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(54) Title: NOVEL MASKED CYTOKINES AND METHODS OF USE THEREOF

(57) Abstract: Provided herein are prodrugs and methods of making and using thereof for stimulating the immune system, or treating cancer, autoimmune or an infectious disease.

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NOVEL MASKED CYTOKINES AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The application claims priority from U.S. Provisional Applications 62/959,973, filed January 11, 2020; 63/027,138, filed May 19, 2020; 63/029,473, filed May 23, 2020; and 63/126,393, filed December 16, 2020. The disclosures of the aforementioned priority applications are incorporated herein by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on January 11, 2021, is named 025471_WO008_SL.txt and is 240,322 bytes in size.

BACKGROUND OF THE INVENTION

[0003] Interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21 play important roles in the proliferation, differentiation, and survival of immune cells. The receptors for these cytokines share a common γ chain (γ C), also known as CD132. Thus, these cytokines are also called common γ C family cytokines.

[0004] IL-2 plays a central role in lymphocyte generation, survival, and homeostasis. It has 133 amino acids and consists of four antiparallel, amphipathic alpha-helices that form a quaternary structure essential for its function (Smith, *Science* (1988) 240:1169-76; Bazan, *Science* (1992) 257:410-13). IL-2 exerts its activities by binding to IL-2 receptors (IL-2R), which consist of up to three individual subunits. Association of the α (CD25 or Tac antigen), β (CD122), and γ C subunits results in a trimeric, high-affinity receptor for IL-2 ($K_D \sim 0.01$ nM). Dimeric IL-2 receptor consisting of the β and γ subunits is termed intermediate-affinity IL-2R ($K_D \sim 1$ nM). The α subunit alone forms the monomeric low affinity IL-2 receptor ($K_D \sim 10$ nM). See, e.g., Kim et al., *Cytokine Growth Factor Rev.* (2006) 17:349-66). Although the dimeric intermediate-affinity IL-2 receptor binds IL-2 with approximately 100-fold lower

affinity than the trimeric high-affinity receptor, both the dimeric and trimeric IL-2 receptors can transmit signal upon IL-2 binding (Minami et al., *Annu Rev Immunol.* (1993) 11:245-68).

[0005] IL-15 is a cytokine with structural similarities to IL-2. IL-15 is secreted by mononuclear phagocytes and other immune cells following viral infection. IL-15 induces proliferation of natural killer (NK) and other cells of the immune system and is involved in the killing of virally infected cells and cancer cells. Like IL-2, IL-15 binds to the IL-2 receptor (IL-2R) β/γ complex, the intermediate affinity receptor, with a K_D of about 1 nM (Giri et al., *EMBO J.* (1994) 13:2822-30). IL-15 binds to IL-15 receptor (IL-15R) α with a much higher affinity ($K_D \sim 0.05$ nM). IL-15R α can associate with the IL-2R β/γ complex to form an IL-15-specific, functional high-affinity ($\alpha\beta\gamma$) receptor (Minami et al., *Annu. Rev. Immunol.* (1993) 11:245-67; Giri et al., *J Leukoc Biol.* (1995) 5745:763-6; and Lehours et al., *Eur Cytokine Netw.* (2000) 11:207-15).

[0006] IL-21 is produced by activated CD4⁺ T cells, T-follicular helper cells, and natural killer T (NKT) cells (Spolski and Leonard, *Ann Rev Immunol.* (2008) 26:57008). IL-21 has been shown to exert pleiotropic effects on the proliferation, differentiation, and cytotoxicity of various classes of lymphoid cells. More recently, IL-21 has been further shown to play a crucial role in the differentiation of CD4⁺ T cells into T-helper 17 (TH₁₇) cells, a subset of T cells associated with development of inflammatory conditions and autoimmune diseases (Korn et al., *Nature* (2007) 448(7152):484-87; Nurieva et al., *Nature* (2007) 448(7152):480-83). The receptor complex of IL-21 is composed of the private chain IL-21R α and the common chain γC (or R γ). Human IL-21 binds to IL-21R α with a very high affinity ($K_D \sim 70$ pM; Zhang et al., *Biochem Biophys Res Commun.* (2003) 300(2):291-6), while binding to IL-21R γ with a relatively low affinity ($K_D \sim 160$ μ M).

[0007] The above cytokines, their muteins, and fusion proteins have been investigated for their potential as therapeutics, with recombinant IL-2 being the first cytokine approved for cancer therapy. However, these cytokine drugs and drug candidates have significant side effects. In addition, their *in vivo* half-lives are often short, even when presented as antibody-cytokine fusion molecules, potentially due to the “PK sink” formed by the receptors of the cytokines on the immune cells.

[0008] Thus, there remains a need to develop cytokine-based cancer therapeutics that are more tumor site-selective and have improved PK and efficacy, while causing fewer side effects.

SUMMARY OF THE INVENTION

[0009] The present disclosure provides a prodrug comprising a cytokine moiety, a masking moiety, and a carrier moiety, wherein the masking moiety binds to the cytokine moiety and inhibits a biological activity of the cytokine; the carrier moiety comprises an antigen-binding moiety that binds to an antigen expressed on the surface of a target cell; and the masking moiety is linked to the carrier moiety without a cleavable peptide linker (e.g., linked indirectly to the carrier moiety, through a non-cleavable peptide linker; or directly, without a peptide linker).

[0010] In some embodiments, the prodrug is activated by cells that express on the cell surface both the antigen and a receptor for the cytokine moiety. In some embodiments, the biological activity of the prodrug is increased by at least 2, 5, or 10 folds at a disease site comprising the cells as compared to a site not comprising the cells. In particular embodiments, the receptor for the cytokine moiety comprises two or more subunits.

[0011] In some embodiments, the antigen is selected from PD-1, PD-L1, CTLA-4, TIGIT, TIM-3, LAG-3, CD25, CD16a, CD16b, NKG2D, NKP44, NKP30, CD19, CD20, CD30, CD38, BCMA, and signal regulatory protein alpha (SIRP alpha, designated CD172a).

[0012] In some embodiments, the cytokine moiety comprises an IL-2 agonist polypeptide, an IL-7 agonist polypeptide, an IL-9 agonist polypeptide, an IL-15 agonist polypeptide, an IL-21 agonist polypeptide, an IL-1 α agonist polypeptide, an IL-1 β agonist polypeptide, an IL-4 agonist polypeptide, an IL-5 agonist polypeptide, an IL-6 agonist polypeptide, an IL-8 agonist polypeptide, an IL-10 agonist polypeptide, an IL-12 agonist polypeptide, an IL-17 agonist polypeptide, an IL-18 agonist polypeptide, an IL-22 agonist polypeptide, an IL-23 agonist polypeptide, an IL-31 agonist polypeptide, an IL-33 agonist polypeptide, an IL-36 agonist polypeptide, an interferon-alpha agonist polypeptide, an interferon gamma agonist polypeptide, a 4-1BB ligand, an OX-40 ligand, or a CD-40 ligand.

