UTI FUSION PROTEINS

FIELD OF THE INVENTION

[0001] The present invention relates to molecular biology, pharmacology, and medicine.

BACKGROUND OF THE INVENTION

[0002] Urinary Trypsin Inhibitor (UTI), also known as ulinastatin, uristatin, urinastatin, ulistin, human inhibitor 30 (HI-30), mingin and bikunin, is a protease inhibitor with a molecular weight of about 40kD. UTI is present in human urine and blood (hUTI) and has a variety of physiological activities such as an inhibitory effect on a family of serine proteases, such as trypsin, α-chymotrypsin, plasmin, cathepsin-G and leukocyte elastase. UTI also has immunomodulatory effect, and it can down-regulate the release of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin (IL-6). In addition, UTI also interferes with PDGF-D (PDGF-DD)/PDGF-BBR active dimer-mediated signaling pathway by neutralizing the dimer.

[0003] hUTI has received marketing authorization and one product is marketed in Japan under the trade name Miraclid and is isolated from human urine. In fact, hUTI isolated from human urine is currently marketed by several manufacturers for treatment of pancreatitis and acute circulatory failure caused by shock.

[0004] UTI is first produced in humans as a presursor protein called AMBP (α1-microglobulin/bikunin precursor), which is encoded on human chromosome 9. The proteolysis of AMBP yields the free UTI containing 143 amino acids. UTI comprises two Kunitz domains that are known to inhibit serine proteases, which are flanked by unstructured amino acids on UTI's N- and C-termini. The two domains are expected to confer differenct specificities of protease inhibition, due to the different amino acids involved in protease binding. By analogy to other serine protease inhibitors (e.g. BPTI, bovine pancreatic trypsin inhibitor), we can estimate that two key amino acids for protease inhibition include Met26 (Kunitz domain 1) and Arg88 (Kunitz domain 2). Little is know about the involvement of different portions of UTI during inhibition of different proteases, but removal of Kunitz domain 1 has been shown to change proteases specificity, uncovering new inhibitory activity against Factor Xa and plasma kallikrien. The full-length UTI does not show inhibition of these two proteases (Morishita et al., Thrombosis Research 1994, vol 73 (3/4) p193-204). UTI also comprises two attached sugars, one O-linked at Ser10 and one

N-linked at Asn45. The half-life of UTI in rodents and humans is 4-30 minutes (Fries et al, International Journal of Biochemistry and Cell Biology, 2000, vol 32, p 125-137).

[0005] A UTI fusion protein should contain optimized sequence of amino acids, including the best start and stop points of any UTI domains, and may be fused to another protein to enhance properties such as expression, purification, half-life, and stability. The exact sequence of the fusion partner needs determination and may include variations in linkers, start/stop points, and/or mutations that may change the functional properties of the fusion partner.

Variants of ulinastatin obtained from urine are known WO199856916, US5792629, US5407915, US5409895, US7019123, and US6583108. The concept of fusion proteins of ulinastatin (and variations thereof) has been disclosed US20080181892, US5541288, and US20080255025. Certain UTI fusion proteins are described in CN 103044554A. The fusion proteins of CN 103044554A relate to specific variants in the Fc domain, presumably to avoid any Fc mediated pharmacological effects (ADCC, CDC). We have surprisingly found that a UTI-Fc with wild type IgG1 is well tolerated and provides significant increase in half-life. Also, compared to the UTI fusion proteins of CN 103044554A the present UTI fusion proteins, in particular SEQ ID NO:1, demonstrate greater thermal stability.

[0006] The present invention provides UTI fusion proteins, pharmaceutical compositions comprising the same, preparation methods, and uses thereof.

SUMMARY OF THE INVENTION

[0007] The present invention provides UTI fusion proteins, comprising a UTI domain and fusion partner wherein the UTI domain is operatively linked to the fusion partner. The present invention provides UTI fusion proteins, comprising a UTI domain and an Fc domain wherein the UTI domain is operatively linked to the Fc domain. The present invention also provides isolated UTI fusion proteins as described herein.

[0008] In some embodiments the present invention provides a UTI fusion protein, comprising a sequence comprising SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:1. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:3. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:5. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:7. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:9. In one embodiment, the

present invention provides a UTI fusion protein comprising SEQ ID NO:11. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:13. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:15. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:17. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:19. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:21. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:23. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:25. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:27. In one embodiment, the present invention provides a UTI fusion protein comprising SEQ ID NO:29.

[0009] According to another embodiment of the present invention, the present invention provides a nucleic acid sequence encoding the UTI fusion proteins comprising the UTI fusion proteins described herein. Further, the invention provides the DNA sequences set forth as SEQ ID NO:2, 4, 6, 8, 10, 12 ,14, 16, 18, 20, 22, 24, 26, 28, and 30. In one embodiment, the nucleic acid encoding a UTI fusion protein further comprises a vector containing control sequences to which the nucleic acid is operably linked. In another embodiment, the present invention provides a host cell comprising a nucleic acid sequence that encodes the UTI fusion protein, such as a mammalian, insect, E. coli or yeast cell, and maintaining the host cell under conditions in which the fusion protein molecule is expressed.

[0010] In another embodiment, the present invention provides a pharmaceutical composition comprising the UTI fusion proteins described herein and a pharmaceutically acceptable carrier or excipient.

[0011] According to a further embodiment of the present invention, there is provided a method of treating UTI-related disorders, comprising administering to a patient in need thereof an effective amount of a UTI fusion protein described herein.

[0012] That is, the present invention provides for the use of a UTI fusion protein as a medicament, including the manufacture of a medicament, and the use of a UTI fusion protein described herein for the treatment of the UTI-related disorders described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 UTI domain structure and glycosylation sites.

[0014] FIG. 2 Two UTI-Fc constructs demonstrating altered linkers.

[0015] FIG. 3 Various UTI-Fc constructs of the present invention.

[0016] FIG. 4 DNA assemble strategy (SLIC) used in UTI fusion construction.

[0017] FIG. 5 Supression of protease activity (trypsin) by UTI and UTI-Fc1, SEQ ID NO:1

[0018] FIG. 6 Supression of protease activity (chymotrypsin) by UTI-Fc1, UFC1, SEQ ID NO:1.

[0019] FIG. 7 Supression of protease activity (multiple proteases) by UTI-Fc1, UFC1, SEQ ID NO:1.

[0020] FIG. 8 Supression of cytokine secreation (IL-6) by UTI and UTI-Fc1, UTI-Fc, SEQ ID NO:1.

[0021] FIG. 9 Purification yields of UTI fusion proteins.

[0022] FIG. 10 Effect of SEQ ID NO:1 on LPS Induced C5a in C3H Mice.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The present invention provides UTI fusion proteins, a UTI domain and fusion partner wherein the UTI domain is operatively linked to the fusion partner. The UTI fusion proteins of the present invention have an inhibitory effect on proteases, including trypsin.

[0024] In some embodiments the fusion partner is an Fc polypeptide. In some embodiments the fusion partner is a human Fc polypeptide. In some embodiments the fusion partner is analog(s) of human Fc polypeptide. In some embodiments the fusion partner is fragment(s) of human Fc polypeptide. In other embodiments the the fusion partner is a mouse Fc polypeptide. In other embodiments the the fusion partner is a rat Fc polypeptide.

[0025] In some embodiments the fusion partner is human albumin. In some embodiments the fusion partner is an analog of human albumin. In some emdiments the fusion partner is a modified human albumin. In some embodiments the fusion partner is a fragment of human albumin.

[0026] In some embodiments the UTI domain is human UTI (hUTI). In some embodiments the UTI domain is an analog of hUTI. In some embodiments the UTI domain is a fragment of hUTI. In some embodiments, the UTI fusion protein comprises a wild-type hUTI domain.

[0027] In some embodiments, the UTI fusion protein comprises a wild-type humanUTI domain and a human Fc domain. In some embodiments, the UTI fusion protein comprises a wild-type hUTI domain, and a linker domain, and a human Fc domain.

[0028] In some embodiments, the UTI fusion protein comprises awild-type humanUTI domain and a human albumin or analog thereof or fragment thereof. In some embodiments,

the UTI fusion protein comprises wild-type hUTI domain, a linker domain, and a human albumin or analog thereof or fragment thereof.

[0029] In some embodiments, the Fc domain binds to an Fc receptor on a human cell. In some embodiments, the serum half-life of the molecule is significantly longer than the serum half-life of the UTI domain alone. In some embodiments, the protease inhibitory activity of the UTI domain of the molecule is the same or greater than the UTI domain alone. In some embodiments, administration of the molecule to a mouse decreases inflammatory reactions, including, but not limited to, decreasing the activation of immune cells or decreasing the production, secretion or activity of cytokines or chemokines.

[0030] It is understood that the UTI domain may be operatively linked to the fusion partner by a linker domain.

[0031] The present invention provides a UTI fusion protein, comprising a UTI domain fused to a polypeptide selected from the group consisting of a) Fc domain, b) an analog of the Fc domain, and c) fragment of the Fc domain wherein the UTI domain is fused to the Fc domain, analog thereof, or fragment thereof by a linker domain. The present invention provides a UTI fusion protein, comprising a hUTI domain fused to a polypeptide selected from the group consisting of a) Fc domain, b) an analog of the Fc domain, and c) fragment of the Fc domain wherein the hUTI domain is fused to the Fc domain, analog thereof, or fragment thereof by a linker domain.

[0032] The present fusion proteins encompass proteins having monomeric and multimeric forms whether prepared by a digest of an intact antibody or produced by other means.

[0033] The terms 'multimer" and "multimeric" refers to proteins in which Fc domains or molecules comprising Fc domains have two or more polypeptide chains associated covalently, non-covalently, or having both covalent and non-covalent interactions. The term multimer includes the term dimer.

[0034] The term "dimer" refers to proteins in which Fc domains or molecules comprising Fc domains have two polypeptide chains associated covalently, non-covalently, or having both covalent and non-covalent interactions. That is, the term "dimer" refers to UTI fusion proteins in which two Fc domains are associated covalently, non-covalently, or having both covalent and non-covalent interactions. More specifically, the term "dimer" refers to UTI fusion proteins in which two Fc domains are associated covalently.

[0035] The present invention provides a UTI fusion protein, comprising a UTI domain fused to a polypeptide selected from the group consisting of a) albumin, b) albumin analogs, c) fragments of albumin. The present invention also provides a UTI fusion protein, comprising

a hUTI domain is fused to a polypeptide selected from the group consisting of a) human albumin, b) albumin analogs, c) fragments of human albumin wherein the hUTI is fused to the albumin, analog thereof, or fragment thereof by a linker domain.

DEFINITION OF TERMS

[0036] The terms used in this specification and claims are defined as set forth below unless otherwise indicated.

[0037] As used herein, the terms "linked," "fused," or "fusion" are used interchangeably.

[0038] These terms refer to the joining together of two more elements or components or domains, by whatever means including chemical conjugation or recombinant means. Methods of chemical conjugation are known in the art.

[0039] A "fusion protein" refers to a polypeptide having two or more portions covalently linked together, where one or more of the portions is derived from different proteins. The two portions may be linked directly by a single peptide bond (e.g., the portions linked directly to each other) or through a peptide linker containing one or more amino acid residues (e.g. with an intervening amino acid or amino acid sequence between the portions). Generally, DNA encoding the two portions and the linker will be in reading frame with each other and are produced using recombinant techniques.

[0040] A "UTI domain" is a protein or peptide that mimics the activity of UTI. It is understood that the UTI domain of the present invention may be altered such that they vary sequences from the naturally occurring or native sequences from which they were derived, while retaining the desired activity of the native sequence. Preferable the UTI domain is native humanUTI (hUTI), analogs, and variants thereof. Variants of hUTI include replacing or modifying one or more amino acids of native hUTI that are not a required structural feature or provide functional activity, including conservative substitutions. Variants of hUTI include removing or inserting one or more amino acids in native hUTI that are not a required structural feature or provide functional activity. Variants of hUTI include replacing or modifying one or more amino acids of native hUTI to modify one or more properties or activities. Variants of hUTI include removing or inserting one or more amino acids in native hUTI to modify one or more UTI properties or activities. Variants of hUTI include removing or altering glycolsylation sites in native humanUTI. Variants of hUTI include removing or altering one or more Kunitz domain. Variants of hUTI can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis.

[0041] The amino acid residue sequence of the recombinant hUTI domain is set forth as SEQ ID NO:31. Generally, the UTI domain includes a sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the recombinant hUTI domain is set forth as SEQ ID NO:31.

[0042] An "Fc domain" is the polypeptide comprising the constant region of an antibody excluding the first constant region immunoglobulin domain and in some cases, part or all of the hinge. Thus, an Fc domain refers to the non-antigen binding portion of an antibody, whether in monomeric or multimeric form. The antibody from which the Fc domain arises is preferably of human origin and may be any of the immunogobulins, although IgG1 and IgG2 are preferred.

