate-limited or solubility-limited absorption within the gastrointestinal (GI) residence time. Methods that can be used to increase protein solubility are useful in high resolution structural studies and pharmaceutical applications. Several studies have succeeded in using site-directed mutagenesis of surface residues to enhance protein solubility. Here, we investigate the intrinsic determinants of protein solubility by studying how mutation on RGD loop of folded proteins influences their solubilities.

[00131] Protein precipitation using ammonium sulfate has been successful in measuring protein solubility. (Trevino, S.R., Scholtz, J.M., and Pace, C.N. (2008). Measuring and increasing protein solubility. Journal of pharmaceutical sciences 97, 4155-4166). Although ammonium sulfate precipitation can give quick and accurate information on relative solubility values of variants of the same protein. This method is experimentally reliable since factors which are difficult to control such as the water/buffer content of lyophilized protein or incidental ions that might get introduced during the course of the experiment become masked by the high concentration of salt. Besides, this method produces precipitated solutions with well-defined aqueous and solid phases,

and it requires relatively small amounts of protein (10 mg or less)—even when studying a highly soluble protein.

[00132] All measurements were performed at room temperature (25 °C) as previously described (Trevino, S.R., Scholtz, J.M., and Pace, C.N. (2008). Measuring and increasing protein solubility. Journal of pharmaceutical sciences 97, 4155-4166. Briefly, three solutions (50 mM buffer, 3.0 M ammonium sulfate in 50 mM buffer, and a protein stock solution in 50 mM buffer) were mixed together in a 0.2 ml PCR tube for a final sample volume of 15 µl with the desired ammonium sulfate and protein concentrations. The sample was allowed to equilibrate for >1 min for amorphous salting-out processes. Then the sample was transferred to 1.5 ml Eppendorf tubes and centrifuged for 1 min at 16,000g for the removal of aggregation. The spectrophotometer was blanked with 495 µl of a 1.1 M ammonium sulfate solution. After centrifugation, 5 µl of the sample was added to the 495 µl blanking solution and mixed to generate a 100-fold dilution for the absorbance measurements.

[00133] Protein solubility determination bt ammonium sulfate method was used for inducing amorphous precipitation (Trevino, S.R., Scholtz, J.M., and Pace, C.N. (2008). Measuring and increasing protein solubility. Journal of pharmaceutical sciences 97, 4155-4166). Solubility curves as a function of ammonium sulfate concentration for proteins were used to indicate the solubility of protein of interest. Solubility of FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32), wild type protein and FNIII 9-10 L1408P (RARGDNPD) variant is 24.4, 19.9 and 4.0 mg/ml (see Table 6 and Fig. 8B). Solubility of FNIII 10, FNIII 10 wild type (SEQ ID NO:2), FNIII 10 (TPRGDMPD) variant (SEQ ID NO:48) and FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6) is 7.3, 5.3 and 27.8 mg/ml (see Table 7 and Fig. 9B). Each solubility value was repeated three times and therefore may be assumed to reflect the relative solubility of WT and its mutants. Taken together, the incorporation of disulfide bond into integrin α5β1-specific FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) and integrin αvβ3-specific FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6) had increased their stability and solubility (see Figs. 8B abd 9B).

Example 7 The Effects on Growth Factor-induced Vascular Tube Formation *in Vitro*

[00134] One of the common used *in vitro* assays to model the reorganization stage of angiogenesis is the tube formation assay (Arnaoutova, I., and Kleinman, H.K. (2010). *In vitro* angiogenesis: endothelial cell tube formation on gelled basement membrane extract. Nature protocols 5, 628-635). The assay measures the ability of endothelial cells, plated at subconfluent densities with the appropriate extracellular matrix support, to form capillary-like structures. Typically, the ability can be quantified by measuring the number, length, or area of these capillary-like structures in microscope images of the culture dish. Given that compounds are able to inhibit tube formation, they should be useful in various diseases, such as cancer, where tumors stimulate new blood vessel formation to receive oxygen and nutrients for growth beyond a relatively small size. Here, we examined the ability of our designed mutants to promote or inhibit tube formation.

[00135] To evaluate the effect of Fn3 mutants on bFGF or VEGF-mediated endothelial tube formation in vitro, 15-well μ-slides (ibidi GmbH) were coated with 10 μL of Matrigel (BD Biosciences). HUVECs preincubated with Fn3 mutants for 15 minutes were added to the wells in M199 containing 2% FBS and endothelial cell growth supplement, and finally with 50 ng/ml bFGF or 20 ng/ml VEGF. The total tube length was measured using ImajeJ software and compared with the control at the indicated times. The micrographs of tube formation were taken and processed by an inverted microscope (Leica DM IRE2) equipped with a N PLAN 10×/0.25 objective lens and a CCD camera (CoolSNAP fx; Photometrics).

Inhibition on VEGF-induced Tube Formation by FNIII 9-10 *(CRARGDNPDC) Variant (SEQ ID NO:32)*

[00136] It was known that integrin α5β1 is involved in VEGF-induced angiogenesis. And blockade of integrin α5β1 could inhibit VEGF-induced angiogenesis *in vitro* and *in vivo* . To assess whether our integrin α5β1-specific antagonist may suppress capillary tube formation and the Matrigel plug assay. Flow cytometry analysis showed that integrin α5β1 is overexpressed on HUVECs. We chose FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) for this study, as it had the strongest binding and robust biophysical property. FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) inhibited VEGF-induced capillary tube formation by HUVECs grown on Matrigel, an extracellular basement membrane matrix (Kleinman et al., 1986), with IC_{50} values of approximately 1.6 μM (**Fig. 10A**). However, FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) did not inhibit bFGF-induced capillary tube formation by HUVECs grown on Matrigel (**Fig. 10B**). The results suggest that our integrin α5β1-specific antagonist can specifically target integrin α5β1 on HUVECs cells and interfere with its involvement in VEGF-inducing tube formation.

No Inhibition on bFGF-induced Tube Formation by FNIII 10 *(CPRGDMPDC) Variant (SEQ ID NO: 6)*

[00137] ^{10}Fn3(CPRGDMPDC) variant (SEQ ID NO:6) did not inhibit VEGF-induced and bFGF-induced capillary tube formation by HUVECs grown on Matrigel respectively. However, FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6) did inhibit bFGF-induced angiogenesis *in vivo* . In addition to tube formation, HUVECs migration also is involved in the process of angiogenesis. Therefore, we speculated that our integrin αvβ3-specific antagonist may interfere with migration but not tube formation under bFGF-inducing condition. This will be further confirmed in bFGF-induced transwell migration assay.

Example 8 *In vivo* Matrigel Plug Angiogenesis Assay

[00138] The Matrigel plug angiogenesis assay is a simple *in vivo* technique to detect the newly formed blood vessels in the transplanted gel plugs in nude mice). The Matrigel matrix composition is comparable to the basement membrane proteins. It can induce differentiation of a variety of cell types such as endothelial cells. The levels of activity of angiogenic or antiangiogenic compounds can be visually assessed by color differences in the plugs compared to the controls. Further quantitation can be performed using a variety of methods like hemoglobin detection. In our case, growth factors (VEGF or bFGF) with or without proteins are mixed with the Matrigel then is injected into the mice to determine the antiangiogenic activities of proteins.

[00139] To assess angiogenic effects *in vivo*, growth factor–reduced liquid Matrigel (0.25 mL) containing heparin (500 U/mL) with combinations of 125 ng bFGF/VEGF and Fn3 mutants were subcutaneously injected into C57BL/6 mice near the abdominal midline. Four days after implantation, mice were euthanized and the Matrigel plugs were surgically removed, photographed with a CMOS camera (600D, Canon), and the hemoglobin content of each Matrigel plug was measured with hemoglobin colorimetric assay kit (Cayman).

Inhibition on VEGF-induced Angiogenesis by FNIII 9-10 *Variant (CRARGDNPDC) (SEQ ID NO:32)*

[00140] We next measured the ability of the FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) to block angiogenesis *in vivo* using a Matrigel plug assay. (Passaniti, R.M. Taylor, R. Pili, Y. Guo, P.V. Long, J.A. Haney, R.R. Pauly, D.S. Grant, G.R. Martin., A simple, quantitative method for assessing angiogenesis and antiangiogenic agents using reconstituted basement membrane, heparin, and fibroblast growth factor., Lab. Invest., 67 (1992), pp. 519–528)). Strikingly, FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) inhibited angiogenesis to

levels approaching that of the negative control (see Fig. 11). It indicates that integrin α5β1 play a role in VEGF-induced angiogenesis and this biological process can be blocked by our designed α5β1-specific antagonist.

Inhibition on bFGF-induced Angiogenesis by FNIII 10 *(CPRGDMPDC) Variant (SEQ ID NO:6)*

[00141] We also measured the ability of the FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6) to block angiogenesis *in vivo* using a Matrigel plug assay. Strikingly, FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6) inhibited angiogenesis to levels approaching that of the negative control (**Fig. 12**). It indicates that integrin αvβ3 play a role in bFGF-induced angiogenesis and this biological process can be blocked by our designed αvβ3-specific antagonist.

Example 9 The Effects on the Growth of Human Tumor Xenografts in SCID Mice

[00142] The major preclinical screen for the development of novel cancer therapeutics is to be achieved by heterotransplantation of human cancer cells into immunodeficient rodents (xenograft models)(Christopher L Morton & Peter J Houghton, NATURE PROTOCOLS. 2007 247-250). These models have identified clinically efficacious agents, and still is the 'workhorse' of the pharmaceutical industry. To uncover the proposed mechanism of therapeutic approaches, molecular characteristics of tumor could be identified by immunohistochemistry staining of tumor bioposies. In this study, we establish two xenograft models to test the anti-tumor activities of two integrin antagonists respectively.

[00143] To assess the effect of FNIII mutant on tumor angiogenesis, NOD-SCID mice were given subcutaneous dorsal injections of 1×10^6 human melanoma / lung carcinoma cells. The mice were given s.c. injections of various amounts of *E. coli*-expressed FNIII mutants (5 or 10 mg/kg body weight) once daily. Tumors were harvested, photographed with a camera (T30, Sony), and sectioned. Intratumoral microvessels and cells were detected using IHC staining with Ab against CD31 (BD Biosciences) and Ki-67 (Leica) respectively. The images were captured using a BX51 microscope (Olympus, Tokyo, Japan). Intratumoral microvessel density and cells were quantified. Briefly, integrated optical density (IOD) of microvessels and cells were calculated in each section of the tumor at 10× magnification by using the Image-Pro Plus software.

Immunohistochemistry.

[00144] All tissue sections were deparaffinized, rehydrated and subjected to heat-induced antigen retrieval by autoclaving them for 6 min in 10 mM Tris-EDTA buffer (pH 9.0). Incubation with 3% H_2O_2 in methanol for 5 min, following 2 washes in TBS, the tissue sections were incubated with protein block (NovoLink™) for 5 min. Then the samples were mixed with primary antibodies in antibody diluents and

incubated at room temperature for 30 min. Following 3 washes in TBS, the sections were incubated with secondary antibodies at room temperature for 10 min. After 3 washes in TBS, the samples were developed using DAB working solution (NovoLink™) for 3 min, counterstained with 0.02% hematoxylin for 5 min, and mounted with xylene. Finally, the sections were visualized using an inverted microscope (IX71; Olympus, Tokyo, Japan).

[00145] **Statistical analysis.** Data are expressed as mean ± SD. Values of $P < .05$ were considered statistically significant.

Inhibition on A375 Tumor Growth by FNIII 9-10 *(CRARGDNPDC) Variant* (SEQ ID NO:32)

[00146] The antiangiogenic activity of FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) encouraged us to determine whether it could suppress pathological angiogenesis. Tumor growth is angiogenesis-dependent, and suppression of angiogenesis has been shown to inhibit tumor growth. To study the possible antitumor activity of FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32), we used human A375 melanoma xenografts. Flow cytometry analysis showed that integrin $\alpha5\beta1$ is overexpressed on A375 tumor cells. *In vivo* subcutaneous administration of FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) resulted in dose-dependent suppression of tumor growth. After a 3-wk treatment, reduction of tumor volumes and weights was observed (see Fig. 13). To elucidate the cellular basis for the observed defects in tumor burden, we evaluated the effects of FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) on proliferation, and angiogenesis of A375-induced tumors by performing immunohistochemistry on paraffin-embedded tumor sections with the appropriate markers. Tumors exhibited a very slight defect in proliferative status, as reflected by the quantification of the cellular Ki67 expression levels. It is consistent with our *in vitro* results that FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32) showed slight inhibition on tumor cell proliferation. Another possible explanation for the observed growth defects may be an inability to efficiently recruit tumor vasculature, as $\beta1$-integrin has been previously implicated in promoting tumor angiogenesis. To test this possibility, we performed immunohistochemical analyses on the tumors by using an anti-CD31 antibody. Interestingly, protein-treated tumors exhibited a different pattern of CD31 staining compared with their proficient counterparts. The number of CD31-positive pixels observed from total vessels within protein-treated tumors was reduced by nearly an average of one-fold. Neovascularization of FNIII 9-10 L1408P (CRARGDNPDC) variant (SEQ ID NO:32)-treated tumors was significantly reduced as compared with control tumors (see Fig. 13). These results reflected a diminution in the average diameter of the tumor-infiltrated vessels observed in A375-induced tumors and suggested an overall impaired blood supply to these tumors. It is in accordance with our *in vitro* results that FNIII 9-10 L1408P (CRARGDNPDC)

variant (SEQ ID NO:32) showed significant suppression on tube formation and Matrigel plug assay. Collectively, these observations indicate that the defects in A375-induced tumor growth and progression by integrin α5β1-antagonist treatment are correlated with reduced angiogenesis but not tumor cell survival.