[0013] In some embodiments, the cytokine moiety comprises an IL-2 agonist polypeptide or an IL-15 agonist polypeptide and the masking moiety comprises an ECD of IL-2 receptor β (IL-2R β ECD) or a functional fragment thereof. In additional embodiments, the cytokine moiety comprises an IL-21 agonist polypeptide and the masking moiety comprises a Fab, a single chain Fv (scFv), or a single domain antibody against IL-21. In other embodiments, the cytokine moiety comprise an IL-2 agonist polypeptide and the masking moiety comprises a Fab, an scFv, or a single domain antibody against IL-2. In additional embodiments, the cytokine moiety

comprises an IL-15 agonist polypeptide, and the masking moiety comprises a Fab, an scFv, or a single domain antibody against IL-15. In other embodiments, the cytokine moiety comprises an IL-15 agonist polypeptide, and the masking moiety comprises a sushi domain of IL-15 receptor α (IL-15R α sushi domain).

[0014] In some embodiments, the cytokine moiety comprises an IL-21 agonist polypeptide comprising SEQ ID NO: 1, or an amino acid sequence at least 90% identical thereto. In other embodiments, the cytokine moiety comprises an IL-2 agonist polypeptide comprising SEQ ID NO: 6 or 62, or an amino acid sequence at least 95% identical thereto. In other embodiments, the cytokine moiety comprises an IL-15 agonist polypeptide comprising SEQ ID NO: 7, or an amino acid sequence at least 95% identical thereto.

[0015] In some embodiments, the masking moiety comprises an extracellular domain (ECD) of a receptor of the cytokine. In particular embodiments, the cytokine moiety comprises an IL-7 agonist polypeptide and the masking moiety comprises an ECD of IL-7 receptor α (IL-7R α ECD) or a functional analog thereof. In particular embodiments, the cytokine moiety is an IL-21 agonist polypeptide and the masking moiety comprises an ECD of IL-21 receptor α (IL-21R α ECD) or a functional analog thereof. In particular embodiments, the masking moiety comprises an IL-21R α ECD or a functional analog thereof comprising an amino acid sequence selected from SEQ ID NO: 12, 13, and 63-73, or at least 90% (e.g., at least 95%) identical thereto. In some embodiments, the masking moiety comprises an IL-2R β ECD or a functional analog thereof comprising SEQ ID NO: 11, or an amino acid sequence at least 95% identical thereto.

[0016] In some embodiments, the masking moiety comprises an scFv that binds the cytokine moiety and inhibits or interferes with the interaction between the cytokine moiety and its receptors. In particular embodiments, the masking moiety is an scFv that binds to human IL-21 and comprises an amino acid sequence of SEQ ID NO: 20 or 21. In particular embodiments, the masking moiety comprises an scFv that binds to IL-2 and inhibits or interferes with the interaction between IL-2 and IL-2R α , the interaction between IL-2 and IL-2R β , and/or the interaction between IL-2 and IL-2R γ , optionally wherein the scFv comprises the heavy chain and light chain CDRs of antibody 4E12B2D10. In some embodiments, the scFv comprises the heavy chain and light chain of antibody 4E12B2D10. In particular embodiments, the heavy chain and light chain amino acid sequences of 4E12B2D10 comprise SEQ ID NO: 60 and 61, respectively. In some embodiments, the masking moiety is an scFv that binds to IL-2 and comprises an amino

acid sequence of SEQ ID NO: 22 or 23, or at least 95% identical as that of SEQ ID NO: 22 or 23. In particular embodiments, the masking moiety comprises an scFv that binds to IL-15 and inhibits or interferes with the interaction between IL-15 and IL-2R β , and/or the interaction between IL-2 and IL-2R γ , optionally wherein the scFv comprises the heavy chain and light chain CDRs of anti-IL-15 antibody 146B7, 146H5, or 404E4, or optionally wherein the scFv comprises the heavy chain and light chain of anti-IL-15 antibody 146B7, 146H5, or 404E4, or optionally wherein the scFv comprises SEQ ID NO: 18 or 19. In some embodiments, an scFv or Fab IL-15 antagonist comprises heavy chain CDR1-3 of an anti-IL-15 antibody selected from 146B7, 146H5, and 404E4; and the light chain CDR1-3 of anti-IL-15 antibody selected from 146B7, 146H5, and 404E4 all of which are described in described in WO2003/017935A2.

[0017] In particular embodiments, the masking moiety comprises an scFv that binds to IL-21 and inhibits or interferes with the interaction between IL-21 and IL-21R α , and/or the interaction between IL-21 and IL-2R γ . In particular embodiments, the masking moiety comprises an scFv that binds to a cytokine selected from IL-2, IL-7, IL-9, IL-15, or IL-21 and inhibits or interferes with the interaction between the cytokine and IL-2R γ .

[0018] In some embodiments, the prodrug has a half-life in a non-human primate or a human that is at least 20 times, at least 50 times, at least 100 times, at least 150 times, or at least 200 times longer than that of the corresponding wild type cytokine.

[0019] In particular embodiments, the prodrug comprises two light chains with an amino acid sequence of SEQ ID NO: 44, and two heavy chain polypeptide chains whose amino acid sequences respectively comprise SEQ ID NOs: 24 and 25; SEQ ID NOs: 35 and 36; SEQ ID NOs: 37 and 36; SEQ ID NOs: 37 and 38; SEQ ID NOs: 39 and 41; or SEQ ID NOs: 42 and 43.

[0020] In particular embodiments, the prodrug comprises two light chains with an amino acid sequence of SEQ ID NO: 50, and two heavy chain polypeptide chains whose amino acid sequences respectively comprise SEQ ID NOs: 51 and 54; SEQ ID NOs: 51 and 55; SEQ ID NOs: 51 and 56; SEQ ID NOs: 52 and 54; SEQ ID NOs: 53 and 58; SEQ ID NOs: 53 and 59; or SEQ ID NOs: 52 and 57.

[0021] In some embodiments, the present disclosure provides a pharmaceutical composition comprising the prodrug of the present disclosure and a pharmaceutically acceptable excipient.

[0022] In some aspects, the present disclosure provides a polynucleotide or polynucleotides encoding the present prodrugs, expression vectors comprising the polynucleotides, and host cells

(e.g., mammalian host cells such as CHO, NS0 cells, and 293T cells) comprising the expression vectors. The present disclosure also provides methods of making the present prodrugs, comprising culturing the host cells under conditions that allow expression of prodrugs and isolating (also purifying) the prodrugs.