[0043] An Fc domain includes the hinge region of the heavy chain. By "hinge" or "hinge region" or "antibody hinge region" or "immunoglobulin hinge region" herein is meant the flexible polypeptide comprising the amino acids between the first and second constant domains of an antibody, just upstream of the papian cleavage. Accordingly, for IgG, an Fc domain comprises immunoglobulin domains CH2 and CH3 and the hinge region between CH1 and CH2. Although the boundaries of the Fc region may vary, the human IgG heavy chain Fc region is usually defined to include residues C226 or P230 to its carboxyl-terminus, wherein the numbering is according to the EU index and in Kabat. In some embodiments, as is more fully described below, amino acid modifications are made to the Fc domain, for example to alter binding to one or more FcγR receptors or to the FcRn receptor.

[0044] Accordingly, in certain embodiments, the term Fc domain includes the hinge region which may be truncated, modified by replacement , deletion and/or insertion and further the modified or unmodified hinge region may be the site of attachment of a linker domain.

[0045] An "analog of an Fc domain" refers to a molecule or sequence that is modified from the native Fc but still comprises a binding site for the salvage receptor. The term analog of an Fc domain includes a molecule or sequence that is humanized from a non-human native Fc. The term analog of an Fc domain also includes a molecule or sequence that lacks, or has modifications of, one or more native Fc residues that affect or are involved in disulfide formation, incompatibility with a host cell, N-terminal heterogeneity upon expression, stability, glycolsylation, interaction with a complement, binding to an Fc salvage receptor and/or interaction with an Fcγ receptor.

[0046] The terms "fragments of the Fc domain" or "fragment of the Fc domain" refers to a native Fc from which one or more sites have been removed where the removed site(s) does not constitute structural features or functional activity that is required by the fusion proteins

of the present invention. Fragments of the Fc domain include deleting residues from the native Fc or truncating the native Fc and may include substitions of the remaining residues. The inserted or altered residues (e.g., the substituted residues) may be natural amino acids or altered amino acids, peptidomimetics, unnatural amino acids, or D-amino acids.

[0047] Generally, the Fc domain includes a sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM, in particular human IgG1 or IgG2.

[0048] The term Fc domain encompasses native Fc and analogs of Fc and includes monomeric and multimeric forms whether prepared by a digest of an intact antibody or produced by other means.

[0049] In certain embodiments, an Fc domain comprises at least a hinge domain (upper, middle, and/or lower hinge region), a CH2 domain (or a variant or fragment thereof), and a CH3 domain (or a variant or fragment thereof). In another embodiment, an Fc domain consists of a hinge domain (upper, middle, and/or lower hinge region), a CH2 domain (or a variant or fragment thereof), and a CH3 domain (or a variant or fragment thereof). In certain other embodiments, an Fc domain consists of a hinge domain (upper, middle, and/or lower hinge region), a CH2 domain (or a variant or fragment thereof), a CH3 domain (or a variant or fragment thereof), and a CH4 domain (or a variant or fragment thereof). In another embodiment, an Fc domain consists of a hinge domain (upper, middle, and/or lower hinge region) and a CH2 domain. In another embodiment, an Fc domain consists of a hinge domain (upper, middle, and/or lower hinge region) and a CH3 domain (or a variant or fragment thereof). In another embodiment, an Fc domain consists of a CH2 domain (or a variant or fragment thereof), and a CH3 domain (or a variant or fragment thereof). In another embodiment, an Fc domain consists of a complete CH2 domain and a complete CH3 domain. In another embodiment, an Fc domain consists of a complete CH2 domain and a complete CH3 domain. In one embodiment, an Fc domain of the invention comprises at least the portion of an Fc molecule known in the art to be required for FcRn binding. In another embodiment, an Fc domain of the invention comprises at least the portion of an Fc molecule known in the art to be required for Protein A binding. In another embodiment, an Fc domain of the invention comprises at least the portion of an Fc molecule known in the art to be required for Protein G binding.

[0050] According to the present invention, an Fc domain generally refers to a polypeptide comprising all or part of the Fc domain of an immunoglobulin heavy-chain. As discussed

above, this includes, but is not limited to polypeptides comprising the entire hinge region, CH1, CH2, and/or CH3 domains as well as fragments of such peptides comprising, for example, the hinge, CH2 and CH3 domains. The Fc domain may be derived from any immunoglobulin of any species and/or subtype, including but not limited to, a human IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM antibody. An Fc domain includes the last two constant region immunoglobulin domains of IgA, IgD, and IgG, the last three constant region immunoglobulin domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM, Fc may include the J chain.

[0051] An Fc domain as used herein encompasses native Fc and Fc variant molecules. As with the Fc variants and native Fc proteins, the term Fc domain includes molecules in monomeric and multimeric form, whether digested from an antibody or produced by other means.

[0052] As set forth herein it is understood, that any Fc domain may be modified such that it varies in amino acid sequence from the native Fc domain of a naturally occurring immunoglobulin molecule. In certain exemplary embodiments, the Fc domain retains an effector function, for example, FcγR binding. In certain exemplary embodiments, the Fc domain lacks an effector function, for example, FcγR binding.

[0053] The Fc domain of the invention may be derived from different immunoglobulin molecules. For example, an Fc domain may comprise a CH2 and/or CH3 domain derived from IgG1 and hinge region derived from IgG3.

[0054] In some embodiments, UTI fusion proteins include an Fc domain. Fc domains useful for producing the UTI fusion proteins of the present invention may be obtained from a number of different sources. In preferred embodiments, an Fc domain of the UTI fusion proteins is derived from a human immunoglobulin. It is understood, however, that the Fc domain may be derived from an immunoglobulin of another mammalian species, including for example, a rodent (e.g. a mouse, rat, rabbit, guinea pig) or non-human primate (e.g. Chimpanzee, Macaque) species. Moreover, the UTI fusion proteins Fc domain or portion thereof may be derived from any immunoglobulin class.

[0055] The terms "wild-type" or "wt" or "native" as used herein is meant an amino acid sequence or a nucleotide sequence that is found in nature, including allelic variations. A wild-type protein, polypeptide, antibody, immunoglobulin, IgG, polynucleotide, DNA, RNA, and the like has an amino acid sequence or a nucleotide sequence that has not been intentionally modified.

[0056] In certain embodiments the UTI fusion proteins of the present invention can employ a linker domain. The linker domain is used to operationally connect a UTI domain to a fusion partner.

[0057] The term "linker domain" refers to polypeptide linkers, non-peptide linkers and combinations thereof. In particular, a linker domain can be a polypeptide. As used herein, the term "linker domain" refers to a sequence which connects two domains in a linear sequence. As used herein, the term "polypeptide linker" refers to a peptide or polypeptide sequence (e.g., a synthetic peptide or polypeptide sequence) which connects two domains in a linear amino acid sequence of a polypeptide chain. For example, polypeptide linkers may be used to connect a UTI domain to an Fc domain. Preferably, such polypeptide linkers can provide flexibility to the polypeptide molecule. A UTI fusion protein of the invention may comprise a linker domain, including a peptide linker.

[0058] For example, a linker domain can be used to connect two domains in a linear amino acid sequence of a polypeptide linker, such as linking a UTI domain with an Fc domain. In certain embodiments a linker domain can be used to connect a UTI domain to a Fc domain. The linker domain can be used to connect the domains in any order. For example, in some embodiments a linker will connect a UTI domain and an Fc domain with the order UTI-linker-Fc, whereas in other embodiments a linker will connect a UTI domain and an Fc domain with the order Fc-linker-UTI, where the polypeptide regions are denoted from N-terminus to C-terminus. Exemplary polypeptide linkers include those that consist of glycine and serine residues, the so-called Gly-Ser polypeptide linkers. As used herein, the term "Gly-Ser polypeptide linker" refers to a peptide that consists of glycine and serine residues. An exemplary Gly-Ser polypeptide linker comprises the amino acid sequence $Ser(Gly_4Ser)_n$ wherein n is an integer 1 to 10, SEQ ID NO:33-42, respectively. In one embodiment, the UTI fusion protein includes one or two Gly-Ser polypeptide linker(s) in which n=l. In one embodiment, the UTI fusion protein includes one or two Gly-Ser polypeptide linker(s) in which n=2. In one embodiment, the UTI fusion protein includes one or two Gly-Ser polypeptide linker(s) in which n=3. In one embodiment, the UTI fusion protein includes one or two Gly-Ser polypeptide linker(s) in which n=4. In one embodiment, the UTI fusion protein includes one or two Gly-Ser polypeptide linker(s) in which n=5. In one embodiment, the UTI fusion protein includes one or two Gly-Ser polypeptide linker(s) in which n=6. In one embodiment, the UTI fusion protein includes one or two Gly-Ser polypeptide linker(s) in which n=7. In one embodiment, the UTI fusion protein includes one or two Gly-Ser polypeptide linker(s) in which n=8. In one embodiment, the UTI fusion protein includes one

or two Gly-Ser polypeptide linker(s) in which n=9. In one embodiment, the UTI fusion protein includes one or two Gly-Ser polypeptide linker(s) in which n=10.

[0059] Another exemplary linker is given in SEQ ID NO:43.

[0060] The term "comprising" means that a compound, i.e., fusion protein, may include additional amino acids on either or both the N- or C-termini. Of course, these additional amino acids should not significantly interfere with the activity of the compound, i.e., fusion protein,.

[0061] The term "amino acid" refers to naturally occurring and synthetic amino acids as well as amino acid analogs and amino acid mimetics that function in a manner similar to naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those encoded amino acids which are later modified, for example, hydroxyproline and phosphoserine. Amino acid analogs refer to compound, i.e., fusion protein,s that have the same basic chemical structure as the naturally occurring amino acids, that is, a carbon atom bound to a hydrogen atom, carboxyl group, an amino group, and an R group. Amino acid analogs have modified R groups, or give rise to modified peptide backbones, but retain the same basic chemical structure as the naturally occurring amino acids.

[0062] The term "amino acid substitution" refers to the replacement of at least one existing amino acid residue in a predetermined or native amino acid sequence with a different "replacement" amino acid.

[0063] The term "amino acid insertion" refers to the insertion of one or more additional amino acids into a predetermined or native amino acid sequence. The insertion can be one, two, three, four, five, or up to twenty amino acid residues.

[0064] The term "amino acid deletion" refers to removal of at least one amino acid from a predetermined or native amino acid sequence. The deletion can be one, two, three, four, five, or up to twenty amino acid residues.

[0065] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein and refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid is a non-natural amino acid, synthetic amino acid, or amino acid mimetic.

[0066] The term "nucleic acid" refers to a deoxyribonucleotide or ribonucleotide and polymers thereof in either single strand or double strand form. The term "nucleic acid" is used interchangeably with gene, nucleotide, polynucleotide, cDNA, DNA, and mRNA. Unless specifically limited the term encompasses nucleic acids containing known analogues

of natural nucleotides that have similar binding propertied as the natural nucleic acid. Unless specifically limited, a particular nucleotide sequence also encompasses conservatively modified variants thereof (for example, those containing degenerate codon substitutions) and complementary sequences as well as the as well as the sequences specifically described.

[0067] The polynucleotides of the present invention can be composed of any polyribonucleotide or polydeoxyribonucleotide, which can be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single or double stranded regions, mixed single or double stranded regions. In addition, the polynucleotides can be triple stranded regions containing RNA or DNA or both RNA and DNA. Modified polynucleotides include modified bases, such as tritylated bases or unusual bases such as inosine. A variety of modification can be made to RNA and DNA, thus polynucleotide includes chemically, enzymactically, or metabolically modified forms.

[0068] The term "derivatized" or derivative" refers to compound, i.e., fusion protein,s that have a cyclic portion, for example, cross-linked between cysteinyl residues, the compound, i.e., fusion protein, is cross-linked, one or more peptidyl linkages is replaced by a non-peptide linkage, or the N-terminus is replaced by a NRR_1, $NRC(O)R_1$, $NRC(O)OR_1$, $NHC(O)NHR_1$, $NRS(O)_2R_2$, succinamide or other group wherein R and R_1 are defined herein and/or the C-terminus is replaced with $C(O)R_3$ or NR_4R_5 , and compound, i.e., fusion protein,s in which amino acid moieties are modified by treatment with agents capable of reacting with selected side chains or terminal residues. R is selected from the group consisting of hydrogen and C_{1-6} alkyl, R_1 is selected from the group consisting of hydrogen and C_{1-6} alkyl, R_2 is selected from the group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, and optionally substituted phenyl; R_3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{3-8} cycloalkyl; R_4 is selected from the group consisting of hydrogen and C_{1-6} alkyl; R_5 is selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl; or R_4 and R_5 are taken together with the nitrogen to which they are attached form a 4 to 7 membered, saturated, ring optionally having 1 additional ring heteroatom selected from the group N, O, and S.

[0069] The term "C_{1-6} alkyl" refers to a straight or branched alkyl chain of one to six carbon atoms.

[0070] The term "C_{3-8} cycloalkyl" refers to monocyclic or bicyclic, saturated or partially (but not fully) unsaturated alkyl ring of three to eight carbon atoms, and includes

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. It is understood that the term includes benzofused cyclopentyl and cyclohexyl.

[0071] The term "optionally substituted phenyl" refers to a phenyl group optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, and trifluoromethyl.