Inhibition on A549 Tumor Growth by FNIII 10 *(CPRGDMPDC) Variant* (SEQ ID NO:6)

The antiangiogenic activity of FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6) encouraged us to determine whether it could suppress pathological angiogenesis. To study the possible antitumor activity of ^{10}Fn3(CPRGDMPDC) variant (SEQ ID NO:6), we used human A549 melanoma xenografts. Flow cytometry analysis showed that integrin αvβ3 is not overexpressed on A549 tumor cells. Surprisingly, *in vivo* subcutaneous administration of FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6) resulted in dose-dependent suppression of tumor growth. After a 3-wk treatment, reduction of tumor volumes and weights was observed (see Fig. 14). To elucidate the cellular basis for the observed defects in tumor burden, we evaluated the effects of FNIII 10 (CPRGDMPDC) variant (SEQ ID NO:6) on proliferation, and angiogenesis of A375-induced tumors by performing immunohistochemistry on paraffin-embedded tumor sections with the appropriate markers. Tumors exhibited dramatic defect in proliferative status, as reflected by the quantification of the cellular Ki67 expression levels (see Fig. 14). .

WHAT IS CLAIMED IS

1. An isolat[ed] polypeptide comprising a modified human fibronectin fragment that comprises human fibronectin type III domain module 10 (FNIII 10), wherein the FNIII 10 comprise[s] an Arg-Gly-Asp (RGD) motif and two Cys substitutions to form a di-sulfide bond, wherein one Cys substitution is N-terminal to the RGD motif and the other Cys substitution is C-terminal *to the* RGD motif, and wherein the FNIII [1]0 comprises an amino acid sequence that is at least 85% homologous to SEQ ID NO:2.
2. The polypeptide of claim 1, wherein the polypeptide inhibits integrin α5β1 or integrin αvβ3 activity and does not inhibit integrin αIIbβ3 activity.
3. The polypeptide of claim 1, wherein the two Cys substitutons are separated by about 6 to about 9 amino acid residues.
4. The polypeptide of claim 3, wherein the two Cys substitutions are separated by 7 or 8 amino acid residues.
5. The polypeptide of claim 1, wherein the FNIII 10 further comprises at least one amino acid substitution at amino acid position 1491, 1492, 1496, 1497 or 1498, and wherein the amino acid substitution at position 1491 is Arg or Ile, the amino acid su*bstitut*ion at position 1492 is Ala or Pro, the amino acid substitution at position 1496 is Met, Asn or Trp, the amino acid substitution at position 1497 is Asn, and the amino acid substitution at position 1498 is Asp or Glu.
6. The polypeptide of claim 5, wherein the two Cys substitutions are Thr to Cys substitution at amino acid position 1491 and Ser to Cys substitution at amino acid position at 1499, and wherein the FNIII 10 comprises the formula Cys^{1491}-X_1-Arg-Gly-Asp-X_2-X_3-X_4-Cys^{1499}, wherein
   X_1 is Gly, Ala or Pro;
   X_2 is Ser, Met, Asn or Trp;
   X_3 is Pro or Asn; and
   X_4 is Ala, Asp or Glu.
7. The polypeptide of claim 6, wherein the polypeptide has the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10 or SEQ ID NO:12.
8. The polypeptide of claim 6, wherein X_1 is Pro, X_2 is Met, X_3 is Pro, and X_4 is Asp.
9. The polypeptide of claim 8, wherein the polypeptide has the amino acid sequence of SEQ ID NO:6.
10. The polypeptide of claim 6, wherein the modified human fibronectin fragment further comprises human fibronectin type III domain module 9 (FNIII 9) that optionally comprises Leu to Pro substitution at amino acid position 1408, and wherein the FNIII 9 and FNIII 10 (FNIII 9-10)

comprises an amino acid sequence that is at least 85% homologous to the amino acid sequence of SEQ ID NO:4.

11. The polypeptide of claim 10, wherein the polypeptide has the amino acid sequence of SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, or SEQ ID NO:26.
12. The polypeptide of claim 11, wherein the polypeptide has the amino acid sequence of SEQ ID NO:20.
13. The polypeptide of claim 6, wherein the polypeptide inhibits integrin αvβ3 activity.
14. The polypeptide of claim 5, wherein the modified human fibronectin fragment further comprises human fibronectin type III domain module 9 (FNIII 9) that optionally comprises Leu to Pro substitution at amino acid position 1408, and wherein the FNIII 9 and FNIII 10 (FNIII 9-10) comprises an amino acid sequence that is at least 85% homologous to the amino acid sequence of SEQ ID NO:4.
15. The polypeptide of claim 14, wherein the two Cys substitutions are Val to Cys substitution at amino acid position 1490 and Ser to Cys substitution at amino acid position 1499, and wherein the FNIII 10 comprises the formula Cys^{1490}-X_1-X_2-Arg-Gly-Asp-X_3-Pro-X_4-Cys^{1499}, wherein
    X_1 is Thr, Arg or Ile;
    X_2 is Gly, Ala or Pro;
    X_3 is Phe, Arg, Asp, Ser, Met or Asn; and
    X_4 is Ala or Asp.
16. The polypeptide of claim 15, wherein the polypeptide has the amino acid sequence of SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO: 108, SEQ ID NO: 109 or SEQ ID NO: 110.
17. The polypeptide of claim 15, wherein X^1 is Arg, X_2 is Ala, X_3 is Asn, and X_4 is Asp.
18. The polypeptide of claim 17, wherein the polypeptide has the amino acid sequence of SEQ ID NO:32.
19. The polypeptide of claim 15, wherein the polypeptide inhibits integrin α5β1 activity.
20. The polypeptide of Claim 15, wherein the human fibronectin type III domain module 9 (FNIII 9) optionally comprises Asn to Ala substitution at amino acid position 1341, His to Pro substitution at amino acid position 1377, Pro to Lys substitution at amino acid 1376, or Pro to Asp substitution at amino acid position 1376.
21. The polypeptide of Claim 20, wherein the polypeptide has the amino acid sequence of SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113 or SEQ ID NO:114.

22. The polypeptide of claim 20, wherein the polypeptide inhibits integrin $\alpha 5\beta 1$ activity.

23. An isolated polypeptide comprising a modified human fibronectin fragment that comprises human fibronectin type III domain module 9 and human fibronectin type III domain module 10 (FNIII 9-10), wherein the FNIII 9 optionally comprises Leu to Pro substitution at amino acid position 1408, wherein the FNIII 9 and the FNIII 10 each comprises at least one amino acid substitution, wherein the amino acid substitution in the FNIII 9 and the FNIII 10 form a non-covalent bond, and wherein the FNIII 9 and FNIII 10 comprises an amino acid sequence that is at least 85% homologous to the amino acid sequence of SEQ ID NO:4 and that is not SEQ ID NO:60.
24. The polypeptide of claim 23, wherein the amino acid substitutions in the FNIII 9 and the FNIII 10 form an interdomain di-sulfide bond.
25. The polypeptide of claim 23, wherein the amino acid substitutions in the FNIII 9 and the FNIII 10 form an interdomain hydrogen bond.
26. The polypeptide of claim 24, wherein the amino acid substitution in the FNIII 9 is Ala to Asp substitution at amino acid position 1340 and the amino acid substitution in the FNIII 10 is Val to Lys substitution at amino acid position 1442.
27. The polypeptide of claim 26, wherein the polypeptide has the amino acid sequence of SEQ ID NO:40.
28. The polypeptide of claim 24, wherein the polypeptide inhibits integrin $\alpha 5\beta 1$ activity.
29. An isolated polypeptide comprising a modified human fibronectin fragment that comprises human fibronectin type III domain module 9 (FNIII 9) and human fibronectin type III domain module 10 (FNIII 10), wherein the FNIII 9 comprises at least one amino acid substitution at the amino acid position 1373 or 1379, and wherein the FNIII 9 and FNIII 10 (FNIII 9-10) comprises an amino acid sequence that is at least 85% homologous to the amino acid sequence of SEQ ID NO:4.
30. The polypeptide of claim 29, wherein the FNIII 9 further comprises Leu to Pro substitution at amino acid position 1408.
31. The polypeptide of claim 30, wherein the amino acid substitution is Asp to Arg substitution at amino acid position 1373 or Arg to Asp substitution at amino acid position 1379.
32. The polypeptide of claim 31, wherein the FNIII 9 comprises both the Asp to Arg substitution at amino acid position 1373 and the Arg to Asp substitution at amino acid position 1379.

33. The polypeptide of claim 30, wherein the polypeptide has the amino acid sequence of SEQ ID NO:42, SEQ ID NO:44, or SEQ ID NO:46.
34. The polypeptide of claim 33, wherein the polypeptide has the amino acid sequence of SEQ ID NO:42.
35. The polypeptide of claim 29, wherein the polypeptide inhibits integrin αvβ3 activity.
36. An isolated polypeptide comprising a modified human fibronectin fragment that comprises human fibronectin type III domain module 10 (FNIII 10) having an amino acid sequence Val^{1490}-X_1-X_2-Arg-Gly-Asp-X_3-X_4-X_5-X_6-Ser^{1500}, wherein

X_1 is Thr or Arg;

X_2 is Ala or Pro;

X_3 is Met, Trp or Asn;

X_4 is Pro or Asn;

X_5 is Asp or Glu; and

X6 is Ser or Gly,

wherein the FNIII 10 comprises an amino acid sequence that is at least 85% homologous to SEQ ID NO:2 and is not SEQ ID NO:50.

37. The polypeptide of claim 36, wherein the polypeptide has the amino acid sequence of SEQ ID NO:48, SEQ ID NO:52, OR SEQ ID NO:54.
38. The polypeptide of claim 37, wherein the polypeptide has the amino acid sequence of SEQ ID NO:48.
39. The polypeptide of claim 36, wherein the modified fibronectin fragment further comprises human fibronectin type III domain module 9 (FNIII 9) that optionally comprise Leu to Pro substitution at amino acid position 1408, and wherein the FNIII 9 and FNIII 10 comprises an amino acid sequence that is at least 85% homologous to the amino acid sequence of SEQ ID NO:4.
40. The polypeptide of claim 39, wherein the polypeptide has the amino acid sequence of SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60 or SEQ ID NO:62.
41. The polypeptide of claim 40, wherein the polypeptide has the amino acid sequence of SEQ ID NO:62.
42. The polypeptide of claim 36, wherein the polypeptide inhibits integrin α5β1 activity and/or integrin αvβ3 activity.

43. A pharmaceutical composition comprising a therapeutically effective amount of the polypeptide of any one of claims 1-42, and a pharmaceutically acceptable excipient, diluent or carrier.
44. A method of inhibiting integrin-mediated cell adhesion, growth, migration or differentiation, comprising the step of contacting a cell with a therapeutically effective amount of the polypeptide of any one of claims 1-42, wherein the integrin is αvβ3 or α5β1.
45. The method of claim 44, wherein the integrin is integrin αvβ3.
46. The method of claim 45, wherein the polypeptide has the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:48 or SEQ ID NO:60.
47. The method of claim 44, wherein the integrin is integrin α5β1.
48. The method of claim 47, wherein the polypeptide has the amino acid sequence of SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:72.
49. A method of inhibiting integrin-mediated cell adhesion, growth, migration or differentiation in a mammal, comprising the step of administering to a mammal the pharmaceutical composition of claim 43, wherein the integrin is αvβ3 or α5β1.
50. The method of claim 49, wherein the integrin is integrin αvβ3.
51. The method of claim 50, wherein the polypeptide has the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:48 or SEQ ID NO:60.
52. The method of claim 49, wherein the integrin is integrin α5β1.
53. The method of claim 62, wherein the polypeptide has the amino acid sequence of SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60 or SEQ ID NO:62.
54. A method of inhibiting tumor cell growth or tumor metastasis comprising contacting a tumor cell with a therapeutically effective amount of the polypeptide of any one of claims 1-42, wherein the tumor cell expresses α5β1 or αvβ3.
55. The method of claim 54, wherein the polypeptide has the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:48, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 of SEQ ID NO:68.
56. The method of claim 54, where the tumor is lung carcinoma, breast tumor, colon tumor, osteosarcoma, pancreatic tumor, ovarian tumor, cervical tumor, glioblastoma, prostate tumor, liver tumor or melanoma.