[0023] An Fc-based IL-21 prodrug molecule was not able to bind to cells such as Mino cells which expresses IL-21 receptors (**FIG. 2**), confirming that the cytokine moieties were masked. It was further shown that the masked molecules with PD-1 antibody as the carrier had minimum activities with the NK92 cells which do not express PD-1 (**FIG. 3**). It was a surprise to the inventors that the PD-1 antibody-based IL-21 prodrug molecules had meaningful activities with the Mino cells prior to activation (**FIGs. 4A and 4B**). Similar observations were made with an IL-2 prodrug (**FIGs. 6A and 6B**) and an IL-15 prodrug (**FIGs. 5A-C**). While not wishing to be bound by any theory, it is hypothesized that cis-binding of the PD-1 antibody to the antigen and the cytokine moiety to the cytokine receptors respectively, wherein both the antigen and the cytokine receptors are expressed on the same cell, led to the undoing of the masking effect of the masking moiety. It is therefore proposed that the prodrugs with the targeting moiety provides a significant selectivity to the cells expressing the antigens targeted by the carried moiety over the ones without the antigens. Surprisingly, it is feasible to construct prodrugs without the need of protease cleavage or removal of the masking moiety.

[0024] The present disclosure provides prodrugs which can be selectively activated at a disease site without the need of protease cleavage or removal of the masking moiety. In one aspect, the present disclosure provides novel cytokines prodrug comprising a cytokine moiety (a cytokine agonist polypeptide), a masking moiety, and a carrier moiety, wherein the masking moiety binds to the cytokine agonist polypeptide and inhibits an intended biological activity of the cytokine; the carrier moiety comprises an antigen binding moiety; the masking moiety is linked directly or indirectly to the carrier moiety through a non-cleavable peptide linker or without a peptide linker; and wherein the activity of the prodrug is higher in stimulating a cell which expresses both the antigen targeted by the carrier moiety and the receptor(s) of the cytokine than its activity in stimulating a cell which expresses the receptor(s) of the cytokine but not the antigen targeted by the carrier moiety.

[0025] In one aspect, the present disclosure provides novel cytokines prodrug comprising a cytokine moiety (a cytokine agonist polypeptide), a masking moiety, and a carrier moiety,

wherein the masking moiety binds to the cytokine agonist polypeptide and inhibits an intended biological activity of the cytokine; the carrier moiety comprises an antigen binding moiety; the masking moiety is linked directly or indirectly to the carrier moiety through a non-cleavable peptide linker or without a peptide linker; and wherein the prodrug is activated at a disease site where there are cells expressing both the antigen targeted by the carrier moiety and the receptor(s) of the cytokine, or a biological activity of the prodrug is increased by at least 2 folds, at least 5 folds, or at least 10 folds at a disease site where there are cells expressing both the antigen targeted by the carrier moiety and the receptor(s) of the cytokine.

[0026] In some embodiments, the prodrug does not contain any cleavable peptide linker.

[0027] In some embodiments, the carrier moiety comprises an antigen-binding moiety, wherein the antigen is expressed on an immune cell. In some embodiments, the carrier moiety comprises an antigen-binding moiety, wherein the antigen is selected from PD-1, PD-L1, CTLA-4, TIGIT, TIM-3, LAG-3, CD25, CD16a, and CD16b.

[0028] In some embodiments, the cytokine moiety comprises a cytokine selected from an IL-2 agonist polypeptide, an IL-7 agonist polypeptide, an IL-9 agonist polypeptide, an IL-15 agonist polypeptide, and an IL-21 agonist polypeptide. In some embodiments, the cytokine is selected from an IL-1 α agonist polypeptide, an IL-1 β agonist polypeptide, an IL-4 agonist polypeptide, an IL-5 agonist polypeptide, an IL-6 agonist polypeptide, an IL-8 agonist polypeptide, an IL-10 agonist polypeptide, an IL-12 agonist polypeptide, an IL-15 agonist polypeptide, an IL-17 agonist polypeptide, an IL-18 agonist polypeptide, an IL-22 agonist polypeptide, an IL-23 agonist polypeptide, an IL-31 agonist polypeptide, an IL-33 agonist polypeptide, an IL-36 agonist polypeptide, an Interferon-alpha agonist polypeptide, interferon gamma, 4-1BB ligand, OX-40 ligand, CD-40 ligand.

[0029] In some embodiments, the masking moiety is an extracellular domain (ECD) of a receptor of the cytokine. In some embodiments, the masking moiety comprises an antibody against the cytokine or a binding fragment of the antibody.

[0030] In some embodiments, the cytokine is an IL-21 agonist polypeptide; and wherein the masking moiety is the extracellular domain of IL-21 receptor α (IL-21R α ECD) or a functional analog thereof. In some embodiments, the cytokine is an IL-2 agonist polypeptide or an IL-15 agonist polypeptide; and wherein the masking moiety is the extracellular domain of IL-2 receptor β (IL-2R β ECD). In some embodiments, the cytokine is an IL-21 agonist polypeptide; and

wherein the masking moiety is a Fab, a single chain Fv (scFv) or a single domain antibody against IL-21.

[0031] In some embodiments, the cytokine is an IL-2 agonist polypeptide; and wherein the masking moiety is a Fab, a single chain Fv (scFv), or a single domain antibody against IL-2.

[0032] In some embodiments, the cytokine is an IL-15 agonist polypeptide; and wherein the masking moiety is a Fab, a single chain Fv (scFv), or a single domain antibody against IL-15. In some embodiments, the cytokine moiety comprises an IL-15 agonist polypeptide, wherein the chimeric molecule further comprises the sushi domain of IL-15 receptor α (IL-15R α sushi domain).

[0033] In some embodiments, the IL-21 agonist polypeptide comprises an amino acid sequence as SEQ ID NO: 1, or at least 90% identical as that of SEQ ID NO: 1. In some embodiments, the masking moiety is IL-21R α -ECD or a functional analog thereof, which comprises an amino acid sequence selected from SEQ ID NO: 12, 63-72, and 73, or at least 90% identical as that of SEQ ID NO: 12. In some embodiments, the masking moiety is an scFv which binds to human IL-21; and wherein the scFv comprises an amino acid sequence of SEQ ID NO: 20 or 21.

[0034] In some embodiments, the IL-2 agonist polypeptide comprises an amino acid sequence of SEQ ID NO: 6, or 61, or at least 95% identical as that of SEQ ID NO: 6, or 61. In some embodiments, the masking moiety comprises the IL-2R β -ECD or a functional analog thereof; wherein the IL-2-R β -ECD comprises an amino acid sequence of SEQ ID NO: 11 or at least 95% identical as that of SEQ ID NO: 11. In some embodiments, the masking moiety is an scFv which binds to IL-2, wherein the scFv interferes with the interaction between IL-2 and IL-2R α . In some embodiments, the masking moiety is an scFv which binds to IL-2, wherein the scFv interferes with the interaction between IL-2 and IL-2R β . In some embodiments, the masking moiety is scFv which binds to IL-2, wherein the scFv interferes with the interaction between IL-2 and IL-2R γ . In some embodiments, the masking moiety is scFv which binds to IL-2, wherein the scFv comprises the same heavy chain and light chain CDRs as that of hybridoma 4E12B2D10. In some embodiments, the masking moiety is an scFv which binds to IL-2, wherein the scFv comprises an amino acid sequence of SEQ ID NO: 22, 23, or at least 95% identical as that of SEQ ID NO: 22, 23.