[0072] PREPARATION

[0073] The compounds, i.e., fusion proteins, of this invention may be prepared by standard synthetic methods, recombinant DNA techniques, or other methods of preparing peptides and fusion proteins. In an exemplary process a hUTI domain is covalently linked to an Fc domain by expression of a DNA construct encoding the UTI domain and the Fc domain and any linker domain.

[0074] Alternative ways to construct a UTI fusion protein are envisioned. In some embodiments, the domain orientation can be altered to construct an Fc-UTI molecule or a UTI-Fc molecule or a UTI-Fc-UTI molecule that retains FcR binding and has active UTI domain.

[0075] In some embodiments, UTI fusion proteins include a wild-type Fc domain that can allow the fusion protein to undergo endocytosis after binding FcRn (Fc neonatal receptor). Thus, the present invention further provides methods for producing the disclosed UTI fusion proteins. These methods encompass culturing a host cell containing isolated nucleic acid(s) encoding the UTI fusion proteins of the invention. As will be appreciated by those in the art, this can be done in a variety of ways, depending on the nature of the UTI fusion protein. In some embodiments, the UTI fusion protein of the invention is produced and can be isolated.

[0076] In general, nucleic acids are provided that encode for the UTI fusion protein of the invention. Such polynucleotides encode for a UTI domain, the fusion partner, and any linker domain. The present invention also contemplates oligonucleotide fragments derived from the disclosed polynucleotides and nucleic acid sequences complementary to these polynucleotides.

[0077] The polynucleotides can be in the form of RNA or DNA. Polynucleotides in the form of DNA, cDNA, genomic DNA, nucleic acid analogs, and synthetic DNA are within the scope of the present invention. The DNA may be double-stranded or single-stranded, and if single stranded, may be the coding (sense) strand or non-coding (anti-sense) strand. The coding sequence that encodes the polypeptide may be identical to the coding sequence provided herein or may be a different coding sequence, which sequence, as a result of the

redundancy or degeneracy of the genetic code, encodes the same polypeptides as the DNA provided herein.

[0078] In some embodiments, nucleic acid(s) encoding the UTI fusion proteins of the invention are incorporated into expression vectors, which can be extrachromosomal or designed to integrate into the genome of the host cell into which it is introduced. Expression vectors can contain any number of appropriate regulatory sequences (including, but not limited to, transcriptional and translational control sequences, promoters, ribosomal binding sites, enhancers, origins of replication, etc.) or other components (selection genes, etc.), all of which are operably linked as is well known in the art. In some cases two nucleic acids are used and each put into a different expression vector (e.g. heavy chain in a first expression vector, light chain in a second expression vector), or alternatively they can be put in the same expression vector. It will be appreciated by those skilled in the art that the design of the expression vector(s), including the selection of regulatory sequences may depend on such factors as the choice of the host cell, the level of expression of protein desired, etc.

[0079] In general, the nucleic acids and/or expression can be introduced into a suitable host cell to create a recombinant host cell using any method appropriate to the host cell selected (e.g., transformation, transfection, electroporation, infection), such that the nucleic acid molecule(s) are operably linked to one or more expression control elements (e.g., in a vector, in a construct created by processes in the cell, integrated into the host cell genome). The resulting recombinant host cell can be maintained under conditions suitable for expression (e.g. in the presence of an inducer, in a suitable non-human animal, in suitable culture media supplemented with appropriate salts, growth factors, antibiotics, nutritional supplements, etc.), whereby the encoded polypeptide(s) are produced. In some cases, the heavy chains are produced in one cell and the light chain in another.

[0080] Mammalian cell lines available as hosts for expression are known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), Manassas, VA including but not limited to Chinese hamster ovary (CHO) cells, HEK 293 cells, NSO cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines. Non-mammalian cells including but not limited to bacterial, yeast, insect, and plants can also be used to express recombinant antibodies. In some embodiments, the antibodies can be produced in transgenic animals such as cows or chickens.

[0081] In an embodiment, the fusion proteins of the invention are encoded by a nucleotide sequence. Nucleotide sequences of the invention can be useful for a number of applications,

including: cloning, gene therapy, protein expression and purification, mutation introduction, DNA vaccination of a host in need thereof, antibody generation for, e.g., passive immunization, PCR, primer and probe generation, siRNA design and generation and the like. In an embodiment, the nucleotide sequence of the invention comprises, consists of, or consists essentially of, a nucleotide sequence selected from SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32.

[0082] In an embodiment, a nucleotide sequence includes a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a nucleotide sequence set forth in SEQ ID NO:2, 4, 6, 8, 10, 12 ,14, 16, 18, 20, 22, 24, 26, 28, 30, or 32. In an embodiment, a nucleotide sequence includes a contiguous nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a contiguous nucleotide sequence set forth in SEQ ID NO:2, 4, 6, 8, 10, 12 ,14, 16, 18, 20, 22, 24, 26, 28, 30, or 32.

[0083] Preferred UTI fusion proteins of the invention comprise a sequence (e.g., at least one Fc domain) derived from a human immunoglobulin sequence. However, sequences may comprise one or more sequences from another mammalian species. For example, a primate Fc domain or nuclease domain may be included in the subject sequence. Alternatively, one or more murine amino acids may be present in a polypeptide. In some embodiments, polypeptide sequences of the invention are not immunogenic and/or have reduced immunogenicity. The UTI fusion proteins of the invention may comprise conservative amino acid substitutions at one or more amino acid residues, e.g., at essential or non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a nonessential amino acid residue in a binding polypeptide is preferably replaced with another amino acid residue from the same side chain family. In another embodiment, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members. Alternatively,

in another embodiment, mutations may be introduced randomly along all or part of a coding sequence, such as by saturation mutagenesis, and the resultant mutants can be incorporated into binding polypeptides of the invention and screened for their ability to bind to the desired target.

[0084] USES

[0085] In one embodiment, the invention provides methods of diagnosing and treating UTI-related conditions. As used herein terms "condition," "disorder," and "disease" relate to any unhealthy or abnormal state. The term "UTI-related conditions" includes conditions, disorders, and diseases in which UTI provides a therapeutic benefit. The term "UTI-related conditions" include conditions characterized by an immunomodulatory or an inflammatory effect. In particular, the term UTI-related conditions include pancreatitis, including acute pancreatitis and chronic pancreatitis, systemic inflammatory response syndrome, acute circulatory failure (e.g., caused by shock), disseminated intravascular coagulation, and multiple organ dysfunction syndrome. The term UTI-related conditions also include use in high-risk surgical patients. The term UTI-related conditions also includes infections of the lung, liver, heart, or kidney. The term UTI-related conditions also includes severe sepsis. The term UTI-related conditions also includes acute lung injury (ALI) caused by SARS viruses or acute respiratory distress syndrome (ARDS).

[0086] In one embodiment, the invention provides methods of treating a UTI-related condition, comprising administering to a patient in need thereof an effective amount, e.g., a pharmaceutically effective amount, of a disclosed UTI fusion protein. In certain embodiments, the condition is one specifically mentioned herein.

[0087] The pharmaceutical compositions of the present invention are prepared in a manner well known in the pharmaceutical art and include at least one of UTI fusion protein of the invention as the active ingredient. Pharmaceutical composition of the UTI fusion proteins used in accordance with the present invention are prepared by mixing a UTI fusion protein having the desired degree of purity with optional pharmaceutically acceptable excipients. The term "pharmaceutically acceptable excipient" refers to those typically used in preparing pharmaceutical compositions and should be pharmaceutically pure and non-toxic in the amounts used. They generally are a solid, semi-solid, or liquid material which in the aggregate can serve as a vehicle or medium for the active ingredient. Some examples of pharmaceutically acceptable excipients are found in Remington's Pharmaceutical Sciences and the Handbook of Pharmaceutical Excipients and include diluents, vehicles, carriers, sustained release matrices, stabilizing agents, preservatives, solvents, suspending agents,

buffers, emulsifiers, dyes, propellants, coating agents, and others. Generally for injection or intravenous administration the UTI fusion proteins of the present invention are in the form of lyophilized formulations, or aqueous solutions.

[0088] Pharmaceutically acceptable excipients are nontoxic to subjects in the amounts used, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[0089] The pharmaceutical compositions herein may also contain more than one active compound, i.e., fusion protein, as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[0090] The pharmaceutical compositions to be used for in vivo administration should be sterile, or nearly so. This is readily accomplished by filtration through sterile filtration membranes.

[0091] The UTI fusion proteins of the invention are administered to a subject, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, or intrathecal injection or infusion or by topical or inhalation routes. Intravenous or subcutaneous administration of the UTI fusion protein is preferred.

[0092] The terms "treat," "treatment," and "treating" include improvement of the conditions described herein. The terms "treat," "treatment," and "treating" include all processes providing slowing, interrupting, arresting, controlling, or stopping of the state or progression of the conditions described herein, but does not necessarily indicate a total elimination of all symptoms or a cure of the condition. The terms "treat," "treatment," and "treating" are

intended to include therapeutic treatment of such disorders. The terms "treat," "treatment," and "treating" are intended to include prophylactic treatment of such disorders.

[0093] As used herein the terms "patient" and "subject" includes humans and non-human animals, for example, mammals, such as mice, rats, guinea pigs, dogs, cats, rabbits, cows, horses, sheep, goats, and pigs. The term also includes birds, fish, reptiles, amphibians, and the like. It is understood that a more particular patient is a human. Also, more particular patients and subjects are non-human mammals, such as mice, rats, and dogs.

[0094] As used herein, the term "effective amount" refers to the amount of compound, i.e., fusion protein, of the invention which treats, upon single or multiple dose administration, a patient suffering from the mentioned condition. An effective amount can be readily determined by the attending diagnostician as a medical professional, such as a physician or a veterinarian as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. For example, a medical professional could start doses of the medicament employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0095] In determining the effective amount, the dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of patient; its size, age, and general health; the specific condition, disorder, or disease involved; the degree of or involvement or the severity of the condition, disorder, or disease, the response of the individual patient; the particular compound, i.e., fusion protein, administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances. Specific amounts can be determined by the skilled person. Although these dosages are based on an average human subject having a mass of about 60 kg to about 70 kg, the physician will be able to determine the appropriate dose for a patient (e.g., an infant) where the mass falls outside of this weight range.

[0096] Dosage regimens are adjusted to provide the desired response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation.

[0097] Parenteral compositions may be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit

contains a predetermined quantity of active compound, i.e., fusion protein, calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0098] The present pharmaceutical compositions are preferably formulated in a unit dose form, each dose typically containing from about 0.5 mg to about 100 mg of a UTI fusion protein of the invention. The term "unit dose form" refers to a physically discrete unit containing a predetermined quantity of active ingredient, in association with a suitable pharmaceutical excipient, by which one or more is used throughout the dosing regimen to produce the desired therapeutic effect. One or more "unit dose form" may be taken to affect the treatment dosage.

[0099] An exemplary, non-limiting range for an effective amount of a UTI fusion protein used in the present invention is about 0.1-100 mg/kg, such as about 0.1-50 mg/kg, for example about 0.1-20 mg/kg, such as about 0.1-10 mg/kg, for instance about 0.5 mg/kg, about such as 0.3 mg/kg, about 1 mg/kg, or about 3 mg/kg. In another embodiment, the UTI fusion protein is administered in a dose of 1 mg/kg or more, such as a dose of from 1 to 20 mg/kg, e.g. a dose of from 5 to 20 mg/kg, e.g. a dose of 8 mg/kg. An exemplary, non-limiting range for an effective amount of a UTI fusion protein used in the present invention is about 1-500 mg/dosage, such as about 1-100 mg/dosage, for example about 1-50 mg/dosage, such as about 1-10 mg/dosage, for instance about 1 mg/dosage, or about 3 mg/dosage, or about 5 mg/dosage.

In one embodiment, the UTI fusion protein is administered by infusion in an every 3 days or weekly dosage of from 10 to 500 mg/dosage. Such administration may be repeated as necessary to maintain the desired therapeutic effect.

[0100] As non-limiting examples, treatment according to the present invention may be provided a dosage of UTI fusion protein in an amount of about 0.1-100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 mg/kg, or alternatively, at least once a week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg/kg after initiation of treatment, or any combination thereof. As non-limiting examples, treatment according to the present invention may be provided a dosage of UTI fusion protein in an amount of about 1-100 mg/dosage, such as 1, 5, 10, 20, 30, 40, 45, 50, 60, 70, 80, 90, 100 150, 200, 250, 300, 350, or 400 mg/dosage. On at least once a day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,

16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 mg/dosage after initiation of treatment, or any combination thereof. On at least one of week 1, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 mg/dosage after initiation of treatment, or any combination thereof.

[0101] The UTI fusion proteins of the invention find use in a variety of applications, including treatment of UTI-related diseases. UTI fusion proteins of the invention may find use in treating diseases with immune system involvement, autoimmune diseases, inflammatory diseases, post-operative inflammatory responses, lysosome-associated diseases, coagulation diseases protease-related diseases and as an adjuvant therapy during surgery.