57. A method of inhibiting tumor growth or tumor metastasis in a mammal comprising administering to a mammal in need thereof the pharmaceutical composition of claim 43, wherein the tumor expresses $\alpha 5\beta 1$ or $\alpha v\beta 3$.
58. The method of claim 57, wherein the polypeptide has the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:48, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60 or SEQ ID NO:62.
59. The method of claim 57, where the tumor is lung carcinoma, breast tumor, colon tumor, osteosarcoma, pancreatic tumor, ovarian tumor, cervical tumor, glioblastoma, prostate tumor, liver tumor or melanoma.
60. A method of inhibiting tumor progression in a mammal comprising administering to a mammal in need thereof the pharmaceutical composition of claim 44, wherein the tumor cell expresses $\alpha v\beta 3$ or $\alpha 5\beta 1$.
61. The method of claim 60, wherein the integrin is $\alpha v\beta 3$ and the polypeptide has the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:48 or SEQ ID NO:60.
62. The method of claim 60, wherein the integrin is $\alpha 5\beta 1$ and the polypeptide has the amino acid sequence of SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:72.
63. The method of claim 60, where the tumor is lung carcinoma, breast tumor, colon tumor, osteosarcoma, pancreatic tumor, ovarian tumor, cervical tumor, glioblastoma, prostate tumor, liver tumor or melanoma.
64. A method of inhibiting tumor metastasis in a mammal comprising administering to a mammal in need thereof the pharmaceutical composition of claim 43, wherein the tumor cell expresses $\alpha v\beta 3$ or $\alpha 5\beta 1$.
65. The method of claim 64, wherein the pharmaceutical composition comprises a polypeptide comprising the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:48, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60 or SEQ ID NO:62.
66. The method of claim 64, where the tumor is lung carcinoma, breast tumor, colon tumor, osteosarcoma, pancreatic tumor, ovarian tumor, cervical tumor, glioblastoma, prostate tumor, liver tumor or melanoma.

67. A method of inhibiting an angiogenesis-related disease in a mammal comprising administering to a mammal in need thereof the pharmaceutical composition of claim 43, wherein the angiogenesis-related disease is cancer, macular degeneration, edema or arthritis.
68. The method of claim 67, wherein the pharmaceutical composition comprises a polypeptide comprising the amino acid sequence of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:48, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:68.
69. An isolated polynucleotide comprising a nucleotide sequence that encodes the polypeptide of any one of claims 1-42.
70. The polynucleotide of claim 69, wherein the polynucleotide comprises a nucleotide sequence of SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:61 or SEQ ID NO:71.
71. An expression vector comprising the polynucleotide of claim 69.
72. A host cell comprising the expression vector of claim 71.
73. A method of preparing a polypeptide comprising the steps of:
    (a) culturing the host cell of claim 72 under conditions effective to allow expression of the polypeptide encoded from the expression vector; and
    (b) recovering the polypeptide from the culture.

SEQUENCE LISTING

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Chuang, Woei-Jer
Chang, Yung-Sheng

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            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc tta ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125
```

```
aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc act ggc cgt gga gac agc ccc gca agc agc aag        528
Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                        552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 4
<211> 184
<212> PRT
<213> Homo sapiens

<400> 4

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160
```

```
Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 5
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 5

```
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc          48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tat tac          96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc         144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct         192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

gga gtt gat tat acc atc act gtg tat gct gtc tgt cct cgt ggt gat         240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Cys Pro Arg Gly Asp
65                  70                  75                  80

atg cct gac tgt agc aag cca att tcc att aat tac cga aca                 282
Met Pro Asp Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 6
<211> 94
<212> PRT
<213> Homo sapiens

<400> 6

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45
```

```
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Cys Pro Arg Gly Asp
65                  70                  75                  80

Met Pro Asp Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 7
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 7

```
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc          48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tat tac          96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc         144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct         192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

gga gtt gat tat acc atc act gtg tat gct gtc tgt ccg cgt gga gac         240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Cys Pro Arg Gly Asp
65                  70                  75                  80

tgg aat gaa tgt agc aag cca att tcc att aat tac cga aca                 282
Trp Asn Glu Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 8
<211> 94
<212> PRT
<213> Homo sapiens

<400> 8

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30
```

```
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Cys Pro Arg Gly Asp
65                  70                  75                  80

Trp Asn Glu Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 9
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 9

```
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc          48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tat tac          96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc         144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct         192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

gga gtt gat tat acc atc act gtg tat gct gtc tgt gct cgt ggt gat         240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Cys Ala Arg Gly Asp
65                  70                  75                  80

aat cct gac tgt agc aag cca att tcc att aat tac cga aca                 282
Asn Pro Asp Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 10
<211> 94
<212> PRT
<213> Homo sapiens

<400> 10

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15
```

```
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Cys Ala Arg Gly Asp
65                  70                  75                  80

Asn Pro Asp Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 11
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 11

```
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc          48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tat tac          96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc         144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct         192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

gga gtt gat tat acc atc act gtg tat gct gtc tgt ggt cgt gga gac         240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Cys Gly Arg Gly Asp
65                  70                  75                  80

agc ccc gca tgt agc aag cca att tcc att aat tac cga aca                 282
Ser Pro Ala Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 12
<211> 94
<212> PRT
<213> Homo sapiens

<400> 12

Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Cys Gly Arg Gly Asp
65 70 75 80

Ser Pro Ala Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 13
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 13
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc 48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tat tac 96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc 144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct 192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

gga gtt gat tat acc atc act gtg tat gct tgt att cct cgt ggt gat 240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Cys Ile Pro Arg Gly Asp
65 70 75 80

atg cct gac tgt agc aag cca att tcc att aat tac cga aca 282
Met Pro Asp Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 14

<211> 94
<212> PRT
<213> Homo sapiens

<400> 14

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Cys Ile Pro Arg Gly Asp
65                  70                  75                  80

Met Pro Asp Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 15
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 15

```
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc          48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tat tac          96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc         144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct         192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

gga gtt gat tat acc atc act gtg tat gct tgt cgt gct cgt ggt gat         240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Cys Arg Ala Arg Gly Asp
65                  70                  75                  80

aat cct gac tgt agc aag cca att tcc att aat tac cga aca                 282
Asn Pro Asp Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
```

85 90

<210> 16
<211> 94
<212> PRT
<213> Homo sapiens

<400> 16

Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Cys Arg Ala Arg Gly Asp
65 70 75 80

Asn Pro Asp Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 17
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 17
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc 48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tat tac 96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc 144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct 192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

gga gtt gat tat acc atc act gtg tat gct tgt act ggt cgt gga gac 240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Cys Thr Gly Arg Gly Asp

65 70 75 80

agc ccc gca tgt agc aag cca att tcc att aat tac cga aca 282
Ser Pro Ala Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 18
<211> 94
<212> PRT
<213> Homo sapiens

<400> 18

Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Cys Thr Gly Arg Gly Asp
65 70 75 80

Ser Pro Ala Cys Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 19
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 19
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac 48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1 5 10 15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac 96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat 144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca 192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro

```
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa        240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc tta ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg        288
Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg        336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa        384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc tgt cct cgt ggt gat atg cct gac tgt agc aag        528
Thr Val Tyr Ala Val Cys Pro Arg Gly Asp Met Pro Asp Cys Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                       552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  20
<211>  184
<212>  PRT
<213>  Homo sapiens

<400>  20

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15


Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30


Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45


Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60


Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80


Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
```

```
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Cys Pro Arg Gly Asp Met Pro Asp Cys Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  21
<211>  552
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(552)

<400>  21
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
```

```
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa        384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc tgt gct cgt ggt gat aat cct gac tgt agc aag        528
Thr Val Tyr Ala Val Cys Ala Arg Gly Asp Asn Pro Asp Cys Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                       552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  22
<211>  184
<212>  PRT
<213>  Homo sapiens

<400>  22

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125
```

```
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Cys Ala Arg Gly Asp Asn Pro Asp Cys Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 23
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 23

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ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag         432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140
```

```
tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc tgt ggt cgt gga gac agc ccc gca tgt agc aag        528
Thr Val Tyr Ala Val Cys Gly Arg Gly Asp Ser Pro Ala Cys Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                       552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 24
<211> 184
<212> PRT
<213> Homo sapiens

<400> 24

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Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Cys Gly Arg Gly Asp Ser Pro Ala Cys Ser Lys
                165                 170                 175
```

```
Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  25
<211>  552
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(552)

<400>  25
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc tta ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag         432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc         480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc tgt ggt cgt gga gac agc ccc gca tgt agc aag         528
Thr Val Tyr Ala Val Cys Gly Arg Gly Asp Ser Pro Ala Cys Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                         552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 26
<211> 184
<212> PRT
<213> Homo sapiens

<400> 26

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                  10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Cys Gly Arg Gly Asp Ser Pro Ala Cys Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 27
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 27

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ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag         432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc         480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct tgt act ggt cgt gga gac agc ccc gca tgt agc aag         528
Thr Val Tyr Ala Cys Thr Gly Arg Gly Asp Ser Pro Ala Cys Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                         552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 28
<211> 184
<212> PRT
<213> Homo sapiens

<400> 28

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15
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```
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Cys Thr Gly Arg Gly Asp Ser Pro Ala Cys Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  29
<211>  552
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(552)

<400>  29
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
```

```
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat        144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca        192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa        240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg        288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg        336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa        384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct tgt att cct cgt ggt gat atg cct gac tgt agc aag        528
Thr Val Tyr Ala Cys Ile Pro Arg Gly Asp Met Pro Asp Cys Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                        552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  30
<211>  184
<212>  PRT
<213>  Homo sapiens

<400>  30

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15


Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30


Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45


Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
```

```
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Cys Ile Pro Arg Gly Asp Met Pro Asp Cys Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  31
<211>  552
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(552)

<400>  31
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac         48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac         96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat        144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca        192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa        240
```

```
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg        288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg        336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa        384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct tgt cgt gct cgt ggt gat aat cct gac tgt agc aag        528
Thr Val Tyr Ala Cys Arg Ala Arg Gly Asp Asn Pro Asp Cys Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                       552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  32
<211>  184
<212>  PRT
<213>  Homo sapiens

<400>  32

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15


Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30


Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45


Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60


Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80


Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95
```

```
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Cys Arg Ala Arg Gly Asp Asn Pro Asp Cys Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 33
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 33

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ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110
```

```
gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa        384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct tgt act ggt cgt gga gac agc ccc gca tgt agc aag        528
Thr Val Tyr Ala Cys Thr Gly Arg Gly Asp Ser Pro Ala Cys Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                       552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 34
<211> 184
<212> PRT
<213> Homo sapiens

<400> 34

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140
```

```
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160


Thr Val Tyr Ala Cys Thr Gly Arg Gly Asp Ser Pro Ala Cys Ser Lys
                165                 170                 175


Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  35
<211>  552
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(552)

<400>  35
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gat aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Asp Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag         432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc         480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160
```

```
act gtg tat gct gtc act ggc cgt gga gac agc ccc gca agc agc aag        528
Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                    552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 36
<211> 184
<212> PRT
<213> Homo sapiens

<400> 36

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Asp Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 37
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 37

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ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                  10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct aaa aca gtg aga tat tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Lys Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag         432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc         480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc act ggc cgt gga gac agc ccc gca agc agc aag         528
Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                         552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 38

<211> 184
<212> PRT
<213> Homo sapiens

<400> 38

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                  10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Lys Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 39
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 39
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gat aac 48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Asp Asn
1 5 10 15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac 96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat 144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca 192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa 240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg 288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg 336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

gat gct cct gct aaa aca gtg aga tat tac agg atc act tac gga gaa 384
Asp Ala Pro Ala Lys Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag 432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc 480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

act gtg tat gct gtc act ggc cgt gga gac agc ccc gca agc agc aag 528
Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
165 170 175

cca att tcc att aat tac cga aca 552
Pro Ile Ser Ile Asn Tyr Arg Thr
180

<210> 40
<211> 184
<212> PRT
<213> Homo sapiens

<400> 40

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Asp Asn
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr

20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Lys Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
165 170 175

Pro Ile Ser Ile Asn Tyr Arg Thr
180

<210> 41
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 41
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac 48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1 5 10 15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac 96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa cgt 144