[0035] In some embodiments, the IL-15 agonist polypeptide comprises an amino acid sequence of SEQ ID NO: 7, or at least 95% identical as that of SEQ ID NO: 7. In some embodiments, the IL-15 prodrug further comprises a sushi domain, which comprises an amino acid sequence of SEQ ID NO: 8, or at least 95% identical as that of SEQ ID NO: 8. In some embodiments, the masking moiety comprises the IL-2R β -ECD or a functional analog thereof; wherein the IL-2-R β -ECD comprises an amino acid sequence of SEQ ID NO: 11 or at least 95% identical as that of SEQ ID NO: 11. In some embodiments, the masking moiety is an scFv which binds to IL-15, wherein the scFv interferes with the interaction between IL-15 and IL-2R β . In some the embodiments, the masking moiety is an scFv which binds to IL-15, wherein the scFv interferes with the interaction between IL-15 and IL-2R γ . In some embodiments, the masking moiety is scFv which binds to IL-15, wherein the scFv comprises the same heavy chain and light chain CDRs as that of the IL-15 antibody 146B7, 146H5, or 404E4. In some embodiments, the masking moiety is scFv which binds to IL-15, wherein the scFv comprises an amino acid sequence of SEQ ID NO: 18 or 19.

[0036] In some embodiments, the human IL-21 agonist polypeptide comprises one or more mutations at position(s) selected from D18, Q19, E109, and K117 (numbering according to SEQ ID NO: 1). In particular embodiments, the human IL-21 agonist polypeptide comprises an amino acid sequence selected from SEQ ID NOs: 1, 2, 3, 4, and 5.

[0037] In some embodiments of the present prodrugs, the cytokine moieties and the masking moieties are fused to the carrier moieties through a noncleavable peptide linker, such as one selected from SEQ ID NOs: 27-34.

[0038] In some embodiments of the present prodrugs, the carrier moiety is an IgG1 antibody that comprises mutations L234A and L235A ("LALA") (EU numbering) or an IgG4 antibody that comprises mutations S228P/L234A/L235A (PAA). Other mutations which lead to the reduced Fc functionality, such as the ones described by Tam et al., *Antibodies* (2017) 6(12):1-34, can also be introduced when the Fc domain or the Fc of an antibody is used as the carrier moiety.

[0039] In particular embodiments, the carrier moiety is an antibody comprising knobs-into-holes mutations, wherein the cytokine moieties and the masking moieties are fused to the different heavy chains of the antibody. In certain embodiments, the knobs-into-holes mutations comprise a T366Y "knob" mutation on a polypeptide chain of the Fc domain or a heavy chain of the antibody, and a Y407T "hole" mutation in the other polypeptide of the Fc domain or the

other heavy chain of the antibody (EU numbering). In certain embodiments, the knobs-into-holes mutations comprise Y349C and/or T366W mutations in the CH3 domain of the “knob chain” and E356C, T366S, L368A, and/or Y407V mutations in the CH3 domain of the “hole chain” (EU numbering).

[0040] In some embodiments, the carrier moiety is an antibody or an antigen-binding fragment thereof that specifically binds to one or more antigens selected from guanyl cyclase C (GCC), carbohydrate antigen 19-9 (CA19-9), glycoprotein A33 (gpA33), mucin 1 (MUC1), carcinoembryonic antigen (CEA), insulin-like growth factor 1 receptor (IGF1-R), human epidermal growth factor receptor 2 (HER2), human epidermal growth factor receptor 3 (HER3), delta-like protein 3 (DLL3), delta-like protein 4 (DLL4), epidermal growth factor receptor (EGFR), glypican-3 (GPC3), c-MET, vascular endothelial growth factor receptor 1 (VEGFR1), vascular endothelial growth factor receptor 2 (VEGFR2), Nectin-4, Liv-1, glycoprotein NMB (GPNMB), prostate specific membrane antigen (PSMA), Trop-2, carbonic anhydrase IX (CA9), endothelin B receptor (ETBR), six transmembrane epithelial antigen of the prostate 1 (STEAP1), folate receptor alpha (FR- α), SLIT and NTRK-like protein 6 (SLITRK6), carbonic anhydrase VI (CA6), ectonucleotide pyrophosphatase/phosphodiesterase family member 3 (ENPP3), mesothelin, trophoblast glycoprotein (TPBG), CD19, CD20, CD22, CD33, CD40, CD56, CD66e, CD70, CD74, CD79b, CD98, CD123, CD138, CD352, CD47, signal-regulatory protein alpha (SIRP α), PD1, Claudin 18.2, Claudin 6, 5T4, BCMA, PD-L1, PD-1, fibroblast activation protein alpha (FAP α), the melanoma-associated chondroitin sulfate proteoglycan (MCSP), and epithelial cellular adhesion molecule (EPCAM). In specific embodiments, the carrier moiety is an antibody or fragment thereof which binds to FAP α or 5T4.

[0041] In another aspect, the present disclosure provides polynucleotides encoding the present prodrugs or fusion molecules, expression vectors comprising the polynucleotides, and host cells (e.g., mammalian host cells such as CHO, NS0 cells, and 293T cells) comprising the expression vectors. The present disclosure also provides methods for making the present prodrugs or fusion molecules, comprising culturing the mammalian host cells under conditions that allow expression of the prodrugs or fusion molecules and isolating the prodrugs or fusion molecules.

[0042] The present disclosure also provides a method of treating a cancer or an infectious disease or stimulating the immune system in a patient (e.g., human patient) in need thereof, comprising administering to the patient a therapeutically effective amount of the cytokine

prodrug, or the pharmaceutical composition of the present disclosure. The patient may have, for example, a viral infection (e.g., HIV, HBV, HCV, or HPV infection), or a cancer selected from the group consisting of breast cancer, lung cancer, pancreatic cancer, esophageal cancer, medullary thyroid cancer, ovarian cancer, uterine cancer, prostate cancer, testicular cancer, colorectal cancer, and stomach cancer. Also provided herein are cytokine prodrugs for use in treating a cancer or an infectious disease or stimulating the immune system in the present method; use of a cytokine prodrug for the manufacture of a medicament for treating a cancer or an infectious disease or stimulating the immune system in the present method; and articles of manufacture (e.g., kits) comprising one or more dosing units of the present cytokine prodrug.

[0043] Also provided herein are prodrugs for use in treating a cancer or an infectious disease or stimulating the immune system in the present method; use of a prodrug for the manufacture of a medicament for treating a cancer or an infectious disease or stimulating the immune system in the present method; and articles of manufacture (e.g., kits) comprising one or more dosing units of the present prodrugs.