UTI fusion proteins of the invention may find use in treating pancreatitis (including endoscopy-induced pancreatitis and acute pancreatitis), arthritis, SARS, systemic inflammatory response syndrome, acute circulatory failure, sepsis, hepatitis, appendicitis, colitis, organ failure, organ damage (including pancreas, kidney, lung), reperfusion injury, Stevens-Johnson syndrome, toxic epidermal necrolysis, shock, ischemic injuries, acute lung injury (including that caused by acute aortic dissection), asthma, lung inflammation, pneumonia (including ventilator-associated), disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), and systemic inflammatory response syndrome.

[0102] UTI fusion proteins of the present invention may find use in inhibiting proteases, including the serine proteases, including, trypsin, chymotrypsin, thrombin, kallikrein, plasmin, elastase, cathepsin, lipase, hyaluronidase, factors IXa, Xa, XIa, and XIIa, and polymorphonuclear leukocyte elastase.

[0103] UTI fusion proteins of the present invention may find use in suppression of proinflammatory mediators, such as cytokines, tumor necrosis factor-alpha, interleukin-1, -1β, -4, -6 and -8, -10 and chemokines.

[0104] UTI fusion proteins of the present invention may find use in treatment of cancer, including the prevention of tumor invasion and metastasis, altered rates of apoptosis, and reduction of loss of renal function in cisplatinum treatment.

[0105] UTI fusion proteins of the present invention may find use to treat AIDS, including as adjunctive treatment.

[0106] EXAMPLES

[0107] Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Efforts have been made to ensure accuracy with

respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for. The practice of the present invention will employ, unless otherwise indicated, conventional methods of protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., T.E. Creighton, Proteins: Structure and Molecular Properties (W.H. Freeman and Company, 1993); A.L. Lehninger, Biochemistry (Worth Publishers, Inc.); Sambrook, et al, Molecular Cloning: A Laboratory J\1anual (2nd Edition, 1989); Methods In Enzymology (S. Colowlck and N. Kaplan eds., Academic Press, Inc.); Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990); Carey and Sundberg Advanced Organic Chemistry 3rd Ed. (Plenum Press) Vols A and B (l992).

[0108] EXAMPLE 1: Construction of DNA vectors encoding UTI fusion proteins.

[0109] Methods for performing molecular biology are known in the art and can be found, for example, in Molecular Cloning: A laboratory Manual 4th edition (Micheal Green and Joseph Sambrook, Cold Spring Harbor Press, 2012).

[0110] A gene encoding UTI-Fc1 was ordered using the GeneArt codon-optimized gene synthesis services from Life Technologies (Carlsbad, CA). The protein sequence is as listed in SEQ ID NO: 1 with a signal peptide, MGWSCIILFLVATATGVHS, added for secretion. Figure 1 shows the general regions of UTI used in the fusion. The gene encoding UTI-Fc1 was ligated into a mammalian expression vector. Mammalian expression vectors are known in the art including pSecTag2/Hygro A, pcDNA4 and pcDNA6 vectors (Life Technologies, Carlsbad CA). The vector was digested with the restriction enzymes, HindIII-HF and EcoRI from New England Biolabs (NEB). This fragment was ligated into the expression vector which provides carbenicillin resistence and had been digested with the same two restriction enzymes. A vector: insert molar ratio of 1:3 was used in ligation. Ligated DNA was transformed into 10-beta chemically competent E.coli cells from NEB, and plated on LB-Carbenicillin plates for overnight growth. Colonies were grown overnight in LB with Carbenicillin and miniprep DNA was prepared by Qiagen's QIAprep Spin Miniprep Kit (Qiagen, Hilden, Germany). DNA was then sequenced using DNA sequencing services from Bio Applied Technologies Joint (BATJ, San Diego). The sequence verified colony was subsequently grown in LB media with carbenicillin for DNA purification with the BenchPro 2100 instrument and MaxiCard from Life Technologies.

[0111] EXAMPLE 2: Construction of DNA vectors encoding variants of UTI-Fc fusion proteins

[0112] SEQ ID NOS:1-28 list DNA and protein sequences of some UTI-Fc fusion proteins. These UTI fusion proteins comprise modifications that alter Ig isotype, linkers, UTI domain, UTI and Fc domain order (N- or C- termimal), UTI species, Fc species, UTI start/stop residues, sugar attachment, protease sensitive sites, and Fc effector function. Some UTI-Fc proteins are depicted in Figures 2 and 3. UTI-Fc fusion proteins comprising three amino acid modifications to Ser (IgG1 Fc3Ser, C154S/P172S/P265S) comprises mutations to alter disulfide bond formation and FcγR functions.

[0113] Creation of UTI-Fc expression constructs

[0114] The nucleotide sequences of the UTI (e.g. wild-type, S10A, and K21S K22S variants) and human Fc3Ser domains were codon optimized for CHO cell expression and synthesized by Life Technologies (Carlsbad, CA). The following constructs were created in a CHO expression vector by assembling UTI and Fc3Ser domains via sequence and ligation-independent cloning (SLIC) method (Li and Elledge 2007 Nature Methods 4(3):251-256): UTI-Fc3Ser, UTI S10A-Fc3Ser, UTI K21S K22S-Fc3Ser, UTI m2-Fc3Ser, UTI L1-Fc3Ser, UTI L2-Fc3Ser (Figure 4A). SLIC-based DNA assembly was done by mixing the linearized vector (30 ng), UTI (100 ng) and Fc3Ser (100 ng) PCR products with appropriate overhang sequences for homologous recombination, and T4 DNA polymerase (0.5 U) in 5 μL volume containing NEBuffer 2 and BSA (New England Biolabs). After 30 min incubation at room temperature, the exonuclease activity of T4 DNA polymerase was quenched by adding 2 mM of dCTP. Then in vitro homologous recombination was done by temperature gradient from 75C to 37C over 30 min. The reaction mixture containing assembled DNA was chemically transformed into TOP10 E. coli (Invitrogen), and plated on LB-agar containing carbenicillin. The open reading frames for the remaining constructs (UTI m1-Fc3Ser, UTI d1-Fc3Ser, UTI d2-Fc3Ser, UTI L3-Fc3Ser, UTI-Fc IgG2, Fc3Ser-UTI, and mouse UTI-mouse IgG1) were codon optimized and synthesized as fusion constructs. These constructs were cloned into the expression vector using SLIC method as described above (Figure 4B). The DNA sequences of all the 13 constructs in the vector were verified by Sanger DNA sequencing.

[0115] EXAMPLE 3: Expression of UTI-Fc fusions in CHO cells.

[0116] A DNA vector encoding UTI-Fc1 was stably transfected into CHO-S cells using Invitrogen's Freestyle MAX Reagent. Bulk cultures were plated into T-flasks and selected using CD CHO supplemented with various concentrations of methionine sulfoximine (MSX) ranging from 50-100 μM. Once the cultures recovered from selection, they were expanded for production and cryopreservation. Multiple production batches were done to support in vitro and in vivo testing. The production process is a 10-14 day fed-batch culture using CD

FortiCHO, CD Efficient Feed B, and CD Efficient Feed C from Invitrogen. The production volumes ranged from 1L – 3L, and the cultures were harvested by centrifugation at 3500 rpm for 1-2 hours followed by sterile filtration of the supernatant and the resulting cell supernatant was used in purification.

[0117] EXAMPLE 4: Purification of UTI-Fc fusion proteins.

[0118] Purification of 2 batches of UTI-Fc1 was done by appling 2.3 liters CHO cell conditioned media with expressed UTI-Fc1 to 30 ml protein A mAb select lx (GE healthcare) equilibrated in 25mM trisodium citrate pH 8.1, 125mM NaCl. The column was washed with 2 column volumes (60ml) 25mM trisodium citrate pH 8.1, 125mM NaCl and then with 2 column volumes (60ml) 25mM trisodium citrate pH 8.1, 2000mM NaCl. The column was then equilibrated with 2 column volumes (60ml) 25mM trisodium citrate pH 8.1, 125mM NaCl. UTI-Fc1 was eluted with a 7 column volume (210 ml) gradient to 100% 25mM citric acid pH 2.9, 125mM NaCl. The UTI-Fc1 eluted as two peaks, a broad, flanking peak at an approximate pH of 5.5 and a sharper peak at an approximate pH of 3.5. Then, the concentrated UTI-Fc was buffer exchanged into a final buffer of TBS pH 7.4 (25mM tris, 130mM NaCl, 2.7 mM KCl pH 7.4) using Amicon Ultra centrifugal concentrators with a 30K M.W.C.O.. Purified protein yields are shown in TABLE 1 and the protein was stored at -80°C for further use.

TABLE 1

Peak name	Peak volume (mL)	Final product conc. (mg/mL)	Final product Yield (mg)	Protein A Column Yield (%)	% of total protein load
1st batch peak	40	10	110	59	52
2nd batch peak	40	11	150	72	68

[0119] EXAMPLE 5: Expression and Purification of additional UTI-Fc fusion proteins.

[0120] On the day of transfection, CHO cells were counted and seeded at density of 2.2x10^6 live cells/mL in 90% of total volume- 900mLs and grown in shaker flasks at 33°C until transfection. Frozen DNA was thawed and added to PEI (Polyethylenimine- a cationic polymer) and AKT. DNA was added at 0.625ug/ 1 million cells. 1L of cells requires 1.25 mg. 90% of the total DNA added is DNA of interest = 1.125mgs. The remaining 10% was

AKT (encodes anti-apoptotic protein) = 0.125mgs. PEI was added at 2.5ug/1 million cells. For a 1 L transfection this was 5mg. The PEI solution was added to the diluted DNA and incubated at room temperature for 15 minutes before addition of the DNA complex to the cells.

[0121] Cultures were grown at 33°C, 5% CO2, and 125rpm. 1 to 4 hours post-transfection, 0.6mM Valproic acid was added. For the 1L transfection, this was 2mL of 300mM stock. On day 1, 1:250 anti-clumping agent was added i.e. 4 mLs /1L and 15% v/v CD Efficient Feed C i.e. 150mLs/1L. On Day 5 and Day 9 15% CD Efficient Feed C was added.

[0122] Cells supernatents were harvested on Day 14, cells were counted and protein titers were determined. Cells were spun down by centrifugation at 3000 rpm for 30 minutes at 4°C. The supernatants were filtered through a 0.2 micron filter and stored at 4°C or frozen at -20°C.

[0123] Purification of UTI-Fc fusions was done by Protein A chromatography. 200mL of cell culture supernant was mixed with 2 ml of MabSelect Sure Protein A Sepharose beads and shaken overnight at 4°C. The bead mixture was then centrifuged in 50ml tubes at 1200 rpm for 5 minutes and the supernatant was discarded. The beads are added to a column and washed thrice with binding buffer (Biorad, Hercules, CA). UTI-fusions were eluted with 8 ml MAPS II Elution buffer (Biorad, Hercules, CA). 2 ml of neutralization solution (1M Tris-HCl pH 8) was added. Samples were then buffer exchanged into 25mM Citrate, 125mM NaCl, pH 5.5 by repeated concentration and dilution with the buffer using Amicon Centrifugal units (30MWCO, 15 mLs, Millipore). Figure 9 lists the purifications results of various UTI fusion proteins.

[0124] EXAMPLE 6: Inhibition of proteases by UTI fusion proteins

[0125] In vitro enzymatic Assay for Trypsin Inhibition by UTI-Fc fusion protein

[0126] Solutions of UTI-Fc1 at various concentrations (≤ 200 nM final concentration) are prepared in 50 mM HEPES, 150 mM NaCl, 20 mM CaCl2 and 0.01% Brij L23, pH 7.4. Activity assays were performed in Greiner 384-well small volume plates. All steps were conducted at ambient temperature.

[0127] Human pancreatic trypsin (1.5nM final concentration) (Athens Research & Technology, Inc) was added to the dilutions then pre-incubated with the test UTI-Fc for 15 minutes. Next, the reaction was initiated with 100 μM (final) of substrate N -Benzoyl-L-arginine-7-amido-4-methylcoumarin hydrochloride SIGMA B7260-25MG. The reaction mixture total volume was 20 l. Trypsin activity was determined via fluorescence. For

example, the fluorescence intensity was determined in kinetic mode over a window of 30 to 60 minutes on a BMG PHERAstar FS or PHERAstar plus using an excitation wavelength of 370 nm and an emission wavelength of 470 nm. Trypsin activity was linearly proportional to the change in fluorescence observed (final – initial). The percent inhibition of Trypsin at a given UTI-Fc concentration was defined as:

[0128] Percent inhibition = 100 * (1-((Fi – Fp)/(Fn - Fp)))

[0129] Where: Fi was the observed fluorescence at a given concentration of test UTI-Fc.

[0130] Fp was the observed fluorescence of a positive control i.e., the average value of 2 to 6 assays in the absence of Trypsin.

[0131] Fn was the observed fluorescence of a negative control i.e., the average value of 2 to 6 assays of Trypsin in the presence of vehicle alone.

[0132] The IC50 (the molar concentration of the compound, i.e., fusion protein, that produces 50% inhibition) of a test compound, i.e., fusion protein, was calculated by non-linear least squares curve fitting of the equation Percent inhibition = Bottom + ((Top-Bottom) / (1 + ((IC50 / [UTI-Fc]) ^ Hill))). Included within the panel of UTI-Fc was one positive control. As shown in Figure 5, humanUTI has an IC50 of ~3 nM.