```
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Arg
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca        192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa        240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg        288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gct gct gcg acc ccc acc agc cta ctg atc agc tgg        336
Asp Leu Glu Val Ala Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa        384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ttt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Phe Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc act ggc cgt gga gac agc ccc gca agc agc aag        528
Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                        552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  42
<211>  184
<212>  PRT
<213>  Homo sapiens

<400>  42

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15


Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30


Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Arg
        35                  40                  45


Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60
```

```
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Ala Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Phe Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 43
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 43

```
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac         48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac         96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat        144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct gat aat tcc atc acc ctc acc aac ctc act cca        192
Arg Val Pro His Ser Asp Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa        240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80
```

```
agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg        288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg        336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa        384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc act ggc cgt gga gac agc ccc gca agc agc aag        528
Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                       552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 44
<211> 184
<212> PRT
<213> Homo sapiens

<400> 44

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Asp Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110
```

```
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 45
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 45

```
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa cgt         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Arg
        35                  40                  45

cga gtg ccc cac tct gat aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Asp Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125
```

```
aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc act ggc cgt gga gac agc ccc gca agc agc aag        528
Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                        552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 46
<211> 184
<212> PRT
<213> Homo sapiens

<400> 46

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Arg
        35                  40                  45

Arg Val Pro His Ser Asp Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160
```

```
Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 47
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 47

```
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc          48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tat tac          96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc         144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct         192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

gga gtt gat tat acc atc act gtg tat gct gtc act cct cgt ggt gat         240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Pro Arg Gly Asp
65                  70                  75                  80

atg cct gac agc agc aag cca att tcc att aat tac cga aca                 282
Met Pro Asp Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 48
<211> 94
<212> PRT
<213> Homo sapiens

<400> 48

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45
```

```
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Pro Arg Gly Asp
65                  70                  75                  80

Met Pro Asp Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 49
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 49

```
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc          48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tat tac          96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc         144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct         192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

gga gtt gat tat acc atc act gtg tat gct gtc act ccg cgt gga gac         240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Pro Arg Gly Asp
65                  70                  75                  80

tgg aat gaa gga agc aag cca att tcc att aat tac cga aca                 282
Trp Asn Glu Gly Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 50
<211> 94
<212> PRT
<213> Homo sapiens

<400> 50

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30
```

```
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Pro Arg Gly Asp
65                  70                  75                  80

Trp Asn Glu Gly Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 51
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 51

```
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc          48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tac tac          96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc         144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct         192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

gga gtt gat tat acc atc act gtg tat gct gtc act gct cgt ggt gat         240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Ala Arg Gly Asp
65                  70                  75                  80

aat cct gac agc agc aag cca att tcc att aat tac cga aca                 282
Asn Pro Asp Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 52
<211> 94
<212> PRT
<213> Homo sapiens

<400> 52

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15
```

```
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Ala Arg Gly Asp
65                  70                  75                  80

Asn Pro Asp Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 53
<211> 282
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(282)

<400> 53

```
gtt tct gat gtt ccg agg gac ctg gaa gtt gtt gct gcg acc ccc acc          48
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

agc cta ctg atc agc tgg gat gct cct gct gtc aca gtg aga tac tac          96
Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
            20                  25                  30

agg atc act tac gga gaa aca gga gga aat agc cct gtc cag gag ttc         144
Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

act gtg cct ggg agc aag tct aca gct acc atc agc ggc ctt aaa cct         192
Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

gga gtt gat tat acc atc act gtg tat gct gtc cgt gct cgt ggt gat         240
Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Arg Ala Arg Gly Asp
65                  70                  75                  80

aat cct gac agc agc aag cca att tcc att aat tac cga aca                 282
Asn Pro Asp Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90
```

<210> 54
<211> 94
<212> PRT
<213> Homo sapiens

<400> 54

Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Arg Ala Arg Gly Asp
65 70 75 80

Asn Pro Asp Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 55
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 55

```
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc tta ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
```

```
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa        384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc act cct cgt ggt gat atg cct gac agc agc aag        528
Thr Val Tyr Ala Val Thr Pro Arg Gly Asp Met Pro Asp Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                        552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 56
<211> 184
<212> PRT
<213> Homo sapiens

<400> 56

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
```

```
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Thr Pro Arg Gly Asp Met Pro Asp Ser Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 57
<211> 552
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(552)

<400> 57

```
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc tta ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag         432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc         480
```

```
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc act ccg cgt gga gac tgg aat gaa gga agc aag        528
Thr Val Tyr Ala Val Thr Pro Arg Gly Asp Trp Asn Glu Gly Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                        552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  58
<211>  184
<212>  PRT
<213>  Homo sapiens

<400>  58

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15


Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30


Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45


Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60


Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80


Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95


Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110


Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125


Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140


Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160


Thr Val Tyr Ala Val Thr Pro Arg Gly Asp Trp Asn Glu Gly Ser Lys
                165                 170                 175
```

```
Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  59
<211>  552
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(552)

<400>  59
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tac tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag         432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc         480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc act gct cgt ggt gat aat cct gac agc agc aag         528
Thr Val Tyr Ala Val Thr Ala Arg Gly Asp Asn Pro Asp Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                         552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 60
<211> 184
<212> PRT
<213> Homo sapiens

<400> 60

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Val Thr Ala Arg Gly Asp Asn Pro Asp Ser Ser Lys
165 170 175

Pro Ile Ser Ile Asn Tyr Arg Thr
180

<210> 61
<211> 552
<212> DNA
<213> Homo sapiens

<220>

<221> CDS
<222> (1)..(552)

<400> 61

```
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac          48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac          96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat         144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca         192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa         240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg         288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg         336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tac tac agg atc act tac gga gaa         384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag         432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc         480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc cgt gct cgt ggt gat aat cct gac agc agc aag         528
Thr Val Tyr Ala Val Arg Ala Arg Gly Asp Asn Pro Asp Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                         552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 62
<211> 184
<212> PRT
<213> Homo sapiens

<400> 62

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15
```

```
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Arg Ala Arg Gly Asp Asn Pro Asp Ser Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180


<210>  63
<211>  184
<212>  PRT
<213>  Homo sapiens

<400>  63

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45
```

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
165 170 175

Pro Ile Ser Ile Asn Tyr Arg Thr
180

<210> 64
<211> 184
<212> PRT
<213> Homo sapiens

<400> 64

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Cys Asn
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Cys Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
165 170 175

Pro Ile Ser Ile Asn Tyr Arg Thr
180

<210> 65
<211> 94
<212> PRT
<213> Homo sapiens

<400> 65

Val Ser Asp Val Pro Arg Asn Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Gly Arg Gly Asp
65 70 75 80

Ser Pro Ala Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 66
<211> 184
<212> PRT

<213> Pan troglodytes

<400> 66

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                  10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Leu Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro Pro Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Ser Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 67
<211> 184
<212> PRT
<213> Bos taurus

<400> 67

```
Ala Leu Asp Ser Pro Ser Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                  10                  15
```

```
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu Asn Met Gly Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro Pro Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Asn Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Ser Lys Glu Glu
65                  70                  75                  80

Ser Leu Pro Leu Val Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Ile Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Ser Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

Pro Val Ser Ile Asn Tyr Arg Thr
            180
```

<210> 68
<211> 184
<212> PRT
<213> Sus scrofa

<400> 68

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val Tyr Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Lys Ile Arg His His Pro Glu His Met Gly Gly Arg Pro Arg Glu Asp
        35                  40                  45
```

Arg Val Pro Pro Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Ile Pro
50 55 60

Gly Val Glu Tyr Val Val Ser Ile Val Ala Val Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Val Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Gln Val Ile Ala Thr Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
165 170 175

Pro Val Ser Ile Asp Tyr Arg Thr
180

<210> 69
<211> 184
<212> PRT
<213> Mus musculus

<400> 69

Gly Leu Asp Ser Pro Thr Gly Phe Asp Ser Ser Asp Ile Thr Ala Asn
1 5 10 15

Ser Phe Thr Val His Trp Val Ala Pro Arg Ala Pro Ile Thr Gly Tyr
20 25 30

Ile Ile Arg His His Ala Glu His Ser Val Gly Arg Pro Arg Gln Asp
35 40 45

Arg Val Pro Pro Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Asn Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Ile Ala Val Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ala Thr Val Ser Asp Ile Pro Arg
85 90 95

Asp Leu Glu Val Ile Ala Ser Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Glu Pro Pro Ala Val Ser Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Asn Asn Ile Lys Pro Gly Ala Asp Tyr Thr Ile
145 150 155 160

Thr Leu Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
165 170 175

Pro Val Ser Ile Asn Tyr Lys Thr
180

<210> 70
<211> 184
<212> PRT
<213> Rattus norvegicus

<400> 70

Gly Leu Asp Ser Pro Thr Gly Phe Asp Ser Ser Asp Val Thr Ala Asn
1 5 10 15

Ser Phe Thr Val His Trp Val Ala Pro Arg Ala Pro Ile Thr Gly Tyr
20 25 30

Ile Ile Arg His His Ala Glu His Ser Ala Gly Arg Pro Arg Gln Asp
35 40 45

Arg Val Pro Pro Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Asn Pro
50 55 60

Gly Thr Glu Tyr Ile Val Thr Ile Ile Ala Val Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Ile Ala Ser Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

```
Glu Pro Pro Ala Val Ser Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125


Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140


Ser Thr Ala Thr Ile Asn Asn Ile Lys Pro Gly Ala Asp Tyr Thr Ile
145                 150                 155                 160


Thr Leu Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175


Pro Val Ser Ile Asn Tyr Gln Thr
            180


<210>  71
<211>  552
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(552)

<400>  71
ggt ctt gat tcc cca act ggc att gac ttt tct gat att act gcc aac         48
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

tct ttt act gtg cac tgg att gct cct cga gcc acc atc act ggc tac         96
Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

agg atc cgc cat cat ccc gag cac ttc agt ggg aga cct cga gaa gat        144
Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

cgg gtg ccc cac tct cgg aat tcc atc acc ctc acc aac ctc act cca        192
Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

ggc aca gag tat gtg gtc agc atc gtt gct ctt aat ggc aga gag gaa        240
Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

agt ccc ccg ttg att ggc caa caa tca aca gtt tct gat gtt ccg agg        288
Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

gac ctg gaa gtt gtt gct gcg acc ccc acc agc cta ctg atc agc tgg        336
Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

gat gct cct gct gtc aca gtg aga tat tac agg atc act tac gga gaa        384
Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125
```

```
aca gga gga aat agc cct gtc cag gag ttc act gtg cct ggg agc aag        432
Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

tct aca gct acc atc agc ggc ctt aaa cct gga gtt gat tat acc atc        480
Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160

act gtg tat gct gtc agg ggc cgt gga gac agc ccc gca agc agc aag        528
Thr Val Tyr Ala Val Arg Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys
                165                 170                 175

cca att tcc att aat tac cga aca                                        552
Pro Ile Ser Ile Asn Tyr Arg Thr
            180
```