[0044] Other features, objectives, and advantages of the invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating embodiments and aspects of the invention, is given by way of illustration only, not limitation. Various changes and modification within the scope of the invention will become apparent to those skilled in the art from the detailed description.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[0045] **FIGs. 1A-E** illustrate a heterodimeric cytokine prodrug wherein the carrier is an antibody. Figure 1A illustrates a prodrug wherein the carrier is a typical antibody with two light chains and two heavy chains. **FIG. 1B** illustrates a prodrug with a bispecific antibody as the carrier, wherein each antigen-binding moiety is monomeric with one antigen-binding moiety comprising a Fab domain and the second antigen-binding moiety comprising an scFv or a single domain antibody. **FIG. 1C** illustrates a prodrug with a bispecific antibody as the carrier, wherein each antigen-binding moiety is dimeric. **FIG. 1D** illustrates a prodrug with a dimeric Fc domain fused to a Fab domain on one of its polypeptide chains and to a cytokine peptide on the other polypeptide chain. The cytokine is fused via its N-terminus to a masking moiety. **FIG. 1E** illustrates a prodrug with a dimeric Fc domain fused to a Fab domain on one of its polypeptide

chains and to a cytokine peptide on the other polypeptide chain. The masking moiety is fused via its N-terminus to a cytokine peptide.

[0046] FIG. 2 shows the binding of PD-1 antibody and Fc-IL-21 fusion molecules and control molecules to Mino cells. The binding was analyzed by FACS.

[0047] FIG. 3 shows the results of a NK-92 cell-based biological activity assay of IL-21 prodrugs prior to and after activation by protease MMP2 and the control molecules. PW04-38 α PD1-IL21-a* and PW09-16 α PD1-IL21-a* are two batches of the same molecule, which is an anti-PD-1 antibody-based IL-21 with IL-21R α -ECD as the masking moiety; PW05-68 α PD1-IL21-scFv is a PD-1 antibody-based IL-21 prodrug with the scFv as the masking moiety. A first control molecule PW04-67 α PD1-IL21no mask is an anti-PD-1 antibody-IL-21 fusion molecule without a mask and having a wild-type IL-21. Another control molecule, PW09-02 α PD1-IL21mucinR9ER76A is an anti-PD-1 antibody-IL-21 fusion molecule without a mask and with an IL-21 mucin with R9E and R76A amino acid substitutions (numbering according to SEQ ID NO: 1). PW04-38 α PD1-IL21-a* activated and PW09-16 α PD1-IL21-a* activated are both the anti-PD-1 antibody-IL-21 wild type fusion molecule whose mask has been cleaved with a protease.

[0048] FIGS. 4A and 4B show the results of the Mino cell-based biological activity assay of PD-1-IL-21 prodrugs prior to and after activation by protease MMP2 and the control molecules. FIG. 4A shows the results after 72 hours of incubation of the cytokine fusion molecules with the Mino cells prior to the analysis. FIG. 4B shows the results after 120 hours of incubation prior to the analysis.

[0049] FIGS. 5A, 5B, and 5C show the results of Ki67 activation of the CD4⁺ T cells in PBMC after treated with an anti-PD-1 antibody (PD-1), an Fc-IL-15 fusion molecule masked with an scFv (215 β), anti-PD1-antibody-IL-15 fusion molecule masked with an scFv (215 γ), an Fc-IL-15 fusion molecule with no mask (215 β ref), and an PD1-antibody-IL-15 fusion molecule with no mask (PD1/IL15 mucin (M2)). FIG. 5A shows the results of Ki67 activation of CD4⁺ T cells without PD-1 expression. FIG. 5B shows the results of Ki67 activation of CD4⁺ T cells with PD-1 expression. FIG. 5C shows the EC₅₀ values of the testing articles with CD4⁺ T cells without and with PD-1 expression. It also shows the fold of changes of the EC₅₀ values between the CD4⁺ T cells without and with PD-1 expression.

[0050] FIGs. 6A and 6B show the results of Ki67 activation of the CD4⁺ T cells in PBMC after treatment with an anti-PD-1 antibody (PD-1), a negative control (an IgG1 antibody), and an anti-PD1-antibody-IL-2 mutein fusion masked with IL-2 receptor β extracellular domain (IL-2R β -ECD) (PD-1/IL2V*). FIG. 6A shows the results of Ki67 activation of CD4⁺ T cells without PD-1 expression. FIG. 6B shows the results of Ki67 activation of CD4⁺ T cells with PD-1 expression.

[0051] FIG. 7 illustrates a novel mechanism of prodrug activation through “cis-binding.” The target cells (right) express both the antigen targeted by the carrier moiety and the receptor for the cytokine moiety. Binding of the prodrug to the antigen on the cell surface brings the prodrug to the proximity of the cytokine receptor on the cell, allowing the cytokine receptor to compete effectively with and displace the masking moiety, leading to cellular signaling by the bound cytokine receptor. No protease cleavage of the masking moiety is necessary to remove the mask and activate the prodrug. On cells expressing the cytokine receptor but not the antigen (left), the cytokine moiety of the prodrug remains masked and inactive.

DETAILED DESCRIPTION OF THE INVENTION

[0052] As used herein and in the appended claims, the singular forms “a,” “or,” and “the” include plural referents unless the context clearly dictates otherwise.

[0053] Reference to “about” a value or parameter herein includes (and describes) variations that are directed to that value or parameter *per se*. For example, description referring to “about X” includes description of “X.” Additionally, use of “about” preceding any series of numbers includes “about” each of the recited numbers in that series. For example, description referring to “about X, Y, or Z” is intended to describe “about X, about Y, or about Z.”

[0054] The term “antigen-binding moiety” refers to a polypeptide or a set of interacting polypeptides that specifically bind to an antigen, and includes, but is not limited to, an antibody (e.g., a monoclonal antibody, a polyclonal antibody, a multi-specific antibody, a dual-specific or bispecific antibody, an anti-idiotypic antibody, or a bifunctional hybrid antibody) or an antigen-binding fragment thereof (e.g., a Fab, a Fab', a F(ab')₂, a Fv, a disulfide linked Fv, an scFv, a single domain antibody (dAb), or a diabody, a single chain antibody, and an Fc-containing polypeptide such as an immunoadhesin). In some embodiments, the antibody may be of any heavy chain isotype (e.g., IgG, IgA, IgM, IgE, or IgD) or subtype (e.g., IgG₁, IgG₂, IgG₃, or

IgG₄). In some embodiments, the antibody may be of any light chain isotype (e.g., kappa or lambda). The antibody may be human, non-human (e.g., from mouse, rat, rabbit, goat, or another non-human animal), chimeric (e.g., with a non-human variable region and a human constant region), or humanized (e.g., with non-human CDRs and human framework and constant regions). In some embodiments, the antibody is a derivatized antibody.