[0133] Measurement of the inhibition of other proteases by UTI-Fc1 was also measured at Reaction Biology Corporation (Malvern, PA). Figure 6 demonstrates UTI-Fc1's inhibition of chymotrypsin. Figure 7 lists the inhibitory constants of UTI-Fc1 for a variety of proteases. UTI-Fc1 inhibits chymotrypsin and plasmin moderately and shows weak inhibition of caspase-1, cathepsin C, and papain.

[0134] EXAMPLE 7: Cellular effects of treatment with UTI fusion proteins

[0135] UTI-Fc1 inhibition of cytokine release was measure in a cell-based assay. BEAS2B cells were seeded at the density of 20,000 cells/well in 96 well plate and cultured using complete BEGM Bullet Kit (Lonza) in CO2 incubator. After 24 hours, the culture media were replaced with plain DMEM for starvation and cells were cultured overnight. Then cells were incubated with fresh plain DMEM containing 100nM trypsin with various concentrations of human urine UTI or recombinant UTI-Fc1 proteins. After 8 hours, culture supernatants were collected and IL-6 protein levels were assessed using human IL-6 DuoSet (R&D Systems).

[0136] The results demonstrate that both UTI and UTI-Fc decreased trypsin-induced IL-6 production in BEAS2B cells. As shown in Figure 8, inhibition was dose-dependent with the IC50 values of 0.40 and 0.41 μg/mL, respectively.

[0137] EXAMPLE 8

[0138] Stability measurements of UTI-Fc molecules - Thermal denaturation

[0139] Assays were performed to measure the thermal and real-time stability. All molecules demonstrated activity in trypsin inhibition. Thermal stability was measured by differential scanning calorimetry on a Microcal VP-DSC calorimeter. Samples were prepared at 1 mg/ml and buffered in 0.25 mM Tris pH7.4, 0.13M NaCl and 0.0027M KCl. Samples were heated from 25°C to 110°C at a rate of 200°C per hour. UTI-Fc1 was compared to Application Publication Number CN 103044554 A, SEQ ID's 2 and 6, which comprise an IgG2 or IgG1 Fc domain respectively. The results are presented in Table 8.

TABLE 8

Protein	DSC Tm1 (oC)	DSC Tm2 (oC)
UTI-Fc1 (SEQ ID NO:1)	70.86	85.79
CN 103044554 A SEQ ID 6	68.72	86.38
CN 103044554 A SEQ ID 2	68.47	79.22

EXAMPLE 9

[0140] Real-time stability measurements

[0141] Real-time stability measurements were performed by incubating SEQ ID NO:1 (UTI-Fc1) or CN 103044554 A, SEQ IDS 2 or 6 at 2-8°C, and 40°C for 0, 2 and 4 weeks in TBS, pH7.4 buffer. The formation of higher and lower molecular weight species was determined by size exclusion chromatography (SEC) and visualized with polyacrilamide gel electrophoresis (PAGE). The concentration of each UTI-Fc was also monitored by determination of the absorbance of the solution at 280nm (A280), using extinction coefficients determine by the protein composition. The UTI-Fc molecules produce two, partially overlapping peaks, when analyzed by SEC. The percentage peak area in each UTI-Fc sample measured by SEC is reported in Table 9 at time = 0 weeks, 2 weeks, and 4 weeks. Also shown is the percentage change in concentration measured by A280 (% Δ (mg/ml)) at time = 2 weeks and 4 weeks. The initial T0 concentration of each sample was UTI-Fc1 = 33.5mg/mL, CN 103044554 A SEQ ID 2 = 8.5mg/mL, and CN 103044554 A SEQ ID 6 = 5.6mg/mL. A variability of 3% is typical for SEC and 15% for individual UV measurements. Analysis by PAGE showed that each UTI-Fc molecule showed the expected banding pattern for full-length UTI-Fc.

TABLE 9.

Protein	SEC	SEC	SEC	% Δ	% Δ

	0 weeks	2 weeks	4 weeks	(mg/ml) 2 weeks	(mg/ml) 4 weeks
UTI-Fc1 (SEQ ID NO:1)	Peak1 35.7% Peak2 64.3%	NA		NA	NA
UTI-Fc1 (SEQ ID NO:1) at 2-8°C	NA	Peak1 36.2% Peak2 63.8%	Peak1 36.1% Peak2 63.9%	9.2%	1.2%
UTI-Fc1 (SEQ ID NO:1) at 40°C	NA	Peak1 37.1% Peak2 62.9%	Peak1 36.8% Peak2 63.2%	0.2%	11.9%
CN 103044554 A SEQ ID 2	Peak1 30.6% Peak2 69.4%	NA	NA	NA	NA
CN 103044554 A SEQ ID 2 at 2-8°C	NA	Peak1 29.0% Peak2 71.0%	Peak1 31.5% Peak2 68.5%	0.2%	2.7%
CN 103044554 A SEQ ID 2 at 40°C	NA	Peak1 28.2% Peak2 71.8%	Peak1 30.3% Peak2 69.7%	1.6%	3.5%
CN 103044554 A SEQ ID 6	Peak 1 36.6% Peak 2 63.4%	NA	NA	NA	NA
CN 103044554 A SEQ ID 6 at 2-8°C	NA	Peak1 34.8% Peak2	Peak1 36.4% Peak2	7.8%	9.5%

		65.2%	63.6%		
CN 103044554 A SEQ ID 6 at 40°C	NA	Peak1 33.9% Peak2 66.1%	Peak1 34.5% Peak2 65.5%	3.6%	6.0%

EXAMPLE 10

[0142] In vivo tests of complement inhibition.

[0143] UTI-Fc1 (SEQ ID NO:1) affects on the complement system were measured in vivo. Female, C3h/HeJ mice were purchased from Jackson Laboratories. Animals are dosed according to the experimental design Table 10. Animals were injected i.p. (100 ul/mouse) 15 minutes post dose with LPS at time zero. Animals were euthanized at 2 and 4 hours post LPS injection by CO2 overdose and blood was collected by cardiac puncture. Blood was transferred to serum separator microtubes and allowed to clot at room temperature for 30 minutes. Subsequently, microtubes were centrifuged at 12,000 rpm for 5 minutes and serum was removed and aliquoted to a 96 well plate. Rosmarinic acid was used as a positive control and used as 3 mg/ml in saline. The 96 well plate was frozen at -20°C. Serum samples were analyzed for C5a content by duoset. Statistical significance was determined using Prism graphing software and effects were considering statistically significant if $p < 0.05$. As shown in Figure 10, SEQ ID NO:1 (UTI-Fc1) significantly reduced C5a at 20, 50, and 100 mg/kg at 4 hours post LPS dose.

TABLE 10: Experimental Design (UTI-Fc1 is SEQ ID:1)

Group	Description	Dose (mg/kg)	Conc. (mg/ml)	Volume (ml/kg)	Route	Stimulation LPS (i.p)	LPS conc. (mg/ml)	Animals
1	naive							8
2	Veh -2 hr	--	--	10	iv	30 ug	0.3	8
3	UTI-Fc1 -2 hr	50	5.0	10	iv	30 ug	0.3	8
4	Ros_2 hr_30mpk	30	3.0	10	sc	30 ug	0.3	8
5	Veh – 4 hr	--	--	10	iv	30 ug	0.3	8
6	UTI-Fc1 -4 hr_5mpk	5	0.5	10	iv	30 ug	0.3	8
7	UTI-Fc1 -4	20	2.0	10	iv	30 ug	0.3	8

	hr_20mpk							
8	UTI-Fc1 -4 hr_50mpk	50	5.0	10	iv	30 ug	0.3	8
9	UTI-Fc1 -4 hr_100mpk	100	10.0	10	iv	30 ug	0.3	8
10	Ros_4 hr_30mpk	30	3.0	10	sc	30 ug	0.3	8

SEQUENCE LISTING

SEQ ID NO:1 UTI-Fc 1 Protein Sequence

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SEQ ID NO:2 UTI-Fc 1 DNA Sequence

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SEQ ID NO:3 UTI-Fc IgG1 3Ser Protein sequence
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SEQ ID NO:5 UTI-Fc IgG2 Ser Protein sequence
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SEQ ID NO:6 UTI-Fc IgG2 Ser DNA sequence

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SEQ ID NO:7 UTI-Fc IgG2 Protein sequence

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SEQ ID NO:8 UTI-Fc IgG2 DNA sequence

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SEQ ID NO:9 UTI-Fc IgG1 3Ser S10A Protein sequence

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SEQ ID NO:11 UTI-Fc IgG1 3Ser m2 Protein sequence

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SEQ ID NO:12 UTI-Fc IgG1 3Ser m2 DNA sequence

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SEQ ID NO:17 UTI-Fc IgG1 3Ser link2 Protein sequence
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WHAT IS CLAIMED IS:

1. A UTI fusion protein, comprising SEQ ID NO:1.

2. An isolated UTI fusion protein comprising SEQ ID NO:1.

3. A fusion protein according to claims 1 or 2 wherein the fusion protein is a dimer wherein the Fc domains are associated covalently.

4. A pharmaceutical composition comprising a UTI fusion protein according to claims 1, 2, or 3 and a pharmaceutically acceptable excipient.

4. The use of a UTI fusion protein according to claims 1, 2, or 3 as a medicament.

5. A method of treating a UTI-related condition comprising administering to a patient in need thereof an effective amount of a UTI fusion protein according to claims 1, 2, or 3.

6. A nucleic acid comprising a polynuceotide sequence encoding SEQ ID NO:1.

7. An expression vector comprising the nucleic acid according to claim 6.

8. A recombinant host cell comprising the expression vector of claim 7.

9. A method of producing a UTI fusion protein, comprising: placing the recombinant host cell of claim 8 in a growth medium, such that the recombinant fusion protein is expressed, and isolating the fusion protein from the cell or growth medium.

SEQUENCE LISTING

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<120> UTI FUSION PROTEINS

<130> UTI-5001-WO

<140>
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<150> 61/943,617
<151> 2014-02-24

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<170> PatentIn version 3.5

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Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
        195                 200                 205

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    210                 215                 220

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
225                 230                 235                 240

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
                245                 250                 255

Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
            260                 265                 270
```

```
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        275                 280                 285

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    290                 295                 300

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
305                 310                 315                 320

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                325                 330                 335

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            340                 345                 350

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        355                 360                 365

Ser Leu Ser Leu Ser Pro Gly
    370                 375
```

<210> 4
<211> 1125
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 4

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gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc       60

aagaaagagg actcctgcca gctgggctac tctgccggcc cttgtatggg catgacctcc      120

cggtacttct acaacggcac ctccatggcc tgcgagacat tccagtacgg cggctgcatg      180

ggcaacggca acaactttgt gacagagaaa gagtgcctgc agacctgcag aaccgtggcc      240

gcctgtaacc tgcctatcgt gcggggaccc tgtcgggcct ttatccagct gtgggccttc      300

gacgccgtga agggcaaatg cgtgctgttc ccctatggcg gctgccaggg aaatggaaac      360

aagttctact ccgagaaaga atgccgcgag tactgtggcg tgccaggcga cggggatgag      420

gaactgctgc gggagcccaa atcttccgac aagacccata cctgtccacc ttgccctgcc      480

cccgagctgc tgggaggatc ctctgtgttc ctgttccccc caaagcccaa ggacaccctg      540

atgatctccc ggacccctga agtgacctgc gtggtggtgg atgtgtccca cgaggatccc      600

gaagtgaagt tcaattggta cgtggacggc gtggaagtgc acaacgccaa gaccaagccc      660
```

agagaggaac agtacaactc cacctaccgg gtggtgtccg tgctgaccgt gctgcaccag 720

gattggctga acggcaaaga gtacaagtgc aaggtgtcca acaaggccct gcctgcctcc 780

atcgaaaaga ccatctccaa ggccaagggc cagccccggg aaccccaggt gtacacactg 840

ccccctagcc gggaagagat gacaaagaac caggtgtccc tgacctgtct cgtgaaggga 900

ttctaccccct ccgatatcgc cgtggaatgg gagtccaacg gccagcctga gaacaactac 960

aagaccaccc cccctgtgct ggactccgac ggctcattct tcctgtactc caagctgaca 1020

gtggacaagt cccggtggca gcagggcaac gtgttctcct gctccgtgat gcacgaggcc 1080

ctgcacaacc actacaccca gaagtccctg tccctgagcc ccggc 1125

<210> 5
<211> 370
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 5

Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Lys Lys Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala
20 25 30

Gly Pro Cys Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser
35 40 45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn
50 55 60

Asn Phe Val Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Thr Val Ala
65 70 75 80

Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln
85 90 95

Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr
100 105 110

Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys
115 120 125

Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg
130 135 140

```
Lys Ser Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
145                 150                 155                 160

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                165                 170                 175

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            180                 185                 190

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Met Glu Val His
        195                 200                 205

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
    210                 215                 220

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
225                 230                 235                 240

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
                245                 250                 255

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            260                 265                 270

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        275                 280                 285

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    290                 295                 300

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
305                 310                 315                 320

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                325                 330                 335

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            340                 345                 350

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        355                 360                 365

Gly Lys
    370
```