<210> 72
<211> 184
<212> PRT
<213> Homo sapiens

<400> 72

```
Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1               5                   10                  15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
            20                  25                  30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
        35                  40                  45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
    50                  55                  60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65                  70                  75                  80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
                85                  90                  95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
            100                 105                 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
        115                 120                 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
    130                 135                 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145                 150                 155                 160
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Pro Ile Ser Ile Asn Tyr Arg Thr
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ccttccccac cctctggccc ccaccttctt ggaggcgaca acccccggga ggcattagaa       180

gggatttttc ccgcaggttg cgaagggaag caaacttggt ggcaacttgc ctcccggtgc       240

gggcgtctct cccccaccgt ctcaacatgc ttaggggtcc ggggcccggg ctgctgctgc       300

tggccgtcca gtgcctgggg acagcggtgc cctccacggg agcctcgaag agcaagagg        359

cag gct cag caa atg gtt cag ccc cag tcc ccg gtg gct gtc agt caa          407
Gln Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln
1               5                   10                  15

agc aag ccc ggt tgt tat gac aat gga aaa cac tat cag ata aat caa          455
Ser Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln
            20                  25                  30

cag tgg gag cgg acc tac cta ggc aat gcg ttg gtt tgt act tgt tat          503
Gln Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr
        35                  40                  45

gga gga agc cga ggt ttt aac tgc gag agt aaa cct gaa gct gaa gag          551
Gly Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu
    50                  55                  60

act tgc ttt gac aag tac act ggg aac act tac cga gtg ggt gac act          599
Thr Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr
65                  70                  75                  80

tat gag cgt cct aaa gac tcc atg atc tgg gac tgt acc tgc atc ggg          647
Tyr Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly
                85                  90                  95

gct ggg cga ggg aga ata agc tgt acc atc gca aac cgc tgc cat gaa          695
Ala Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu
            100                 105                 110

ggg ggt cag tcc tac aag att ggt gac acc tgg agg aga cca cat gag          743
Gly Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu
        115                 120                 125
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act ggt ggt tac atg tta gag tgt gtg tgt ctt ggt aat gga aaa gga          791
Thr Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly
    130                 135                 140

gaa tgg acc tgc aag ccc ata gct gag aag tgt ttt gat cat gct gct          839
Glu Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala
145                 150                 155                 160

ggg act tcc tat gtg gtc gga gaa acg tgg gag aag ccc tac caa ggc          887
Gly Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly
                165                 170                 175

tgg atg atg gta gat tgt act tgc ctg gga gaa ggc agc gga cgc atc          935
Trp Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile
            180                 185                 190

act tgc act tct aga aat aga tgc aac gat cag gac aca agg aca tcc          983
Thr Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser
        195                 200                 205

tat aga att gga gac acc tgg agc aag aag gat aat cga gga aac ctg         1031
Tyr Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu
    210                 215                 220

ctc cag tgc atc tgc aca ggc aac ggc cga gga gag tgg aag tgt gag         1079
Leu Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu
225                 230                 235                 240

agg cac acc tct gtg cag acc aca tcg agc gga tct ggc ccc ttc acc         1127
Arg His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr
                245                 250                 255

gat gtt cgt gca gct gtt tac caa ccg cag cct cac ccc cag cct cct         1175
Asp Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro
            260                 265                 270

ccc tat ggc cac tgt gtc aca gac agt ggt gtg gtc tac tct gtg ggg         1223
Pro Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly
        275                 280                 285

atg cag tgg ctg aag aca caa gga aat aag caa atg ctt tgc acg tgc         1271
Met Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys
    290                 295                 300

ctg ggc aac gga gtc agc tgc caa gag aca gct gta acc cag act tac         1319
Leu Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr
305                 310                 315                 320

ggt ggc aac tca aat gga gag cca tgt gtc tta cca ttc acc tac aat         1367
Gly Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn
                325                 330                 335

ggc agg acg ttc tac tcc tgc acc aca gaa ggg cga cag gac gga cat         1415
Gly Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His
            340                 345                 350

ctt tgg tgc agc aca act tcg aat tat gag cag gac cag aaa tac tct         1463
Leu Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser
        355                 360                 365

ttc tgc aca gac cac act gtt ttg gtt cag act cga gga gga aat tcc         1511
Phe Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser
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    370                 375                 380

aat ggt gcc ttg tgc cac ttc ccc ttc cta tac aac aac cac aat tac       1559
Asn Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr
385                 390                 395                 400

act gat tgc act tct gag ggc aga aga gac aac atg aag tgg tgt ggg       1607
Thr Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met Lys Trp Cys Gly
                405                 410                 415

acc aca cag aac tat gat gcc gac cag aag ttt ggg ttc tgc ccc atg       1655
Thr Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly Phe Cys Pro Met
            420                 425                 430

gct gcc cac gag gaa atc tgc aca acc aat gaa ggg gtc atg tac cgc       1703
Ala Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly Val Met Tyr Arg
        435                 440                 445

att gga gat cag tgg gat aag cag cat gac atg ggt cac atg atg agg       1751
Ile Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly His Met Met Arg
    450                 455                 460

tgc acg tgt gtt ggg aat ggt cgt ggg gaa tgg aca tgc att gcc tac       1799
Cys Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr Cys Ile Ala Tyr
465                 470                 475                 480

tcg cag ctt cga gat cag tgc att gtt gat gac atc act tac aat gtg       1847
Ser Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile Thr Tyr Asn Val
                485                 490                 495

aac gac aca ttc cac aag cgt cat gaa gag ggg cac atg ctg aac tgt       1895
Asn Asp Thr Phe His Lys Arg His Glu Glu Gly His Met Leu Asn Cys
            500                 505                 510

aca tgc ttc ggt cag ggt cgg ggc agg tgg aag tgt gat ccc gtc gac       1943
Thr Cys Phe Gly Gln Gly Arg Gly Arg Trp Lys Cys Asp Pro Val Asp
        515                 520                 525

caa tgc cag gat tca gag act ggg acg ttt tat caa att gga gat tca       1991
Gln Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln Ile Gly Asp Ser
    530                 535                 540

tgg gag aag tat gtg cat ggt gtc aga tac cag tgc tac tgc tat ggc       2039
Trp Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys Tyr Cys Tyr Gly
545                 550                 555                 560

cgt ggc att ggg gag tgg cat tgc caa cct tta cag acc tat cca agc       2087
Arg Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln Thr Tyr Pro Ser
                565                 570                 575

tca agt ggt cct gtc gaa gta ttt atc act gag act ccg agt cag ccc       2135
Ser Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr Pro Ser Gln Pro
            580                 585                 590

aac tcc cac ccc atc cag tgg aat gca cca cag cca tct cac att tcc       2183
Asn Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro Ser His Ile Ser
        595                 600                 605

aag tac att ctc agg tgg aga cct aaa aat tct gta ggc cgt tgg aag       2231
Lys Tyr Ile Leu Arg Trp Arg Pro Lys Asn Ser Val Gly Arg Trp Lys
    610                 615                 620

gaa gct acc ata cca ggc cac tta aac tcc tac acc atc aaa ggc ctg       2279
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Glu Ala Thr Ile Pro Gly His Leu Asn Ser Tyr Thr Ile Lys Gly Leu
625                 630                 635                 640

aag cct ggt gtg gta tac gag ggc cag ctc atc agc atc cag cag tac       2327
Lys Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser Ile Gln Gln Tyr
                645                 650                 655

ggc cac caa gaa gtg act cgc ttt gac ttc acc acc acc agc acc agc       2375
Gly His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr Thr Ser Thr Ser
            660                 665                 670

aca cct gtg acc agc aac acc gtg aca gga gag acg act ccc ttt tct       2423
Thr Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr Thr Pro Phe Ser
        675                 680                 685

cct ctt gtg gcc act tct gaa tct gtg acc gaa atc aca gcc agt agc       2471
Pro Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile Thr Ala Ser Ser
    690                 695                 700

ttt gtg gtc tcc tgg gtc tca gct tcc gac acc gtg tcg gga ttc cgg       2519
Phe Val Val Ser Trp Val Ser Ala Ser Asp Thr Val Ser Gly Phe Arg
705                 710                 715                 720

gtg gaa tat gag ctg agt gag gag gga gat gag cca cag tac ctg gat       2567
Val Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro Gln Tyr Leu Asp
                725                 730                 735

ctt cca agc aca gcc act tct gtg aac atc cct gac ctg ctt cct ggc       2615
Leu Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp Leu Leu Pro Gly
            740                 745                 750

cga aaa tac att gta aat gtc tat cag ata tct gag gat ggg gag cag       2663
Arg Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu Asp Gly Glu Gln
        755                 760                 765

agt ttg atc ctg tct act tca caa aca aca gcg cct gat gcc cct cct       2711
Ser Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro Asp Ala Pro Pro
    770                 775                 780

gac ccg act gtg gac caa gtt gat gac acc tca att gtt gtt cgc tgg       2759
Asp Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile Val Val Arg Trp
785                 790                 795                 800

agc aga ccc cag gct ccc atc aca ggg tac aga ata gtc tat tcg cca       2807
Ser Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile Val Tyr Ser Pro
                805                 810                 815

tca gta gaa ggt agc agc aca gaa ctc aac ctt cct gaa act gca aac       2855
Ser Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro Glu Thr Ala Asn
            820                 825                 830

tcc gtc acc ctc agt gac ttg caa cct ggt gtt cag tat aac atc act       2903
Ser Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln Tyr Asn Ile Thr
        835                 840                 845

atc tat gct gtg gaa gaa aat caa gaa agt aca cct gtt gtc att caa       2951
Ile Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro Val Val Ile Gln
    850                 855                 860

caa gaa acc act ggc acc cca cgc tca gat aca gtg ccc tct ccc agg       2999
Gln Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val Pro Ser Pro Arg
865                 870                 875                 880
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gac ctg cag ttt gtg gaa gtg aca gac gtg aag gtc acc atc atg tgg       3047
Asp Leu Gln Phe Val Glu Val Thr Asp Val Lys Val Thr Ile Met Trp
                885                 890                 895

aca ccg cct gag agt gca gtg acc ggc tac cgt gtg gat gtg atc ccc       3095
Thr Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro
            900                 905                 910

gtc aac ctg cct ggc gag cac ggg cag agg ctg ccc atc agc agg aac       3143
Val Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro Ile Ser Arg Asn
        915                 920                 925