[0055] As used herein, the phrase “against,” “binding to,” or “specifically binding to” in the context of the interaction between two molecules is intended to mean that the binding has a K_D not more than 1000 nM (e.g., not more than 100, 10, or 1 nM; such as less than 1 nM, 1-10 nM, 10-100 nM, or 100-1000 nM) as measured by common methods in the art (e.g., surface plasmon resonance, ELISA, and the like).

[0056] The term “cytokine agonist polypeptide” refers to a wildtype cytokine, or an analog thereof. An analog of a wildtype cytokine has the same biological specificity (e.g., binding to the same receptor(s) and activating the same target cells) as the wildtype cytokine, although the activity level of the analog may be different from that of the wildtype cytokine. The analog may be, for example, a mutein (i.e., mutated polypeptide) of the wildtype cytokine, and may comprise at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten mutations relative to the wildtype cytokine.

[0057] The term “cytokine antagonist,” “masking moiety,” or “cytokine mask” refers to a moiety (e.g., a polypeptide) that binds to a cytokine and thereby inhibits the cytokine from binding to its receptor on the surface of a target cell and/or exerting its biological functions while being bound by the antagonist or mask. Examples of a cytokine antagonist or mask include, without limitations, a polypeptide derived from an extracellular domain of the cytokine’s natural receptor that makes contact with the cytokine.

[0058] The term “effective amount” or “therapeutically effective amount” refers to an amount of a compound or composition sufficient to treat a specified disorder, condition, or disease (e.g., ameliorate, palliate, lessen, and/or delay one or more of its symptoms). In reference to a disease such as cancer, an effective amount may be an amount sufficient to delay cancer development or progression (e.g., decrease tumor growth rate, and/or delay or prevent tumor angiogenesis, metastasis, or infiltration of cancer cells into peripheral organs), reduce the number of epithelioid cells, cause cancer regression (e.g., shrink or eradicate a tumor), and/or prevent or delay cancer occurrence or recurrence. An effective amount can be administered in one or more doses.

[0059] The term “functional analog” refers to a molecule that has the same biological specificity (e.g., binding to the same ligand) and/or activity (e.g., activating or inhibiting a target cell) as a reference molecule.

[0060] The term “fused” or “fusion” in reference to two polypeptide sequences refers to the joining of the two polypeptide sequences through a backbone peptide bond. Two polypeptides may be fused directly or through a peptide linker that is one or more amino acids long. A fusion polypeptide may be made by recombinant technology from a coding sequence containing the respective coding sequences for the two fusion partners, with or without a coding sequence for a peptide linker in between. In some embodiments, fusion encompasses chemical conjugation.

[0061] The term “pharmaceutically acceptable excipient” when used to refer to an ingredient in a composition means that the excipient is suitable for administration to a treatment subject, including a human subject, without undue deleterious side effects to the subject and without affecting the biological activity of the active pharmaceutical ingredient (API).

[0062] The term “prodrug” refers to a therapeutic molecule that is inactive or has low activity in vitro or in the circulation while its activity is increased at the site of a disease.

[0063] The term “subject” refers to a mammal and includes, but is not limited to, a human, a pet (e.g., a canine or a feline), a farm animal (e.g., cattle or horse), a rodent, or a primate.

[0064] As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, one or more of the following: alleviating one or more symptoms resulting from a disease, diminishing the extent of a disease, ameliorating a disease state, stabilizing a disease (e.g., preventing or delaying the worsening or progression of the disease), preventing or delaying the spread (e.g., metastasis) of a disease, preventing or delaying the recurrence of a disease, providing partial or total remission of a disease, decreasing the dose of one or more other medications required to treat a disease, increasing the patient’s quality of life, and/or prolonging survival. The methods of the present disclosure contemplate any one or more of these aspects of treatment.

[0065] It is to be understood that one, some, or all the properties of the various embodiments described herein may be combined to form other embodiments of the present invention. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described thereunder.

I. Cytokine Prodrugs

[0066] The present disclosure provides cytokine prodrugs that become more active at the site of a disease. The prodrugs comprise a cytokine agonist polypeptide (cytokine moiety) a carrier moiety, and a masking moiety. The cytokine moiety is linked, with or without a peptide linker (e.g., a noncleavable peptide linker), to the carrier moiety and is masked (bound) by the masking moiety. The masking moiety may be linked to the cytokine moiety or to the carrier moiety with or without a peptide linker (e.g., a noncleavable peptide linker). Alternatively, the cytokine moiety is linked, with or without a peptide linker (e.g., a noncleavable peptide linker), to the masking moiety, which in turn is linked, with or without a peptide linker (e.g., a noncleavable peptide linker), to the carrier moiety.

[0067] The carrier moiety comprises an antigen-binding domain that binds to an antigen on a target cell (e.g., a tumor cell or an immune cell). In some embodiments, the carrier comprises an antibody. *See, e.g., FIG. 1A*. In some embodiments, the carrier moiety comprises a bispecific antibody, which binds to two different antigens, as illustrated on **FIGs. 1B and 1C**.

[0068] The masking moiety may comprise, for example, an extracellular domain (ECD) of a cytokine receptor, where the ECD is linked to the cytokine moiety (*see, e.g., FIGs. 1D and 1E*) and/or to the carrier moiety through a non-cleavable linker (*see, e.g., FIGs. 1A-C and 1E*). The mask binds to and inhibits the cytokine moiety's biological functions. These prodrugs can engage the target cell via "cis-binding" of a cytokine receptor and an antigen expressed on the cell surface, leading to increased activity of the prodrug without cleavage and removal of the masking moiety. The cytokine moiety of the prodrugs may increase in activity at a target site (e.g., at a tumor site or the surrounding environment), where both the antigen targeted by the carrier and a receptor of the cytokine are expressed on the same cell. Examples of such prodrugs are illustrated in **FIGs. 1A-E** and the "cis-binding" mechanism of action is illustrated in **FIG. 7**.

A. Cytokine Moieties of the Prodrugs

[0069] In some embodiments, the cytokine moiety comprises an IL-2 agonist polypeptide. In some embodiments, the IL-2 agonist polypeptide is an IL-2 mutein having mutations R38S/F42A/Y45A/E62A or F42A/Y45A/L72G (numbering according to SEQ ID NO: 6). In some embodiments, the IL-2 mutein of the present disclosure may comprise a mutation at T3, D20, K35, R38, F42, F44, Y45, E62, E68, L72, A73, N88, N90, C125, and Q126 (numbering

according to SEQ ID NO: 6). In certain embodiments, the novel IL-2 mutein comprises mutations at R38, F42, Y45, and A73 (numbering according to SEQ ID NO: 6).