<210> 6
<211> 1110

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 6
gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc 60

aagaaagagg actcctgcca gctgggctac tctgccggcc cttgtatggg catgacctcc 120

cggtacttct acaacggcac ctccatggcc tgcgagacat tccagtacgg cggctgcatg 180

ggcaacggca acaactttgt gacagagaaa gagtgcctgc agacctgcag aaccgtggcc 240

gcctgtaacc tgcctatcgt gcggggaccc tgtcgggcct ttatccagct gtgggccttc 300

gacgccgtga agggcaaatg cgtgctgttc ccctatggcg gctgccaggg aaatggaaac 360

aagttctact ccgagaaaga atgccgcgag tactgtggcg tgccaggcga cggggatgag 420

gaactgctgc ggaaatcctg tgtcgagtgc ccaccgtgcc cagcaccacc tgtggcagga 480

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 540

gaggtcacgt gcgtggtggt ggacgtgagc cacgaagacc ccgaggtcca gttcaactgg 600

tacgtggacg gcatggaggt gcataatgcc aagacaaagc cacgggagga gcagttcaac 660

agcacgttcc gtgtggtcag cgtcctcacc gtcgtgcacc aggactggct gaacggcaag 720

gagtacaagt gcaaggtctc caacaaaggc ctcccagccc ccatcgagaa aaccatctcc 780

aaaaccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 840

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctaccc cagcgacatc 900

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac acctcccatg 960

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 1020

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacaca 1080

cagaagagcc tctccctgtc tccgggtaaa 1110

<210> 7
<211> 370
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 7
Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

```
Thr Glu Val Thr Lys Lys Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala
            20                  25                  30

Gly Pro Cys Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser
        35                  40                  45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn
    50                  55                  60

Asn Phe Val Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Thr Val Ala
65                  70                  75                  80

Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln
                85                  90                  95

Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr
            100                 105                 110

Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys
        115                 120                 125

Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg
    130                 135                 140

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
145                 150                 155                 160

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                165                 170                 175

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            180                 185                 190

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Met Glu Val His
        195                 200                 205

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
    210                 215                 220

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
225                 230                 235                 240

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
                245                 250                 255

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            260                 265                 270
```

```
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        275                 280                 285

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    290                 295                 300

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
305                 310                 315                 320

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                325                 330                 335

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            340                 345                 350

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        355                 360                 365

Gly Lys
    370
```

<210> 8
<211> 1110
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 8

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gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc        60

aagaaagagg actcctgcca gctgggctac tctgccggcc cttgtatggg catgacctcc       120

cggtacttct acaacggcac ctccatggcc tgcgagacat tccagtacgg cggctgcatg       180

ggcaacggca acaactttgt gacagagaaa gagtgcctgc agacctgcag aaccgtggcc       240

gcctgtaacc tgcctatcgt gcggggaccc tgtcgggcct ttatccagct gtgggccttc       300

gacgccgtga agggcaaatg cgtgctgttc ccctatggcg gctgccaggg aaatggaaac       360

aagttctact ccgagaaaga atgccgcgag tactgtggcg tgccaggcga cggggatgag       420

gaactgctgc ggaaatgttg tgtcgagtgc ccaccgtgcc cagcaccacc tgtggcagga       480

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct       540

gaggtcacgt gcgtggtggt ggacgtgagc cacgaagacc ccgaggtcca gttcaactgg       600

tacgtggacg gcatggaggt gcataatgcc aagacaaagc cacgggagga gcagttcaac       660

agcacgttcc gtgtggtcag cgtcctcacc gtcgtgcacc aggactggct gaacggcaag       720
```

gagtacaagt gcaaggtctc caacaaaggc ctcccagccc ccatcgagaa aaccatctcc 780

aaaaccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggaggag 840

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctaccc cagcgacatc 900

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac acctcccatg 960

ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 1020

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacaca 1080

cagaagagcc tctccctgtc tccgggtaaa 1110

<210> 9
<211> 375
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 9
Ala Val Leu Pro Gln Glu Glu Glu Gly Ala Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Lys Lys Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala
20 25 30

Gly Pro Cys Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser
35 40 45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn
50 55 60

Asn Phe Val Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Thr Val Ala
65 70 75 80

Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln
85 90 95

Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr
100 105 110

Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys
115 120 125

Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg
130 135 140

```
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
145                 150                 155                 160

Pro Glu Leu Leu Gly Gly Ser Ser Val Phe Leu Phe Pro Pro Lys Pro
                165                 170                 175

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            180                 185                 190

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
        195                 200                 205

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    210                 215                 220

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
225                 230                 235                 240

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
                245                 250                 255

Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
            260                 265                 270

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        275                 280                 285

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    290                 295                 300

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
305                 310                 315                 320

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                325                 330                 335

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            340                 345                 350

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        355                 360                 365

Ser Leu Ser Leu Ser Pro Gly
    370                 375
```

<210> 10
<211> 1125
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 10
gctgtgctgc ctcaggaaga ggaaggcgca ggcggaggcc agctcgtgac cgaagtgacc 60

aagaaagagg actcctgcca gctgggctac tctgccggcc cttgtatggg catgacctcc 120

cggtacttct acaacggcac ctccatggcc tgcgagacat tccagtacgg cggctgcatg 180

ggcaacggca acaactttgt gacagagaaa gagtgcctgc agacctgcag aaccgtggcc 240

gcctgtaacc tgcctatcgt gcggggaccc tgtcgggcct ttatccagct gtgggccttc 300

gacgccgtga agggcaaatg cgtgctgttc ccctatggcg gctgccaggg aaatggaaac 360

aagttctact ccgagaaaga atgccgcgag tactgtggcg tgccaggcga cggggatgag 420

gaactgctgc gggagcccaa atcttccgac aagacccata cctgtccacc ttgccctgcc 480

cccgagctgc tgggaggatc ctctgtgttc ctgttccccc caaagcccaa ggacaccctg 540

atgatctccc ggacccctga agtgacctgc gtggtggtgg atgtgtccca cgaggatccc 600

gaagtgaagt tcaattggta cgtggacggc gtggaagtgc acaacgccaa gaccaagccc 660

agagaggaac agtacaactc cacctaccgg gtggtgtccg tgctgaccgt gctgcaccag 720

gattggctga acggcaaaga gtacaagtgc aaggtgtcca acaaggccct gcctgcctcc 780

atcgaaaaga ccatctccaa ggccaagggc cagccccggg aaccccaggt gtacacactg 840

ccccctagcc gggaagagat gacaaagaac caggtgtccc tgacctgtct cgtgaaggga 900

ttctaccccct ccgatatcgc cgtggaatgg gagtccaacg gccagcctga gaacaactac 960

aagaccaccc cccctgtgct ggactccgac ggctcattct tcctgtactc caagctgaca 1020

gtggacaagt cccggtggca gcagggcaac gtgttctcct gctccgtgat gcacgaggcc 1080

ctgcacaacc actacaccca gaagtccctg tccctgagcc ccggc 1125

<210> 11
<211> 353
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 11
Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala Gly Pro Cys Met Gly Met
1 5 10 15

Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser Met Ala Cys Glu Thr Phe

```
            20                  25                  30

Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn Asn Phe Val Thr Glu Lys
        35                  40                  45

Glu Cys Leu Gln Thr Cys Arg Thr Val Ala Ala Cys Asn Leu Pro Ile
    50                  55                  60

Val Arg Gly Pro Cys Arg Ala Phe Ile Gln Leu Trp Ala Phe Asp Ala
65                  70                  75                  80

Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn
                85                  90                  95

Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val
            100                 105                 110

Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Glu Pro Lys Ser Ser Asp
        115                 120                 125

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
    130                 135                 140

Ser Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
145                 150                 155                 160

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
                165                 170                 175

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
            180                 185                 190

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
        195                 200                 205

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
    210                 215                 220

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu
225                 230                 235                 240

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
                245                 250                 255

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
            260                 265                 270
```

```
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
        275                 280                 285

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
    290                 295                 300

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
305                 310                 315                 320

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
                325                 330                 335

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
            340                 345                 350

Gly
```

<210> 12
<211> 1059
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 12

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gaggactcct gccagctggg ctactctgcc ggcccttgta tgggcatgac ctcccggtac       60

ttctacaacg gcacctccat ggcctgcgag acattccagt acggcggctg catgggcaac      120

ggcaacaact ttgtgacaga gaaagagtgc ctgcagacct gcagaaccgt ggccgcctgt      180

aacctgccta tcgtgcgggg accctgtcgg gcctttatcc agctgtgggc cttcgacgcc      240

gtgaagggca aatgcgtgct gttcccctat ggcggctgcc agggaaatgg aaacaagttc      300

tactccgaga aagaatgccg cgagtactgt ggcgtgccag gcgacgggga tgaggaactg      360

ctgcgggagc ccaaatcttc cgacaagacc catacctgtc caccttgccc tgcccccgag      420

ctgctgggag gatcctctgt gttcctgttc cccccaaagc ccaaggacac cctgatgatc      480

tcccggaccc ctgaagtgac ctgcgtggtg gtggatgtgt cccacgagga tcccgaagtg      540

aagttcaatt ggtacgtgga cggcgtggaa gtgcacaacg ccaagaccaa gcccagagag      600

gaacagtaca actccaccta ccgggtggtg tccgtgctga ccgtgctgca ccaggattgg      660

ctgaacggca aagagtacaa gtgcaaggtg tccaacaagg ccctgcctgc ctccatcgaa      720

aagaccatct ccaaggccaa gggccagccc cgggaacccc aggtgtacac actgcccccc      780

agccgggaag agatgacaaa gaaccaggtg tccctgacct gtctcgtgaa gggattctac      840
```

ccctccgata tcgccgtgga atgggagtcc aacggccagc ctgagaacaa ctacaagacc 900

acccccccctg tgctggactc cgacggctca ttcttcctgt actccaagct gacagtggac 960

aagtcccggt ggcagcaggg caacgtgttc tcctgctccg tgatgcacga ggccctgcac 1020

aaccactaca cccagaagtc cctgtccctg agccccggc 1059

<210> 13
<211> 253
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 13

Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Lys Lys Glu Pro Lys Ser Ser Asp Lys Thr His Thr
20 25 30

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Ser Ser Val Phe
35 40 45

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
50 55 60

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
65 70 75 80

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
85 90 95

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
100 105 110

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
115 120 125

Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser
130 135 140

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
145 150 155 160

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
165 170 175

```
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
            180                 185                 190


Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
        195                 200                 205


Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
    210                 215                 220


Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
225                 230                 235                 240


Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                245                 250


<210> 14
<211> 759
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 14
gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc       60

aagaaagagc ccaaatcttc cgacaagacc catacctgtc caccttgccc tgcccccgag      120

ctgctgggag gatcctctgt gttcctgttc cccccaaagc ccaaggacac cctgatgatc      180

tcccggaccc ctgaagtgac ctgcgtggtg gtggatgtgt cccacgagga tcccgaagtg      240

aagttcaatt ggtacgtgga cggcgtggaa gtgcacaacg ccaagaccaa gcccagagag      300

gaacagtaca actccaccta ccgggtggtg tccgtgctga ccgtgctgca ccaggattgg      360

ctgaacggca aagagtacaa gtgcaaggtg tccaacaagg ccctgcctgc ctccatcgaa      420

aagaccatct ccaaggccaa gggccagccc cgggaacccc aggtgtacac actgcccccc      480

agccgggaag agatgacaaa gaaccaggtg tccctgacct gtctcgtgaa gggattctac      540

ccctccgata tcgccgtgga atgggagtcc aacggccagc ctgagaacaa ctacaagacc      600

acccccccctg tgctggactc cgacggctca ttcttcctgt actccaagct gacagtggac      660

aagtcccggt ggcagcaggg caacgtgttc tcctgctccg tgatgcacga ggccctgcac      720

aaccactaca cccagaagtc cctgtccctg agccccggc                              759


<210> 15
<211> 384
<212> PRT
<213> Artificial Sequence
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 15
Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Lys Lys Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala
20 25 30

Gly Pro Cys Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser
35 40 45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn
50 55 60

Asn Phe Val Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Thr Val Ala
65 70 75 80

Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln
85 90 95

Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr
100 105 110

Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys
115 120 125

Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys Ser Ser Asp Lys
145 150 155 160

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Ser
165 170 175

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
180 185 190

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
195 200 205

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
210 215 220

```
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
225                 230                 235                 240

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
                245                 250                 255

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu Lys
            260                 265                 270

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        275                 280                 285

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    290                 295                 300

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
305                 310                 315                 320

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
                325                 330                 335

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
            340                 345                 350

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
        355                 360                 365

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    370                 375                 380