acc ttt gca gaa gtc acc ggg ctg tcc cct ggg gtc acc tat tac ttc       3191
Thr Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe
    930                 935                 940

aaa gtc ttt gca gtg agc cat ggg agg gag agc aag cct ctg act gct       3239
Lys Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Ala
945                 950                 955                 960

caa cag aca acc aaa ctg gat gct ccc act aac ctc cag ttt gtc aat       3287
Gln Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn
                965                 970                 975

gaa act gat tct act gtc ctg gtg aga tgg act cca cct cgg gcc cag       3335
Glu Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln
            980                 985                 990

ata aca gga tac cga ctg acc gtg  ggc ctt acc cga aga  gga cag ccc     3383
Ile Thr Gly Tyr Arg Leu Thr Val  Gly Leu Thr Arg Arg  Gly Gln Pro
        995                 1000                1005

agg cag  tac aat gtg ggt ccc  tct gtc tcc aag tac  cca ctg agg       3428
Arg Gln  Tyr Asn Val Gly Pro  Ser Val Ser Lys Tyr  Pro Leu Arg
    1010                1015                1020

aat ctg  cag cct gca tct gag  tac acc gta tcc ctc  gtg gcc ata       3473
Asn Leu  Gln Pro Ala Ser Glu  Tyr Thr Val Ser Leu  Val Ala Ile
    1025                1030                1035

aag ggc  aac caa gag agc ccc  aaa gcc act gga gtc  ttt acc aca       3518
Lys Gly  Asn Gln Glu Ser Pro  Lys Ala Thr Gly Val  Phe Thr Thr
    1040                1045                1050

ctg cag  cct ggg agc tct att  cca cct tac aac acc  gag gtg act       3563
Leu Gln  Pro Gly Ser Ser Ile  Pro Pro Tyr Asn Thr  Glu Val Thr
    1055                1060                1065

gag acc  acc att gtg atc aca  tgg acg cct gct cca  aga att ggt       3608
Glu Thr  Thr Ile Val Ile Thr  Trp Thr Pro Ala Pro  Arg Ile Gly
    1070                1075                1080

ttt aag  ctg ggt gta cga cca  agc cag gga gga gag  gca cca cga       3653
Phe Lys  Leu Gly Val Arg Pro  Ser Gln Gly Gly Glu  Ala Pro Arg
    1085                1090                1095

gaa gtg  act tca gac tca gga  agc atc gtt gtg tcc  ggc ttg act       3698
Glu Val  Thr Ser Asp Ser Gly  Ser Ile Val Val Ser  Gly Leu Thr
    1100                1105                1110

cca gga  gta gaa tac gtc tac  acc atc caa gtc ctg  aga gat gga       3743
Pro Gly  Val Glu Tyr Val Tyr  Thr Ile Gln Val Leu  Arg Asp Gly
    1115                1120                1125
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cag gaa  aga gat gcg cca att  gta aac aaa gtg gtg  aca cca ttg        3788
Gln Glu  Arg Asp Ala Pro Ile  Val Asn Lys Val Val  Thr Pro Leu
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tct cca  cca aca aac ttg cat  ctg gag gca aac cct  gac act gga        3833
Ser Pro  Pro Thr Asn Leu His  Leu Glu Ala Asn Pro  Asp Thr Gly
    1145                 1150                 1155

gtg ctc  aca gtc tcc tgg gag  agg agc acc acc cca  gac att act        3878
Val Leu  Thr Val Ser Trp Glu  Arg Ser Thr Thr Pro  Asp Ile Thr
    1160                 1165                 1170

ggt tat  aga att acc aca acc  cct aca aac ggc cag  cag gga aat        3923
Gly Tyr  Arg Ile Thr Thr Thr  Pro Thr Asn Gly Gln  Gln Gly Asn
    1175                 1180                 1185

tct ttg  gaa gaa gtg gtc cat  gct gat cag agc tcc  tgc act ttt        3968
Ser Leu  Glu Glu Val Val His  Ala Asp Gln Ser Ser  Cys Thr Phe
    1190                 1195                 1200

gat aac  ctg agt ccc ggc ctg  gag tac aat gtc agt  gtt tac act        4013
Asp Asn  Leu Ser Pro Gly Leu  Glu Tyr Asn Val Ser  Val Tyr Thr
    1205                 1210                 1215

gtc aag  gat gac aag gaa agt  gtc cct atc tct gat  acc atc atc        4058
Val Lys  Asp Asp Lys Glu Ser  Val Pro Ile Ser Asp  Thr Ile Ile
    1220                 1225                 1230

cca gct  gtt cct cct ccc act  gac ctg cga ttc acc  aac att ggt        4103
Pro Ala  Val Pro Pro Pro Thr  Asp Leu Arg Phe Thr  Asn Ile Gly
    1235                 1240                 1245

cca gac  acc atg cgt gtc acc  tgg gct cca ccc cca  tcc att gat        4148
Pro Asp  Thr Met Arg Val Thr  Trp Ala Pro Pro Pro  Ser Ile Asp
    1250                 1255                 1260

tta acc  aac ttc ctg gtg cgt  tac tca cct gtg aaa  aat gag gaa        4193
Leu Thr  Asn Phe Leu Val Arg  Tyr Ser Pro Val Lys  Asn Glu Glu
    1265                 1270                 1275

gat gtt  gca gag ttg tca att  tct cct tca gac aat  gca gtg gtc        4238
Asp Val  Ala Glu Leu Ser Ile  Ser Pro Ser Asp Asn  Ala Val Val
    1280                 1285                 1290

tta aca  aat ctc ctg cct ggt  aca gaa tat gta gtg  agt gtc tcc        4283
Leu Thr  Asn Leu Leu Pro Gly  Thr Glu Tyr Val Val  Ser Val Ser
    1295                 1300                 1305

agt gtc  tac gaa caa cat gag  agc aca cct ctt aga  gga aga cag        4328
Ser Val  Tyr Glu Gln His Glu  Ser Thr Pro Leu Arg  Gly Arg Gln
    1310                 1315                 1320

aaa aca  ggt ctt gat tcc cca  act ggc att gac ttt  tct gat att        4373
Lys Thr  Gly Leu Asp Ser Pro  Thr Gly Ile Asp Phe  Ser Asp Ile
    1325                 1330                 1335

act gcc  aac tct ttt act gtg  cac tgg att gct cct  cga gcc acc        4418
Thr Ala  Asn Ser Phe Thr Val  His Trp Ile Ala Pro  Arg Ala Thr
    1340                 1345                 1350

atc act  ggc tac agg atc cgc  cat cat ccc gag cac  ttc agt ggg        4463
Ile Thr  Gly Tyr Arg Ile Arg  His His Pro Glu His  Phe Ser Gly
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    1355                1360                1365

aga cct  cga gaa gat cgg gtg  ccc cac tct cgg aat  tcc atc acc        4508
Arg Pro  Arg Glu Asp Arg Val  Pro His Ser Arg Asn  Ser Ile Thr
    1370                1375                1380

ctc acc  aac ctc act cca ggc  aca gag tat gtg gtc  agc atc gtt        4553
Leu Thr  Asn Leu Thr Pro Gly  Thr Glu Tyr Val Val  Ser Ile Val
    1385                1390                1395

gct ctt  aat ggc aga gag gaa  agt ccc tta ttg att  ggc caa caa        4598
Ala Leu  Asn Gly Arg Glu Glu  Ser Pro Leu Leu Ile  Gly Gln Gln
    1400                1405                1410

tca aca  gtt tct gat gtt ccg  agg gac ctg gaa gtt  gtt gct gcg        4643
Ser Thr  Val Ser Asp Val Pro  Arg Asp Leu Glu Val  Val Ala Ala
    1415                1420                1425

acc ccc  acc agc cta ctg atc  agc tgg gat gct cct  gct gtc aca        4688
Thr Pro  Thr Ser Leu Leu Ile  Ser Trp Asp Ala Pro  Ala Val Thr
    1430                1435                1440

gtg aga  tat tac agg atc act  tac gga gag aca gga  gga aat agc        4733
Val Arg  Tyr Tyr Arg Ile Thr  Tyr Gly Glu Thr Gly  Gly Asn Ser
    1445                1450                1455

cct gtc  cag gag ttc act gtg  cct ggg agc aag tct  aca gct acc        4778
Pro Val  Gln Glu Phe Thr Val  Pro Gly Ser Lys Ser  Thr Ala Thr
    1460                1465                1470

atc agc  ggc ctt aaa cct gga  gtt gat tat acc atc  act gtg tat        4823
Ile Ser  Gly Leu Lys Pro Gly  Val Asp Tyr Thr Ile  Thr Val Tyr
    1475                1480                1485

gct gtc  act ggc cgt gga gac  agc ccc gca agc agc  aag cca att        4868
Ala Val  Thr Gly Arg Gly Asp  Ser Pro Ala Ser Ser  Lys Pro Ile
    1490                1495                1500

tcc att  aat tac cga aca gaa  att gac aaa cca tcc  cag atg caa        4913
Ser Ile  Asn Tyr Arg Thr Glu  Ile Asp Lys Pro Ser  Gln Met Gln
    1505                1510                1515

gtg acc  gat gtt cag gac aac  agc att agt gtc aag  tgg ctg cct        4958
Val Thr  Asp Val Gln Asp Asn  Ser Ile Ser Val Lys  Trp Leu Pro
    1520                1525                1530

tca agt  tcc cct gtt act ggt  tac aga gta acc acc  act ccc aaa        5003
Ser Ser  Ser Pro Val Thr Gly  Tyr Arg Val Thr Thr  Thr Pro Lys
    1535                1540                1545

aat gga  cca gga cca aca aaa  act aaa act gca ggt  cca gat caa        5048
Asn Gly  Pro Gly Pro Thr Lys  Thr Lys Thr Ala Gly  Pro Asp Gln
    1550                1555                1560

aca gaa  atg act att gaa ggc  ttg cag ccc aca gtg  gag tat gtg        5093
Thr Glu  Met Thr Ile Glu Gly  Leu Gln Pro Thr Val  Glu Tyr Val
    1565                1570                1575

gtt agt  gtc tat gct cag aat  cca agc gga gag agt  cag cct ctg        5138
Val Ser  Val Tyr Ala Gln Asn  Pro Ser Gly Glu Ser  Gln Pro Leu
    1580                1585                1590

gtt cag  act gca gta acc act  att cct gca cca act  gac ctg aag        5183
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Val Gln  Thr Ala Val Thr Thr  Ile Pro Ala Pro Thr  Asp Leu Lys
    1595                1600                1605

ttc act  cag gtc aca ccc aca  agc ctg agc gcc cag  tgg aca cca        5228
Phe Thr  Gln Val Thr Pro Thr  Ser Leu Ser Ala Gln  Trp Thr Pro
    1610                1615                1620

ccc aat  gtt cag ctc act gga  tat cga gtg cgg gtg  acc ccc aag        5273
Pro Asn  Val Gln Leu Thr Gly  Tyr Arg Val Arg Val  Thr Pro Lys
    1625                1630                1635

gag aag  acc gga cca atg aaa  gaa atc aac ctt gct  cct gac agc        5318
Glu Lys  Thr Gly Pro Met Lys  Glu Ile Asn Leu Ala  Pro Asp Ser
    1640                1645                1650

tca tcc  gtg gtt gta tca gga  ctt atg gtg gcc acc  aaa tat gaa        5363
Ser Ser  Val Val Val Ser Gly  Leu Met Val Ala Thr  Lys Tyr Glu
    1655                1660                1665

gtg agt  gtc tat gct ctt aag  gac act ttg aca agc  aga cca gct        5408
Val Ser  Val Tyr Ala Leu Lys  Asp Thr Leu Thr Ser  Arg Pro Ala
    1670                1675                1680

cag gga  gtt gtc acc act ctg  gag aat gtc agc cca  cca aga agg        5453
Gln Gly  Val Val Thr Thr Leu  Glu Asn Val Ser Pro  Pro Arg Arg
    1685                1690                1695

gct cgt  gtg aca gat gct act  gag acc acc atc acc  att agc tgg        5498
Ala Arg  Val Thr Asp Ala Thr  Glu Thr Thr Ile Thr  Ile Ser Trp
    1700                1705                1710

aga acc  aag act gag acg atc  act ggc ttc caa gtt  gat gcc gtt        5543
Arg Thr  Lys Thr Glu Thr Ile  Thr Gly Phe Gln Val  Asp Ala Val
    1715                1720                1725

cca gcc  aat ggc cag act cca  atc cag aga acc atc  aag cca gat        5588
Pro Ala  Asn Gly Gln Thr Pro  Ile Gln Arg Thr Ile  Lys Pro Asp
    1730                1735                1740

gtc aga  agc tac acc atc aca  ggt tta caa cca ggc  act gac tac        5633
Val Arg  Ser Tyr Thr Ile Thr  Gly Leu Gln Pro Gly  Thr Asp Tyr
    1745                1750                1755

aag atc  tac ctg tac acc ttg  aat gac aat gct cgg  agc tcc cct        5678
Lys Ile  Tyr Leu Tyr Thr Leu  Asn Asp Asn Ala Arg  Ser Ser Pro
    1760                1765                1770

gtg gtc  atc gac gcc tcc act  gcc att gat gca cca  tcc aac ctg        5723
Val Val  Ile Asp Ala Ser Thr  Ala Ile Asp Ala Pro  Ser Asn Leu
    1775                1780                1785

cgt ttc  ctg gcc acc aca ccc  aat tcc ttg ctg gta  tca tgg cag        5768
Arg Phe  Leu Ala Thr Thr Pro  Asn Ser Leu Leu Val  Ser Trp Gln
    1790                1795                1800

ccg cca  cgt gcc agg att acc  ggc tac atc atc aag  tat gag aag        5813
Pro Pro  Arg Ala Arg Ile Thr  Gly Tyr Ile Ile Lys  Tyr Glu Lys
    1805                1810                1815

cct ggg  tct cct ccc aga gaa  gtg gtc cct cgg ccc  cgc cct ggt        5858
Pro Gly  Ser Pro Pro Arg Glu  Val Val Pro Arg Pro  Arg Pro Gly
    1820                1825                1830
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gtc aca  gag gct act att act  ggc ctg gaa ccg gga  acc gaa tat        5903
Val Thr  Glu Ala Thr Ile Thr  Gly Leu Glu Pro Gly  Thr Glu Tyr
    1835                 1840                 1845

aca att  tat gtc att gcc ctg  aag aat aat cag aag  agc gag ccc        5948
Thr Ile  Tyr Val Ile Ala Leu  Lys Asn Asn Gln Lys  Ser Glu Pro
    1850                 1855                 1860

ctg att  gga agg aaa aag aca  gac gag ctt ccc caa  ctg gta acc        5993
Leu Ile  Gly Arg Lys Lys Thr  Asp Glu Leu Pro Gln  Leu Val Thr
    1865                 1870                 1875

ctt cca  cac ccc aat ctt cat  gga cca gag atc ttg  gat gtt cct        6038
Leu Pro  His Pro Asn Leu His  Gly Pro Glu Ile Leu  Asp Val Pro
    1880                 1885                 1890

tcc aca  gtt caa aag acc cct  ttc gtc acc cac cct  ggg tat gac        6083
Ser Thr  Val Gln Lys Thr Pro  Phe Val Thr His Pro  Gly Tyr Asp
    1895                 1900                 1905

act gga  aat ggt att cag ctt  cct ggc act tct ggt  cag caa ccc        6128
Thr Gly  Asn Gly Ile Gln Leu  Pro Gly Thr Ser Gly  Gln Gln Pro
    1910                 1915                 1920

agt gtt  ggg caa caa atg atc  ttt gag gaa cat ggt  ttt agg cgg        6173
Ser Val  Gly Gln Gln Met Ile  Phe Glu Glu His Gly  Phe Arg Arg
    1925                 1930                 1935

acc aca  ccg ccc aca acg gcc  acc ccc ata agg cat  agg cca aga        6218
Thr Thr  Pro Pro Thr Thr Ala  Thr Pro Ile Arg His  Arg Pro Arg
    1940                 1945                 1950

cca tac  ccg ccg aat gta ggt  gag gaa atc caa att  ggt cac atc        6263
Pro Tyr  Pro Pro Asn Val Gly  Glu Glu Ile Gln Ile  Gly His Ile
    1955                 1960                 1965

ccc agg  gaa gat gta gac tat  cac ctg tac cca cac  ggt ccg gga        6308
Pro Arg  Glu Asp Val Asp Tyr  His Leu Tyr Pro His  Gly Pro Gly
    1970                 1975                 1980