[0070] In some embodiments, the cytokine moiety of the prodrug comprises an IL-15 agonist polypeptide. In some embodiments, the human IL-15 polypeptide comprises one or more mutations selected from N1A, N1D, N4A, N4D, I6T, S7A, D8A, D8T, D8E, D8N, K10A, K10D, K11A, K11D, E46, V49, L45, S51, L52, D61A, D61N, T62L, T62A, E64A, E64L, E64K, E64Q, N65A, N65L, N65D, L66D, L66E, I67D, I67E, I68S, I68E, L69S, L69E, N72A, N72D, V63E, V63D, L66E, L66D, I67E, I67D, Q108E, N112A, N1D/D61N, N1D/E64Q, N4D/D61N, N4D/E64Q, D8N/D61N, D8N/E64Q, D61N/E64Q, E64Q/Q108E, N1D/N4D/D8N, D61N/E64Q/N65D, N1D/D61N/E64Q, N1D/Q108E, N1D/D61N/E64Q/Q108E, N4D/D61N/E64Q/Q108E, and D30N/E64Q/N65D (numbering according SEQ ID NO: 7). In some embodiments, the IL-15 prodrug further comprises a sushi domain. In some embodiments, the sushi domain comprises an amino acid sequence of SEQ ID NO: 8 or at least 95% identical as that of SEQ ID NO: 8.

[0071] In some embodiments, the cytokine moiety comprises an IL-21 agonist polypeptide. In some embodiments, the IL-21 agonist polypeptide may be a wildtype IL-21 polypeptide such as a wildtype human IL-21 (e.g., SEQ ID NO: 1), or an IL-21 mutein derived from a human IL-21, e.g., one with an amino acid sequence selected from SEQ ID NOs: 2-5. The IL-21 mutein may have significantly reduced affinity for IL-21R α or IL-21R α R γ , as compared to wild type IL-21. In some embodiments, the IL-21 mutein has a binding affinity for the high-affinity IL-2R α that is 5 times, 10 times, 20 times, 50 times, 100 times, 300 times, 500 times, 1,000 times, or 10,000 times lower compared to wild type IL-21. Unless otherwise indicated, all residue numbers in IL-21 and IL-21 muteins described herein are in accordance with the numbering in SEQ ID NO: 1.

B. Masking Moieties of the Prodrugs

[0072] The masking moiety, in the present prodrug may comprise a peptide or an antibody or antibody fragment that binds to the cytokine moiety in the prodrug, masking the cytokine moiety and inhibiting its biological functions. In some embodiments, the masking moiety is operationally linked to the rest of the prodrug through a non-cleavable peptide linker.

[0073] By way of example, the prodrug comprises an IL-2 agonist polypeptide and the masking moiety comprises a peptide or antibody, or antigen-binding fragment thereof, that binds IL-2 and interferes with the binding of the IL-2 to its cognate receptors. In some embodiments,

the masking moiety reduces biological activities of the IL-2 moiety while masked. In some embodiments, the IL-2 antagonist comprises an IL-2R β or IL-2R γ extracellular domain or its functional analog, such as one derived from human IL-2R β or human IL-2R γ (e.g., SEQ ID NO: 11 or 13). In some embodiments, the IL-2 masking moiety comprises a peptide identified through a peptide library screening. In some embodiments, the IL-2 masking moiety comprises an antibody or fragment thereof that blocks the binding of IL-2 or IL-2 muteins to an IL-2 receptor. In some embodiments, the masking moiety comprises an scFv of an antibody against IL-2. In some embodiments, the masking moiety comprises an amino acid sequence of SEQ ID NO: 22 or 23, or at least 95% identical as that of SEQ ID NO: 22 or 23.

[0074] By way of another example, the prodrug comprises an IL-21 agonist polypeptide and the masking moiety comprises a peptide or antibody, or antigen-binding fragment thereof, that binds IL-21 and interferes with the binding of the IL-21 to its cognate receptors. In some embodiments, the masking moiety reduces biological activities of the IL-21 moiety while masked. In some embodiments, the IL-21 antagonist comprises an IL-21R α or IL-21R γ extracellular domain or its functional analog, such as one derived from human IL-21R α or human IL-21R γ (e.g., SEQ ID NO: 12 or 13). In some embodiments, the IL-21 masking moiety comprises a peptide identified through a peptide library screening. In some embodiments, the IL-21 masking moiety comprises an antibody or fragment thereof that blocks the binding of IL-21 or IL-21 muteins to an IL-21 receptor. In some embodiments, the masking moiety comprises an scFv of an antibody against IL-21. In some embodiments, the masking moiety comprises an amino acid sequence of SEQ ID NO: 20 or 21, or at least 95% identical as that of SEQ ID NO: 20 or 21.

[0075] By way of another example, the prodrug comprises a masking moiety of any cytokine disclosed herein, including, but not limited to a cytokine selected from IL-7 agonist polypeptide, an IL-9 agonist polypeptide, an IL-15 agonist polypeptide, an IL-1 α agonist polypeptide, an IL-1 β agonist polypeptide, an IL-4 agonist polypeptide, an IL-5 agonist polypeptide, an IL-6 agonist polypeptide, an IL-8 agonist polypeptide, an IL-10 agonist polypeptide, an IL-12 agonist polypeptide, an IL-17 agonist polypeptide, an IL-18 agonist polypeptide, an IL-22 agonist polypeptide, an IL-23 agonist polypeptide, an IL-31 agonist polypeptide, an IL-33 agonist polypeptide, an IL-36 agonist polypeptide, an Interferon-alpha agonist polypeptide, an interferon gamma agonist polypeptide, a 4-1BB ligand, an OX-40 ligand, and a CD-40 ligand.

C. Carrier Moieties of the Prodrugs

[0076] The carrier moieties of the present prodrugs comprise an antigen-binding domain and optionally other domains. The carrier moiety improves the PK profiles such as serum half-life of the cytokine agonist polypeptide, and also targets the cytokine agonist polypeptide to a target site in the body, such as a tumor site.

1. Antigen-Binding Domains of Carrier Moieties

[0077] The carrier moiety comprises an antigen-binding domain and may be an antibody or an antigen-binding fragment thereof, or an immunoadhesin. In some embodiments, the antigen-binding carrier moiety is a full-length antibody with two heavy chains and two light chains, a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a Fv fragment, a disulfide linked Fv fragment, a single domain antibody, a nanobody, or a single-chain variable fragment (scFv). In some embodiments, the antigen-binding moiety is a bispecific antigen-binding moiety and can bind to two different antigens or two different epitopes on the same antigen. The antigen-binding moiety may provide additional and potentially synergetic therapeutic efficacy to the cytokine agonist polypeptide.

[0078] The cytokine agonist polypeptide and its mask may be fused to the N-terminus or C-terminus of the light chain(s) and/or heavy chain(s) of the antigen-binding moiety. By way of example, the IL-21 agonist polypeptide and its mask may be fused to the antibody heavy chain or an antigen-binding fragment thereof or to the antibody light chain or an antigen-binding fragment thereof. In some embodiments, one terminus of the IL-21 agonist polypeptide is fused to the C-terminus of one or both heavy chains of an antibody, and the IL-21 mask is fused to the other terminus of the IL-21 agonist polypeptide through a non-cleavable peptide linker. In some embodiments, the IL-21 agonist polypeptide is fused to the C-terminus of one of the heavy chains of an antibody, and the IL-21 mask is fused to the C-terminus of the other heavy chain of the antibody through a non-cleavable peptide linker, wherein the two heavy chains contain mutations that allow the specific pairing of the two different heavy chains.