<210> 16
<211> 1152
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 16
gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc       60

aagaaagagg actcctgcca gctgggctac tctgccggcc cttgtatggg catgacctcc      120

cggtacttct acaacggcac ctccatggcc tgcgagacat tccagtacgg cggctgcatg      180

ggcaacggca acaactttgt gacagagaaa gagtgcctgc agacctgcag aaccgtggcc      240

gcctgtaacc tgcctatcgt gcggggaccc tgtcgggcct ttatccagct gtgggccttc      300

gacgccgtga agggcaaatg cgtgctgttc ccctatggcg gctgccaggg aaatggaaac      360
```

aagttctact ccgagaaaga atgccgcgag tactgtggcg tgccaggcga cggggatgag 420

gaactgctgg gaggtggtgg atcaggtggc ggaggatcag agcccaaatc ttccgacaag 480

acccatacct gtccaccttg ccctgccccc gagctgctgg gaggatcctc tgtgttcctg 540

ttcccccaa agcccaagga caccctgatg atctcccgga cccctgaagt gacctgcgtg 600

gtggtggatg tgtcccacga ggatcccgaa gtgaagttca attggtacgt ggacggcgtg 660

gaagtgcaca acgccaagac caagcccaga gaggaacagt acaactccac ctaccgggtg 720

gtgtccgtgc tgaccgtgct gcaccaggat tggctgaacg gcaaagagta caagtgcaag 780

gtgtccaaca aggccctgcc tgcctccatc gaaaagacca tctccaaggc caagggccag 840

ccccgggaac cccaggtgta cacactgccc cctagccggg aagagatgac aaagaaccag 900

gtgtccctga cctgtctcgt gaagggattc taccctccg atatcgccgt ggaatgggag 960

tccaacggcc agcctgagaa caactacaag accacccccc ctgtgctgga ctccgacggc 1020

tcattcttcc tgtactccaa gctgacagtg gacaagtccc ggtggcagca gggcaacgtg 1080

ttctcctgct ccgtgatgca cgaggccctg cacaaccact acacccagaa gtccctgtcc 1140

ctgagccccg gc 1152

<210> 17
<211> 365
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 17
Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Lys Lys Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala
20 25 30

Gly Pro Cys Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser
35 40 45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn
50 55 60

Asn Phe Val Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Thr Val Ala
65 70 75 80

Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln
85 90 95

```
Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr
            100                 105                 110

Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys
        115                 120                 125

Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg
    130                 135                 140

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Ser Ser Val Phe
145                 150                 155                 160

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                165                 170                 175

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            180                 185                 190

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        195                 200                 205

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    210                 215                 220

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
225                 230                 235                 240

Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser
                245                 250                 255

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            260                 265                 270

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        275                 280                 285

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    290                 295                 300

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
305                 310                 315                 320

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                325                 330                 335

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            340                 345                 350
```

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
355 360 365

<210> 18
<211> 1095
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 18
gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc 60

aagaaagagg actcctgcca gctgggctac tctgccggcc cttgtatggg catgacctcc 120

cggtacttct acaacggcac ctccatggcc tgcgagacat tccagtacgg cggctgcatg 180

ggcaacggca acaactttgt gacagagaaa gagtgcctgc agacctgcag aaccgtggcc 240

gcctgtaacc tgcctatcgt gcggggaccc tgtcgggcct ttatccagct gtgggccttc 300

gacgccgtga agggcaaatg cgtgctgttc ccctatggcg gctgccaggg aaatggaaac 360

aagttctact ccgagaaaga atgccgcgag tactgtggcg tgccaggcga cggggatgag 420

gaactgctgc ggtgtccacc ttgccctgcc cccgagctgc tgggaggatc ctctgtgttc 480

ctgttccccc caaagcccaa ggacaccctg atgatctccc ggacccctga agtgacctgc 540

gtggtggtgg atgtgtccca cgaggatccc gaagtgaagt tcaattggta cgtggacggc 600

gtggaagtgc acaacgccaa gaccaagccc agagaggaac agtacaactc cacctaccgg 660

gtggtgtccg tgctgaccgt gctgcaccag gattggctga acggcaaaga gtacaagtgc 720

aaggtgtcca acaaggccct gcctgcctcc atcgaaaaga ccatctccaa ggccaagggc 780

cagccccggg aaccccaggt gtacacactg ccccctagcc gggaagagat gacaaagaac 840

caggtgtccc tgacctgtct cgtgaaggga ttctaccct ccgatatcgc cgtggaatgg 900

gagtccaacg gccagcctga gaacaactac aagaccaccc cccctgtgct ggactccgac 960

ggctcattct tcctgtactc caagctgaca gtggacaagt cccggtggca gcagggcaac 1020

gtgttctcct gctccgtgat gcacgaggcc ctgcacaacc actacaccca gaagtccctg 1080

tccctgagcc ccggc 1095

<210> 19
<211> 343
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 19
Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Lys Lys Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala
20 25 30

Gly Pro Cys Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser
35 40 45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn
50 55 60

Asn Phe Val Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Thr Val Ala
65 70 75 80

Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln
85 90 95

Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr
100 105 110

Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys
115 120 125

Arg Glu Tyr Cys Gly Val Ser Ser Val Phe Leu Phe Pro Pro Lys Pro
130 135 140

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
145 150 155 160

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
165 170 175

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
180 185 190

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
195 200 205

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
210 215 220

Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
225 230 235 240

```
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
                245                 250                 255

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
            260                 265                 270

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
        275                 280                 285

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
    290                 295                 300

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
305                 310                 315                 320

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
                325                 330                 335

Ser Leu Ser Leu Ser Pro Gly
            340
```

<210> 20
<211> 1029
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 20

```
gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc        60

aagaaagagg actcctgcca gctgggctac tctgccggcc cttgtatggg catgacctcc       120

cggtacttct acaacggcac ctccatggcc tgcgagacat tccagtacgg cggctgcatg       180

ggcaacggca acaactttgt gacagagaaa gagtgcctgc agacctgcag aaccgtggcc       240

gcctgtaacc tgcctatcgt gcggggaccc tgtcgggcct ttatccagct gtgggccttc       300

gacgccgtga agggcaaatg cgtgctgttc ccctatggcg gctgccaggg aaatggaaac       360

aagttctact ccgagaaaga atgccgcgag tactgtggcg tgtcctctgt gttcctgttc       420

cccccaaagc ccaaggacac cctgatgatc tcccggaccc ctgaagtgac ctgcgtggtg       480

gtggatgtgt cccacgagga tcccgaagtg aagttcaatt ggtacgtgga cggcgtggaa       540

gtgcacaacg ccaagaccaa gcccagagag gaacagtaca actccaccta ccgggtggtg       600

tccgtgctga ccgtgctgca ccaggattgg ctgaacggca aagagtacaa gtgcaaggtg       660

tccaacaagg ccctgcctgc ctccatcgaa aagaccatct ccaaggccaa gggccagccc       720
```

cgggaacccc aggtgtacac actgcccccct agccgggaag agatgacaaa gaaccaggtg 780

tccctgacct gtctcgtgaa gggattctac ccctccgata tcgccgtgga atgggagtcc 840

aacggccagc ctgagaacaa ctacaagacc acccccccctg tgctggactc cgacggctca 900

ttcttcctgt actccaagct gacagtggac aagtcccggt ggcagcaggg caacgtgttc 960

tcctgctccg tgatgcacga ggccctgcac aaccactaca cccagaagtc cctgtccctg 1020

agccccggc 1029

<210> 21
<211> 375
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 21
Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Ser Ser Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala
20 25 30

Gly Pro Cys Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser
35 40 45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn
50 55 60

Asn Phe Val Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Thr Val Ala
65 70 75 80

Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln
85 90 95

Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr
100 105 110

Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys
115 120 125

Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg
130 135 140

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
145 150 155 160

```
Pro Glu Leu Leu Gly Gly Ser Ser Val Phe Leu Phe Pro Pro Lys Pro
                165                 170                 175

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            180                 185                 190

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
        195                 200                 205

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    210                 215                 220

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
225                 230                 235                 240

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
                245                 250                 255

Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
            260                 265                 270

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        275                 280                 285

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    290                 295                 300

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
305                 310                 315                 320

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                325                 330                 335

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            340                 345                 350

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        355                 360                 365

Ser Leu Ser Leu Ser Pro Gly
    370                 375
```

<210> 22
<211> 1125
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 22
gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc 60

tcctccgagg actcctgcca gctgggctac tctgccggcc cttgtatggg catgacctcc 120

cggtacttct acaacggcac ctccatggcc tgcgagacat tccagtacgg cggctgcatg 180

ggcaacggca acaactttgt gacagagaaa gagtgcctgc agacctgcag aaccgtggcc 240

gcctgtaacc tgcctatcgt gcggggaccc tgtcgggcct ttatccagct gtgggccttc 300

gacgccgtga agggcaaatg cgtgctgttc ccctatggcg gctgccaggg aaatggaaac 360

aagttctact ccgagaaaga atgccgcgag tactgtggcg tgccaggcga cggggatgag 420

gaactgctgc gggagcccaa atcttccgac aagacccata cctgtccacc ttgccctgcc 480

cccgagctgc tgggaggatc ctctgtgttc ctgttccccc caaagcccaa ggacaccctg 540

atgatctccc ggacccctga agtgacctgc gtggtggtgg atgtgtccca cgaggatccc 600

gaagtgaagt tcaattggta cgtggacggc gtggaagtgc acaacgccaa gaccaagccc 660

agagaggaac agtacaactc cacctaccgg gtggtgtccg tgctgaccgt gctgcaccag 720

gattggctga acggcaaaga gtacaagtgc aaggtgtcca acaaggccct gcctgcctcc 780

atcgaaaaga ccatctccaa ggccaagggc cagccccggg aaccccaggt gtacacactg 840

ccccctagcc gggaagagat gacaaagaac caggtgtccc tgacctgtct cgtgaaggga 900

ttctaccccct ccgatatcgc cgtggaatgg gagtccaacg gccagcctga gaacaactac 960

aagaccaccc cccctgtgct ggactccgac ggctcattct tcctgtactc caagctgaca 1020

gtggacaagt cccggtggca gcagggcaac gtgttctcct gctccgtgat gcacgaggcc 1080

ctgcacaacc actacaccca gaagtccctg tccctgagcc ccggc 1125

<210> 23
<211> 320
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 23
Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Lys Lys Thr Val Ala Ala Cys Asn Leu Pro Ile Val
20 25 30

```
Arg Gly Pro Cys Arg Ala Phe Ile Gln Leu Trp Ala Phe Asp Ala Val
        35                  40                  45

Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly
    50                  55                  60

Asn Lys Phe Tyr Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro
65                  70                  75                  80

Gly Asp Gly Asp Glu Glu Leu Leu Arg Glu Pro Lys Ser Ser Asp Lys
                85                  90                  95

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Ser
            100                 105                 110

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        115                 120                 125

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    130                 135                 140

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
145                 150                 155                 160

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                165                 170                 175

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            180                 185                 190

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu Lys
        195                 200                 205

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    210                 215                 220

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
225                 230                 235                 240

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                245                 250                 255

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            260                 265                 270

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        275                 280                 285
```

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
290 295 300

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
305 310 315 320

<210> 24
<211> 960
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 24
gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc 60

aagaaaaccg tggccgcctg taacctgcct atcgtgcggg gaccctgtcg ggcctttatc 120

cagctgtggg ccttcgacgc cgtgaagggc aaatgcgtgc tgttccccta tggcggctgc 180

cagggaaatg gaaacaagtt ctactccgag aaagaatgcc gcgagtactg tggcgtgcca 240

ggcgacgggg atgaggaact gctgcgggag cccaaatctt ccgacaagac ccatacctgt 300

ccaccttgcc ctgcccccga gctgctggga ggatcctctg tgttcctgtt ccccccaaag 360

cccaaggaca ccctgatgat ctcccggacc cctgaagtga cctgcgtggt ggtggatgtg 420

tcccacgagg atcccgaagt gaagttcaat tggtacgtgg acggcgtgga agtgcacaac 480

gccaagacca agcccagaga ggaacagtac aactccacct accgggtggt gtccgtgctg 540

accgtgctgc accaggattg gctgaacggc aaagagtaca agtgcaaggt gtccaacaag 600

gccctgcctg cctccatcga aaagaccatc tccaaggcca agggccagcc ccgggaaccc 660

caggtgtaca cactgccccc tagccgggaa gagatgacaa agaaccaggt gtccctgacc 720

tgtctcgtga agggattcta cccctccgat atcgccgtgg aatgggagtc caacggccag 780

cctgagaaca actacaagac cacccccccc gtgctggact ccgacggctc attcttcctg 840

tactccaagc tgacagtgga caagtcccgg tggcagcagg gcaacgtgtt ctcctgctcc 900

gtgatgcacg aggccctgca caaccactac acccagaagt ccctgtccct gagccccggc 960

<210> 25
<211> 308
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 25
Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Lys Lys Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala
20 25 30

Gly Pro Cys Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser
35 40 45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn
50 55 60

Asn Phe Val Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Glu Pro Lys
65 70 75 80

Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
85 90 95

Leu Gly Gly Ser Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
100 105 110

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
115 120 125

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
130 135 140

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
145 150 155 160

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
165 170 175

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
180 185 190

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
195 200 205

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
210 215 220

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
225 230 235 240

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr

245 250 255

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
260 265 270

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
275 280 285

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
290 295 300

Leu Ser Pro Gly
305

<210> 26
<211> 924
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 26
gctgtgctgc ctcaggaaga ggaaggctct ggcggaggcc agctcgtgac cgaagtgacc 60

aagaaagagg actcctgcca gctgggctac tctgccggcc cttgtatggg catgacctcc 120

cggtacttct acaacggcac ctccatggcc tgcgagacat tccagtacgg cggctgcatg 180

ggcaacggca acaactttgt gacagagaaa gagtgcctgc agacctgcag agagcccaaa 240

tcttccgaca agacccatac ctgtccacct tgccctgccc ccgagctgct gggaggatcc 300

tctgtgttcc tgttcccccc aaagcccaag gacaccctga tgatctcccg gacccctgaa 360

gtgacctgcg tggtggtgga tgtgtcccac gaggatcccg aagtgaagtt caattggtac 420

gtggacggcg tggaagtgca caacgccaag accaagccca gagaggaaca gtacaactcc 480

acctaccggg tggtgtccgt gctgaccgtg ctgcaccagg attggctgaa cggcaaagag 540

tacaagtgca aggtgtccaa caaggccctg cctgcctcca tcgaaaagac catctccaag 600

gccaagggcc agccccggga accccaggtg tacacactgc cccctagccg ggaagagatg 660

acaaagaacc aggtgtccct gacctgtctc gtgaagggat tctacccctc cgatatcgcc 720

gtggaatggg agtccaacgg ccagcctgag aacaactaca agaccacccc ccctgtgctg 780

gactccgacg gctcattctt cctgtactcc aagctgacag tggacaagtc ccggtggcag 840

cagggcaacg tgttctcctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 900

aagtccctgt ccctgagccc cggc 924

<210> 27
<211> 374
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 27