ctc aat  cca aat gcc tct aca  gga caa gaa gct ctc  tct cag aca        6353
Leu Asn  Pro Asn Ala Ser Thr  Gly Gln Glu Ala Leu  Ser Gln Thr
    1985                 1990                 1995

acc atc  tca tgg gcc cca ttc  cag gac act tct gag  tac atc att        6398
Thr Ile  Ser Trp Ala Pro Phe  Gln Asp Thr Ser Glu  Tyr Ile Ile
    2000                 2005                 2010

tca tgt  cat cct gtt ggc act  gat gaa gaa ccc tta  cag ttc agg        6443
Ser Cys  His Pro Val Gly Thr  Asp Glu Glu Pro Leu  Gln Phe Arg
    2015                 2020                 2025

gtt cct  gga act tct acc agt  gcc act ctg aca ggc  ctc acc aga        6488
Val Pro  Gly Thr Ser Thr Ser  Ala Thr Leu Thr Gly  Leu Thr Arg
    2030                 2035                 2040

ggt gcc  acc tac aac atc ata  gtg gag gca ctg aaa  gac cag cag        6533
Gly Ala  Thr Tyr Asn Ile Ile  Val Glu Ala Leu Lys  Asp Gln Gln
    2045                 2050                 2055

agg cat  aag gtt cgg gaa gag  gtt gtt acc gtg ggc  aac tct gtc        6578
Arg His  Lys Val Arg Glu Glu  Val Val Thr Val Gly  Asn Ser Val
    2060                 2065                 2070
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aac gaa  ggc ttg aac caa cct  acg gat gac tcg tgc  ttt gac ccc        6623
Asn Glu  Gly Leu Asn Gln Pro  Thr Asp Asp Ser Cys  Phe Asp Pro
    2075                 2080                 2085

tac aca  gtt tcc cat tat gcc  gtt gga gat gag tgg  gaa cga atg        6668
Tyr Thr  Val Ser His Tyr Ala  Val Gly Asp Glu Trp  Glu Arg Met
    2090                 2095                 2100

tct gaa  tca ggc ttt aaa ctg  ttg tgc cag tgc tta  ggc ttt gga        6713
Ser Glu  Ser Gly Phe Lys Leu  Leu Cys Gln Cys Leu  Gly Phe Gly
    2105                 2110                 2115

agt ggt  cat ttc aga tgt gat  tca tct aga tgg tgc  cat gac aat        6758
Ser Gly  His Phe Arg Cys Asp  Ser Ser Arg Trp Cys  His Asp Asn
    2120                 2125                 2130

ggt gtg  aac tac aag att gga  gag aag tgg gac cgt  cag gga gaa        6803
Gly Val  Asn Tyr Lys Ile Gly  Glu Lys Trp Asp Arg  Gln Gly Glu
    2135                 2140                 2145

aat ggc  cag atg atg agc tgc  aca tgt ctt ggg aac  gga aaa gga        6848
Asn Gly  Gln Met Met Ser Cys  Thr Cys Leu Gly Asn  Gly Lys Gly
    2150                 2155                 2160

gaa ttc  aag tgt gac cct cat  gag gca acg tgt tat  gat gat ggg        6893
Glu Phe  Lys Cys Asp Pro His  Glu Ala Thr Cys Tyr  Asp Asp Gly
    2165                 2170                 2175

aag aca  tac cac gta gga gaa  cag tgg cag aag gaa  tat ctc ggt        6938
Lys Thr  Tyr His Val Gly Glu  Gln Trp Gln Lys Glu  Tyr Leu Gly
    2180                 2185                 2190

gcc att  tgc tcc tgc aca tgc  ttt gga ggc cag cgg  ggc tgg cgc        6983
Ala Ile  Cys Ser Cys Thr Cys  Phe Gly Gly Gln Arg  Gly Trp Arg
    2195                 2200                 2205

tgt gac  aac tgc cgc aga cct  ggg ggt gaa ccc agt  ccc gaa ggc        7028
Cys Asp  Asn Cys Arg Arg Pro  Gly Gly Glu Pro Ser  Pro Glu Gly
    2210                 2215                 2220

act act  ggc cag tcc tac aac  cag tat tct cag aga  tac cat cag        7073
Thr Thr  Gly Gln Ser Tyr Asn  Gln Tyr Ser Gln Arg  Tyr His Gln
    2225                 2230                 2235

aga aca  aac act aat gtt aat  tgc cca att gag tgc  ttc atg cct        7118
Arg Thr  Asn Thr Asn Val Asn  Cys Pro Ile Glu Cys  Phe Met Pro
    2240                 2245                 2250

tta gat  gta cag gct gac aga  gaa gat tcc cga gag  taaatcatct        7164
Leu Asp  Val Gln Ala Asp Arg  Glu Asp Ser Arg Glu
    2255                 2260                 2265

ttccaatcca gaggaacaag catgtctctc tgccaagatc catctaaact ggagtgatgt    7224

tagcagaccc agcttagagt tcttctttct ttcttaagcc ctttgctctg gaggaagttc    7284

tccagcttca gctcaactca cagcttctcc aagcatcacc ctgggagttt cctgagggtt    7344

ttctcataaa tgagggctgc acattgcctg ttctgcttcg aagtattcaa taccgctcag    7404

tattttaaat gaagtgattc taagatttgg tttgggatca ataggaaagc atatgcagcc    7464
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aaccaagatg caaatgtttt gaaatgatat gaccaaaatt ttaagtagga aagtcaccca 7524

aacacttctg ctttcactta agtgtctggc ccgcaatact gtaggaacaa gcatgatctt 7584

gttactgtga tattttaaat atccacagta ctcacttttt ccaaatgatc ctagtaattg 7644

cctagaaata tctttctctt acctgttatt tatcaatttt tcccagtatt tttatacgga 7704

aaaaattgta ttgaaaacac ttagtatgca gttgataaga ggaatttggt ataattatgg 7764

tgggtgatta ttttttatac tgtatgtgcc aaagctttac tactgtggaa agacaactgt 7824

tttaataaaa gatttacatt ccacaacttg aagttcatct atttgatata agacaccttc 7884

gggggaaata attcctgtga atattctttt tcaattcagc aaacatttga aaatctatga 7944

tgtgcaagtc taattgttga tttcagtaca agattttcta aatcagttgc tacaaaaact 8004

gattggtttt tgtcacttca tctcttcact aatggagata gctttacact ttctgcttta 8064

atagatttaa gtggacccca atatttatta aaattgctag tttaccgttc agaagtataa 8124

tagaaataat ctttagttgc tcttttctaa ccattgtaat tcttcccttc ttccctccac 8184

ctttccttca ttgaataaac ctctgttcaa agagattgcc tgcaagggaa ataaaaatga 8244

ctaagatatt aaaaaaaaaa aaaaaaaa 8272

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<211> 2265
<212> PRT
<213> Homo sapiens

<400> 74

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Ser Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln
20 25 30

Gln Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr
35 40 45

Gly Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu
50 55 60

Thr Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr
65 70 75 80

Tyr Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly
85 90 95

Ala Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu
100 105 110

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Gly Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu
        115                 120                 125

Thr Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly
    130                 135                 140

Glu Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala
145                 150                 155                 160

Gly Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly
                165                 170                 175

Trp Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile
            180                 185                 190

Thr Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser
        195                 200                 205

Tyr Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu
    210                 215                 220

Leu Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu
225                 230                 235                 240

Arg His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr
                245                 250                 255

Asp Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro
            260                 265                 270

Pro Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly
        275                 280                 285

Met Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys
    290                 295                 300

Leu Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr
305                 310                 315                 320

Gly Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn
                325                 330                 335

Gly Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His
            340                 345                 350

Leu Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser
        355                 360                 365
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Phe Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser
    370                 375                 380

Asn Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr
385                 390                 395                 400

Thr Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met Lys Trp Cys Gly
                405                 410                 415

Thr Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly Phe Cys Pro Met
            420                 425                 430

Ala Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly Val Met Tyr Arg
        435                 440                 445

Ile Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly His Met Met Arg
    450                 455                 460

Cys Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr Cys Ile Ala Tyr
465                 470                 475                 480

Ser Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile Thr Tyr Asn Val
                485                 490                 495

Asn Asp Thr Phe His Lys Arg His Glu Glu Gly His Met Leu Asn Cys
            500                 505                 510

Thr Cys Phe Gly Gln Gly Arg Gly Arg Trp Lys Cys Asp Pro Val Asp
        515                 520                 525

Gln Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln Ile Gly Asp Ser
    530                 535                 540

Trp Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys Tyr Cys Tyr Gly
545                 550                 555                 560

Arg Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln Thr Tyr Pro Ser
                565                 570                 575

Ser Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr Pro Ser Gln Pro
            580                 585                 590

Asn Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro Ser His Ile Ser
        595                 600                 605

Lys Tyr Ile Leu Arg Trp Arg Pro Lys Asn Ser Val Gly Arg Trp Lys
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610 615 620

Glu Ala Thr Ile Pro Gly His Leu Asn Ser Tyr Thr Ile Lys Gly Leu
625 630 635 640

Lys Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser Ile Gln Gln Tyr
645 650 655

Gly His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr Thr Ser Thr Ser
660 665 670

Thr Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr Thr Pro Phe Ser
675 680 685

Pro Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile Thr Ala Ser Ser
690 695 700

Phe Val Val Ser Trp Val Ser Ala Ser Asp Thr Val Ser Gly Phe Arg
705 710 715 720

Val Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro Gln Tyr Leu Asp
725 730 735

Leu Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp Leu Leu Pro Gly
740 745 750

Arg Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu Asp Gly Glu Gln
755 760 765

Ser Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro Asp Ala Pro Pro
770 775 780

Asp Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile Val Val Arg Trp
785 790 795 800

Ser Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile Val Tyr Ser Pro
805 810 815

Ser Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro Glu Thr Ala Asn
820 825 830

Ser Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln Tyr Asn Ile Thr
835 840 845

Ile Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro Val Val Ile Gln
850 855 860

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Gln Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val Pro Ser Pro Arg
865                 870                 875                 880

Asp Leu Gln Phe Val Glu Val Thr Asp Val Lys Val Thr Ile Met Trp
                885                 890                 895

Thr Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro
            900                 905                 910

Val Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro Ile Ser Arg Asn
        915                 920                 925

Thr Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe
    930                 935                 940

Lys Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Ala
945                 950                 955                 960

Gln Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn
                965                 970                 975

Glu Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln
            980                 985                 990

Ile Thr Gly Tyr Arg Leu Thr Val  Gly Leu Thr Arg Arg  Gly Gln Pro
        995                 1000                1005

Arg Gln  Tyr Asn Val Gly Pro  Ser Val Ser Lys Tyr  Pro Leu Arg
    1010                1015                1020

Asn Leu  Gln Pro Ala Ser Glu  Tyr Thr Val Ser Leu  Val Ala Ile
    1025                1030                1035

Lys Gly  Asn Gln Glu Ser Pro  Lys Ala Thr Gly Val  Phe Thr Thr
    1040                1045                1050

Leu Gln  Pro Gly Ser Ser Ile  Pro Pro Tyr Asn Thr  Glu Val Thr
    1055                1060                1065

Glu Thr  Thr Ile Val Ile Thr  Trp Thr Pro Ala Pro  Arg Ile Gly
    1070                1075                1080

Phe Lys  Leu Gly Val Arg Pro  Ser Gln Gly Gly Glu  Ala Pro Arg
    1085                1090                1095

Glu Val  Thr Ser Asp Ser Gly  Ser Ile Val Val Ser  Gly Leu Thr
    1100                1105                1110
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Pro Gly  Val Glu Tyr Val Tyr  Thr Ile Gln Val Leu  Arg Asp Gly
    1115                1120                1125

Gln Glu  Arg Asp Ala Pro Ile  Val Asn Lys Val Val  Thr Pro Leu
    1130                1135                1140

Ser Pro  Pro Thr Asn Leu His  Leu Glu Ala Asn Pro  Asp Thr Gly
    1145                1150                1155

Val Leu  Thr Val Ser Trp Glu  Arg Ser Thr Thr Pro  Asp Ile Thr
    1160                1165                1170