```
Ala Val Leu Pro Gln Glu Ser Glu Gly Ser Gly Thr Glu Pro Leu Ile
1               5                  10                  15

Thr Gly Thr Leu Lys Lys Glu Asp Ser Cys Gln Leu Asn Tyr Ser Glu
            20                  25                  30

Gly Pro Cys Leu Gly Met Gln Glu Arg Tyr Tyr Tyr Asn Gly Ala Ser
        35                  40                  45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Leu Gly Asn Gly Asn
    50                  55                  60

Asn Phe Ile Ser Glu Lys Asp Cys Leu Gln Thr Cys Arg Thr Ile Ala
65                  70                  75                  80

Ala Cys Asn Leu Pro Ile Val Gln Gly Pro Cys Arg Ala Phe Ile Lys
                85                  90                  95

Leu Trp Ala Phe Asp Ala Ala Gln Gly Lys Cys Ile Gln Phe His Tyr
            100                 105                 110

Gly Gly Cys Lys Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys
        115                 120                 125

Lys Glu Tyr Cys Gly Val Pro Gly Asp Gly Tyr Glu Glu Leu Ile Arg
    130                 135                 140

Ser Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr
145                 150                 155                 160

Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
                165                 170                 175

Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp
            180                 185                 190

Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp
        195                 200                 205
```

```
Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn
    210                 215                 220

Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp
225                 230                 235                 240

Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro
                245                 250                 255

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala
            260                 265                 270

Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp
        275                 280                 285

Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile
    290                 295                 300

Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn
305                 310                 315                 320

Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys
                325                 330                 335

Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys
            340                 345                 350

Ser Val Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu
        355                 360                 365

Ser His Ser Pro Gly Lys
    370
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<210> 28
<211> 1122
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 28
gcagtgctgc cccaagagag tgaggggtca gggactgagc cactaataac tgggaccctc 60

aagaaagaag actcctgcca gctcaattac tcagaaggcc cctgcctagg gatgcaagag 120

aggtattact acaacggcgc ttccatggcc tgcgagacct ttcaatatgg gggttgccta 180

ggcaacggca acaacttcat ctctgagaag gactgtctgc agacatgtcg gaccatagcg 240

gcctgcaatc tccccatagt ccaaggcccc tgccgagcct tcataaagct ctgggcattt 300

gatgcagcac aagggaagtg catccaattc cactacgggg gctgcaaagg caacggcaac 360

aaattctact ctgagaagga atgcaaagag tactgtggag tccctggtga tgggtacgag 420

gaactaatac gcagtaaaat cgtgcctcgg gactgcggct gcaagccctg catctgcacc 480

gtgcccgagg tgtcctccgt gttcatcttc ccacccaagc ccaaggacgt gctgaccatc 540

accctgaccc ccaaagtgac ctgcgtggtg gtggacatct ccaaggacga ccccgaggtg 600

cagttcagtt ggttcgtgga cgacgtggaa gtgcacaccg cccagaccca gcccagagag 660

gaacagttca actccacctt cagatccgtg tccgagctgc ccatcatgca ccaggactgg 720

ctgaacggca aagagttcaa gtgcagagtg aactccgccg ccttcccagc ccccatcgaa 780

aagaccatct ccaagaccaa gggcagaccc aaggcccccc aggtgtacac catccccca 840

cccaaagaac agatggccaa ggacaaggtg tccctgacct gcatgatcac cgatttcttc 900

ccagaggaca tcaccgtgga atggcagtgg aacggccagc ccgccgagaa ctacaagaac 960

acccagccca tcatggacac cgacggctcc tacttcgtgt actccaagct gaacgtgcag 1020

aagtccaact gggaggccgg caacaccttc acctgtagcg tgctgcacga gggcctgcac 1080

aaccaccaca ccgagaagtc cctgtcccac tcccccggca ag 1122

<210> 29
<211> 391
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 29
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Ser Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln

```
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly
225                 230                 235                 240

Gly Ser Gly Gly Gly Gly Ser Ala Val Leu Pro Gln Glu Glu Glu Gly
                245                 250                 255

Ser Gly Gly Gly Gln Leu Val Thr Glu Val Thr Lys Lys Glu Asp Ser
            260                 265                 270

Cys Gln Leu Gly Tyr Ser Ala Gly Pro Cys Met Gly Met Thr Ser Arg
        275                 280                 285

Tyr Phe Tyr Asn Gly Thr Ser Met Ala Cys Glu Thr Phe Gln Tyr Gly
    290                 295                 300

Gly Cys Met Gly Asn Gly Asn Asn Phe Val Thr Glu Lys Glu Cys Leu
305                 310                 315                 320

Gln Thr Cys Arg Thr Val Ala Ala Cys Asn Leu Pro Ile Val Arg Gly
                325                 330                 335
```

Pro Cys Arg Ala Phe Ile Gln Leu Trp Ala Phe Asp Ala Val Lys Gly
340 345 350

Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys Gln Gly Asn Gly Asn Lys
355 360 365

Phe Tyr Ser Glu Lys Glu Cys Arg Glu Tyr Cys Gly Val Pro Gly Asp
370 375 380

Gly Asp Glu Glu Leu Leu Arg
385 390

<210> 30
<211> 1173
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 30
gagcccaaat cttccgacaa gacccatacc tgtccacctt gccctgcccc cgagctgctg 60

ggaggatcct ctgtgttcct gttcccccca aagcccaagg acaccctgat gatctcccgg 120

acccctgaag tgacctgcgt ggtggtggat gtgtcccacg aggatcccga agtgaagttc 180

aattggtacg tggacggcgt ggaagtgcac aacgccaaga ccaagcccag agaggaacag 240

tacaactcca cctaccgggt ggtgtccgtg ctgaccgtgc tgcaccagga ttggctgaac 300

ggcaaagagt acaagtgcaa ggtgtccaac aaggccctgc ctgcctccat cgaaaagacc 360

atctccaagg ccaagggcca gccccgggaa ccccaggtgt acacactgcc ccctagccgg 420

gaagagatga caaagaacca ggtgtccctg acctgtctcg tgaagggatt ctacccctcc 480

gatatcgccg tggaatggga gtccaacggc cagcctgaga acaactacaa gaccaccccc 540

cctgtgctgg actccgacgg ctcattcttc ctgtactcca agctgacagt ggacaagtcc 600

cggtggcagc agggcaacgt gttctcctgc tccgtgatgc acgaggccct gcacaaccac 660

tacacccaga agtccctgtc cctgagcccc ggcaagggag gtggtggatc aggaggtgga 720

ggttccggtg gcggaggatc agctgtgctg cctcaggaag aggaaggctc tggcggaggc 780

cagctcgtga ccgaagtgac caagaaagag gactcctgcc agctgggcta ctctgccggc 840

ccttgtatgg gcatgacctc ccggtacttc tacaacggca cctccatggc ctgcgagaca 900

ttccagtacg gcggctgcat gggcaacggc aacaactttg tgacagagaa agagtgcctg 960

cagacctgca gaaccgtggc cgcctgtaac ctgcctatcg tgcggggacc ctgtcgggcc 1020

tttatccagc tgtgggcctt cgacgccgtg aagggcaaat gcgtgctgtt cccctatggc 1080

ggctgccagg gaaatggaaa caagttctac tccgagaaag aatgccgcga gtactgtggc 1140

gtgccaggcg acggggatga ggaactgctg cgg 1173

<210> 31
<211> 147
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 31
Ala Val Leu Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val
1 5 10 15

Thr Glu Val Thr Lys Lys Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala
20 25 30

Gly Pro Cys Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser
35 40 45

Met Ala Cys Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn
50 55 60

Asn Phe Val Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Thr Val Ala
65 70 75 80

Ala Cys Asn Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln
85 90 95

Leu Trp Ala Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr
100 105 110

Gly Gly Cys Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys
115 120 125

Arg Glu Tyr Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg
130 135 140

Phe Ser Asn
145

<210> 32
<211> 352
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 32
Met Arg Ser Leu Gly Ala Leu Leu Leu Leu Leu Ser Ala Cys Leu Ala
1 5 10 15

Val Ser Ala Gly Pro Val Pro Thr Pro Pro Asp Asn Ile Gln Val Gln
20 25 30

Glu Asn Phe Asn Ile Ser Arg Ile Tyr Gly Lys Trp Tyr Asn Leu Ala
35 40 45

Ile Gly Ser Thr Cys Pro Trp Leu Lys Lys Ile Met Asp Arg Met Thr
50 55 60

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

Met Thr Ser Thr Arg Trp Arg Lys Gly Val Cys Glu Glu Thr Ser Gly
85 90 95

Ala Tyr Glu Lys Thr Asp Thr Asp Gly Lys Phe Leu Tyr His Lys Ser
100 105 110

Lys Trp Asn Ile Thr Met Glu Ser Tyr Val Val His Thr Asn Tyr Asp
115 120 125

Glu Tyr Ala Ile Phe Leu Thr Lys Lys Phe Ser Arg His His Gly Pro
130 135 140

Thr Ile Thr Ala Lys Leu Tyr Gly Arg Ala Pro Gln Leu Arg Glu Thr
145 150 155 160

Leu Leu Gln Asp Phe Arg Val Val Ala Gln Gly Val Gly Ile Pro Glu
165 170 175

Asp Ser Ile Phe Thr Met Ala Asp Arg Gly Glu Cys Val Pro Gly Glu
180 185 190

Gln Glu Pro Glu Pro Ile Leu Ile Pro Arg Val Arg Arg Ala Val Leu
195 200 205

Pro Gln Glu Glu Glu Gly Ser Gly Gly Gly Gln Leu Val Thr Glu Val
210 215 220

Thr Lys Lys Glu Asp Ser Cys Gln Leu Gly Tyr Ser Ala Gly Pro Cys
225 230 235 240

Met Gly Met Thr Ser Arg Tyr Phe Tyr Asn Gly Thr Ser Met Ala Cys
245 250 255

Glu Thr Phe Gln Tyr Gly Gly Cys Met Gly Asn Gly Asn Asn Phe Val
260 265 270

Thr Glu Lys Glu Cys Leu Gln Thr Cys Arg Thr Val Ala Ala Cys Asn
275 280 285

Leu Pro Ile Val Arg Gly Pro Cys Arg Ala Phe Ile Gln Leu Trp Ala
290 295 300

Phe Asp Ala Val Lys Gly Lys Cys Val Leu Phe Pro Tyr Gly Gly Cys
305 310 315 320

Gln Gly Asn Gly Asn Lys Phe Tyr Ser Glu Lys Glu Cys Arg Glu Tyr
325 330 335

Cys Gly Val Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Phe Ser Asn
340 345 350

<210> 33
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 33
Ser Gly Gly Gly Gly Ser
1 5

<210> 34
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 34
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 35
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 35
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1   5   10   15

<210> 36
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 36
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1   5   10   15

Gly Gly Gly Gly Ser
            20

<210> 37
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 37
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1   5   10   15

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
            20   25

<210> 38
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 38
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1   5   10   15

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> 39
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 39
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
20 25 30

Gly Gly Gly Ser
35

<210> 40
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 40
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
20 25 30

Gly Gly Gly Ser Gly Gly Gly Gly Ser
35 40

<210> 41
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 41
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser

1 5 10 15

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
20 25 30

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
35 40 45

<210> 42
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 42
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
20 25 30

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
35 40 45

Gly Gly Ser
50

<210> 43
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 43
Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 44
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 44
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1   5   10   15

Val His Ser

<210> 45
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 45
Pro Gly Asp Gly Asp Glu Glu Leu Leu Arg Glu Pro Lys Ser Ser Asp
1   5   10   15

Lys Thr His

<210> 46
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 46
Pro Gly Asp Gly Asp Glu Glu Leu Leu Gly Ser Gly Gly Gly Gly Asp
1   5   10   15

Lys Thr His

<210> 47
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 47
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1   5   10

<210> 48

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 48
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15