Gly Tyr  Arg Ile Thr Thr Thr  Pro Thr Asn Gly Gln  Gln Gly Asn
    1175                1180                1185

Ser Leu  Glu Glu Val Val His  Ala Asp Gln Ser Ser  Cys Thr Phe
    1190                1195                1200

Asp Asn  Leu Ser Pro Gly Leu  Glu Tyr Asn Val Ser  Val Tyr Thr
    1205                1210                1215

Val Lys  Asp Asp Lys Glu Ser  Val Pro Ile Ser Asp  Thr Ile Ile
    1220                1225                1230

Pro Ala  Val Pro Pro Pro Thr  Asp Leu Arg Phe Thr  Asn Ile Gly
    1235                1240                1245

Pro Asp  Thr Met Arg Val Thr  Trp Ala Pro Pro Pro  Ser Ile Asp
    1250                1255                1260

Leu Thr  Asn Phe Leu Val Arg  Tyr Ser Pro Val Lys  Asn Glu Glu
    1265                1270                1275

Asp Val  Ala Glu Leu Ser Ile  Ser Pro Ser Asp Asn  Ala Val Val
    1280                1285                1290

Leu Thr  Asn Leu Leu Pro Gly  Thr Glu Tyr Val Val  Ser Val Ser
    1295                1300                1305

Ser Val  Tyr Glu Gln His Glu  Ser Thr Pro Leu Arg  Gly Arg Gln
    1310                1315                1320

Lys Thr  Gly Leu Asp Ser Pro  Thr Gly Ile Asp Phe  Ser Asp Ile
    1325                1330                1335

Thr Ala  Asn Ser Phe Thr Val  His Trp Ile Ala Pro  Arg Ala Thr
    1340                1345                1350
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Ile Thr  Gly Tyr Arg Ile Arg  His His Pro Glu His  Phe Ser Gly
    1355                1360                1365

Arg Pro  Arg Glu Asp Arg Val  Pro His Ser Arg Asn  Ser Ile Thr
    1370                1375                1380

Leu Thr  Asn Leu Thr Pro Gly  Thr Glu Tyr Val Val  Ser Ile Val
    1385                1390                1395

Ala Leu  Asn Gly Arg Glu Glu  Ser Pro Leu Leu Ile  Gly Gln Gln
    1400                1405                1410

Ser Thr  Val Ser Asp Val Pro  Arg Asp Leu Glu Val  Val Ala Ala
    1415                1420                1425

Thr Pro  Thr Ser Leu Leu Ile  Ser Trp Asp Ala Pro  Ala Val Thr
    1430                1435                1440

Val Arg  Tyr Tyr Arg Ile Thr  Tyr Gly Glu Thr Gly  Gly Asn Ser
    1445                1450                1455

Pro Val  Gln Glu Phe Thr Val  Pro Gly Ser Lys Ser  Thr Ala Thr
    1460                1465                1470

Ile Ser  Gly Leu Lys Pro Gly  Val Asp Tyr Thr Ile  Thr Val Tyr
    1475                1480                1485

Ala Val  Thr Gly Arg Gly Asp  Ser Pro Ala Ser Ser  Lys Pro Ile
    1490                1495                1500

Ser Ile  Asn Tyr Arg Thr Glu  Ile Asp Lys Pro Ser  Gln Met Gln
    1505                1510                1515

Val Thr  Asp Val Gln Asp Asn  Ser Ile Ser Val Lys  Trp Leu Pro
    1520                1525                1530

Ser Ser  Ser Pro Val Thr Gly  Tyr Arg Val Thr Thr  Thr Pro Lys
    1535                1540                1545

Asn Gly  Pro Gly Pro Thr Lys  Thr Lys Thr Ala Gly  Pro Asp Gln
    1550                1555                1560

Thr Glu  Met Thr Ile Glu Gly  Leu Gln Pro Thr Val  Glu Tyr Val
    1565                1570                1575

Val Ser  Val Tyr Ala Gln Asn  Pro Ser Gly Glu Ser  Gln Pro Leu
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1580 1585 1590

Val Gln Thr Ala Val Thr Thr Ile Pro Ala Pro Thr Asp Leu Lys
1595 1600 1605

Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro
1610 1615 1620

Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys
1625 1630 1635

Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser
1640 1645 1650

Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu
1655 1660 1665

Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala
1670 1675 1680

Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg
1685 1690 1695

Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp
1700 1705 1710

Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val
1715 1720 1725

Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp
1730 1735 1740

Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr
1745 1750 1755

Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro
1760 1765 1770

Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu
1775 1780 1785

Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu Val Ser Trp Gln
1790 1795 1800

Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys Tyr Glu Lys
1805 1810 1815

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Pro Gly  Ser Pro Pro Arg Glu  Val Val Pro Arg Pro  Arg Pro Gly
    1820                 1825                 1830

Val Thr  Glu Ala Thr Ile Thr  Gly Leu Glu Pro Gly  Thr Glu Tyr
    1835                 1840                 1845

Thr Ile  Tyr Val Ile Ala Leu  Lys Asn Asn Gln Lys  Ser Glu Pro
    1850                 1855                 1860

Leu Ile  Gly Arg Lys Lys Thr  Asp Glu Leu Pro Gln  Leu Val Thr
    1865                 1870                 1875

Leu Pro  His Pro Asn Leu His  Gly Pro Glu Ile Leu  Asp Val Pro
    1880                 1885                 1890

Ser Thr  Val Gln Lys Thr Pro  Phe Val Thr His Pro  Gly Tyr Asp
    1895                 1900                 1905

Thr Gly  Asn Gly Ile Gln Leu  Pro Gly Thr Ser Gly  Gln Gln Pro
    1910                 1915                 1920

Ser Val  Gly Gln Gln Met Ile  Phe Glu Glu His Gly  Phe Arg Arg
    1925                 1930                 1935

Thr Thr  Pro Pro Thr Thr Ala  Thr Pro Ile Arg His  Arg Pro Arg
    1940                 1945                 1950

Pro Tyr  Pro Pro Asn Val Gly  Glu Glu Ile Gln Ile  Gly His Ile
    1955                 1960                 1965

Pro Arg  Glu Asp Val Asp Tyr  His Leu Tyr Pro His  Gly Pro Gly
    1970                 1975                 1980

Leu Asn  Pro Asn Ala Ser Thr  Gly Gln Glu Ala Leu  Ser Gln Thr
    1985                 1990                 1995

Thr Ile  Ser Trp Ala Pro Phe  Gln Asp Thr Ser Glu  Tyr Ile Ile
    2000                 2005                 2010

Ser Cys  His Pro Val Gly Thr  Asp Glu Glu Pro Leu  Gln Phe Arg
    2015                 2020                 2025

Val Pro  Gly Thr Ser Thr Ser  Ala Thr Leu Thr Gly  Leu Thr Arg
    2030                 2035                 2040

Gly Ala  Thr Tyr Asn Ile Ile  Val Glu Ala Leu Lys  Asp Gln Gln
    2045                 2050                 2055
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Arg His  Lys Val Arg Glu Glu  Val Val Thr Val Gly  Asn Ser Val
    2060                 2065                 2070

Asn Glu  Gly Leu Asn Gln Pro  Thr Asp Asp Ser Cys  Phe Asp Pro
    2075                 2080                 2085

Tyr Thr  Val Ser His Tyr Ala  Val Gly Asp Glu Trp  Glu Arg Met
    2090                 2095                 2100

Ser Glu  Ser Gly Phe Lys Leu  Leu Cys Gln Cys Leu  Gly Phe Gly
    2105                 2110                 2115

Ser Gly  His Phe Arg Cys Asp  Ser Ser Arg Trp Cys  His Asp Asn
    2120                 2125                 2130

Gly Val  Asn Tyr Lys Ile Gly  Glu Lys Trp Asp Arg  Gln Gly Glu
    2135                 2140                 2145

Asn Gly  Gln Met Met Ser Cys  Thr Cys Leu Gly Asn  Gly Lys Gly
    2150                 2155                 2160

Glu Phe  Lys Cys Asp Pro His  Glu Ala Thr Cys Tyr  Asp Asp Gly
    2165                 2170                 2175

Lys Thr  Tyr His Val Gly Glu  Gln Trp Gln Lys Glu  Tyr Leu Gly
    2180                 2185                 2190

Ala Ile  Cys Ser Cys Thr Cys  Phe Gly Gly Gln Arg  Gly Trp Arg
    2195                 2200                 2205

Cys Asp  Asn Cys Arg Arg Pro  Gly Gly Glu Pro Ser  Pro Glu Gly
    2210                 2215                 2220

Thr Thr  Gly Gln Ser Tyr Asn  Gln Tyr Ser Gln Arg  Tyr His Gln
    2225                 2230                 2235

Arg Thr  Asn Thr Asn Val Asn  Cys Pro Ile Glu Cys  Phe Met Pro
    2240                 2245                 2250

Leu Asp  Val Gln Ala Asp Arg  Glu Asp Ser Arg Glu
    2255                 2260                 2265
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<223> Synthetic primer

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catatgcata tgcaccacca ccaccaccac gtttctgatg ttccga 46

<210> 78
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<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer

<400> 78
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<210> 79
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer

<400> 79
aggcatatca ccacgaggag tgacagcata 30

<210> 80
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer

<400> 80

cgtggtgata atcctgacag cagcaag 27

<210> 81
<211> 30
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<213> Artificial Sequence

<220>
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attccagtct ccacgcggag tgacagcata 30

<210> 84
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<400> 84
tatgctgtcc gtgctcgtgg tgat 24

<210> 85
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<400> 85
accacgagca cggacagcat acac 24

<210> 86
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agtcccccgt tgattggc 18

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caacggggga ctttcctc 18

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ccgaggaatc tggaagttg 19

<210> 89
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<400> 89
cagattcctc ggaacatc 18

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agagttatca gtaatatcag aaaagtcaat 30

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gctaaaacag tgagatatta caggatc 27

<210> 93
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<400> 93
cactgtttta gcaggagcat ccca 24

<210> 94
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<400> 94
gaacgtcggg tgccc 15

<210> 95
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<400> 95
ccgacgttca cgaggtct 18

<210> 96
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<400> 96
gtgccccact ctgataattc catcacc 27

<210> 97
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<400> 97
ggtgatggaa ttatcagagt ggggcac 27

<210> 98
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<400> 98
cgtggtgata atcctgactg tagcaagcca 30

<210> 99
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<210> 101
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aggcatatca ccacgaggac agacagcata 30

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<400> 102
ggagactgga atgaatgtag caagcca 27

<210> 103
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<400> 103
attccagtct ccacgcggac agacagcata 30

<210> 104
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cgtggtgata atcctgactg tagcaagcca 30

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<210> 106
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<400> 106
ggtcgtggag acagccccgc atgtagcaag cca 33

<210> 107
<211> 27
<212> DNA
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<400> 107
gtctccacga ccagtacaag catacac 27

<210> 108
<211> 185
<212> PRT
<213> Homo sapiens

<400> 108

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Val Cys Arg Ala Arg Gly Asp Phe Pro Asp Cys Ser
165 170 175

Lys Pro Ile Ser Ile Asn Tyr Arg Thr
180 185

<210> 109
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<212> PRT
<213> HOMO SAPIENS

<400> 109

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Val Cys Arg Ala Arg Gly Asp Arg Pro Asp Cys Ser
165 170 175

Lys Pro Ile Ser Ile Asn Tyr Arg Thr
180 185

<210> 110
<211> 185
<212> PRT
<213> Homo sapiens

<400> 110

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Val Cys Arg Ala Arg Gly Asp Asp Pro Asp Cys Ser
165 170 175

Lys Pro Ile Ser Ile Asn Tyr Arg Thr
180 185

<210> 111
<211> 184
<212> PRT
<213> Homo sapiens

<400> 111

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Ala
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr

20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Cys Arg Ala Arg Gly Asp Asn Pro Asp Cys Ser Lys
165 170 175

Pro Ile Ser Ile Asn Tyr Arg Thr
180

<210> 112
<211> 184
<212> PRT
<213> Homo sapiens

<400> 112

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Pro Pro Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro

50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Cys Arg Ala Arg Gly Asp Asn Pro Asp Cys Ser Lys
165 170 175

Pro Ile Ser Ile Asn Tyr Arg Thr
180

<210> 113
<211> 184
<212> PRT
<213> Homo sapiens

<400> 113

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Lys His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg

85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu
115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Cys Arg Ala Arg Gly Asp Asn Pro Asp Cys Ser Lys
165 170 175

Pro Ile Ser Ile Asn Tyr Arg Thr
180

<210> 114
<211> 184
<212> PRT
<213> Homo sapiens

<400> 114

Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn
1 5 10 15

Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr
20 25 30

Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp
35 40 45

Arg Val Asp His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro
50 55 60

Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu
65 70 75 80

Ser Pro Pro Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg
85 90 95

Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp
100 105 110

Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu

115 120 125

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys
130 135 140

Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile
145 150 155 160

Thr Val Tyr Ala Cys Arg Ala Arg Gly Asp Asn Pro Asp Cys Ser Lys
165 170 175

Pro Ile Ser Ile Asn Tyr Arg Thr
180