[0079] Strategies for forming heterodimers are well known (*see, e.g.*, Spies et al., *Mol Imm.* (2015) 67(2)(A):95-106). For example, the two heavy chain polypeptides in the prodrug may form stable heterodimers through "knobs-into-holes" mutations. "Knobs-into-holes" mutations are made to promote the formation of the heterodimers of the antibody heavy chains and are commonly used to make bispecific antibodies (*see, e.g.*, U.S. Pat. 8,642,745). For example, the

Fc domain of the antibody may comprise a T366W mutation in the CH3 domain of the “knob chain” and T366S, L368A, and/or Y407V mutations in the CH3 domain of the “hole chain.” An additional interchain disulfide bridge between the CH3 domains can also be used, e.g., by introducing a Y349C mutation into the CH3 domain of the “knobs chain” and an E356C or S354C mutation into the CH3 domain of the “hole chain” (*see, e.g., Merchant et al., Nature Biotech* (1998) 16:677-81). In other embodiments, the antibody moiety may comprise Y349C and/or T366W mutations in one of the two CH3 domains, and E356C, T366S, L368A, and/or Y407V mutations in the other CH3 domain. In certain embodiments, the antibody moiety may comprise Y349C and/or T366W mutations in one of the two CH3 domains, and S354C (or E356C), T366S, L368A, and/or Y407V mutations in the other CH3 domain, with the additional Y349C mutation in one CH3 domain and the additional E356C or S354C mutation in the other CH3 domain, forming an interchain disulfide bridge (numbering always according to EU index of Kabat; Kabat et al., “Sequences of Proteins of Immunological Interest,” 5th ed., Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). Other knobs-into-holes technologies, such as those described in EP1870459A1, can be used alternatively or additionally. Thus, another example of knobs-into-holes mutations for an antibody moiety is having R409D/K370E mutations in the CH3 domain of the “knob chain” and D399K/E357K mutations in the CH3 domain of the “hole chain” (EU numbering).

[0080] In some embodiments, the antigen-binding moiety in the prodrug is an antibody that comprises L234A and L235A (“LALA”) mutations in its Fc domain. The LALA mutations eliminate complement binding and fixation as well as Fcγ dependent ADCC (*see, e.g., Hezareh et al. J. Virol.* (2001) 75(24):12161-8). In further embodiments, the LALA mutations are present in the antibody moiety in addition to the knobs-into-holes mutations.

[0081] In some embodiments, the antigen-binding moiety is an antibody that comprises the M252Y/S254T/T256E (“YTE”) mutations in the Fc domain. The YTE mutations allow the simultaneous modulation of serum half-life, tissue distribution and activity of IgG₁ (*see Dall’Acqua et al., J Biol Chem.* (2006) 281:23514-24; and Robbie et al., *Antimicrob Agents Chemother.* (2013) 57(12):6147-53). In further embodiments, the YTE mutations are present in the antibody in addition to the knobs-into-holes mutations. In particular embodiments, the antibody has YTE, LALA and knobs-into-holes mutations or any combination thereof.

[0082] In particular embodiments, the antigen-binding moiety is an antibody, or antigen-binding fragment thereof, that binds to an antigen on the surface of a target cell, such as an immune cell. Immune cells are well known in the art. Non-limiting examples of immune cells include T cells, NK cells, and macrophages. The antigen-binding moiety may have the ability to activate the immune cell and enhance its anti-cancer activity. The antibody may or may not have ADCC activity. The antigen-binding moiety may also be further conjugated to a cytotoxic drug. In some embodiments, the antigen-binding moiety may bind to PD-1, LAG-3, TIM-3, TIGIT, CTLA-4, or TGF-beta. In other embodiments, the antigen-binding moiety may bind to an antigen on the surface of a target cell, such as a tumor cell. For example, the antigen-binding moiety may bind to FAP alpha, 5T4, Trop-2, PD-L1, HER-2, EGFR, Claudin 18.2, DLL-3, GCP3, or carcinoembryonic antigen (CEA).

[0083] In some embodiments, the antigen-binding moiety binds to guanylyl cyclase C (GCC), carbohydrate antigen 19-9 (CA19-9), glycoprotein A33 (gpA33), mucin 1 (MUC1), insulin-like growth factor 1 receptor (IGF1-R), human epidermal growth factor receptor 2 (HER2), human epidermal growth factor receptor 3 (HER3), delta-like protein 3 (DLL3), delta-like protein 4 (DLL4), epidermal growth factor receptor (EGFR), glypican-3 (GPC3), c-MET, vascular endothelial growth factor receptor 1 (VEGFR1), vascular endothelial growth factor receptor 2 (VEGFR2), Nectin-4, Liv-1, glycoprotein NMB (GPNMB), prostates-specific membrane antigen (PSMA), Trop-2, carbonic anhydrase IX (CA9), endothelin B receptor (ETBR), six transmembrane epithelial antigen of the prostate 1 (STEAP1), folate receptor alpha (FR- α), SLIT and NTRK-like protein 6 (SLITRK6), carbonic anhydrase VI (CA6), ectonucleotide pyrophosphatase/phosphodiesterase family member 3 (ENPP3), mesothelin, trophoblast glycoprotein (TPBG), CD19, CD20, CD22, CD33, CD40, CD56, CD66e, CD70, CD74, CD79b, CD98, CD123, CD138, CD352, CD47, signal-regulatory protein alpha (SIRP α), Claudin 18.2, Claudin 6, BCMA, or EPCAM. In some embodiments, the antigen-binding moiety binds to an epidermal growth factor (EGF)-like domain of DLL3. In some embodiments, the antigen-binding moiety binds to a Delta/Serrate/Lag2 (DSL)-like domain of DLL3. In some embodiments, the antigen-binding moiety binds to an epitope located after the 374th amino acid of GPC3. In some embodiments, the antigen-binding moiety binds to a heparin sulfate glycan of GPC3. In some embodiments, the antigen-binding moiety binds to Claudin 18.2 and does not

bind to Claudin 18.1. In some embodiments, the antigen-binding moiety binds to Claudin 18.1 with at least 10 times weaker binding affinity than to Claudin 18.2.

[0084] Exemplary antigen-binding moieties include trastuzumab, rituximab, brentuximab, cetuximab, panitumumab, GC33 (or a humanized version thereof), anti-EGFR antibody mAb806 (or a humanized version thereof), anti-dPNAG antibody F598, and antigen-binding fragments thereof. In some embodiments, the antigen-binding moiety has at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to trastuzumab, rituximab, brentuximab, cetuximab, or panitumumab, GC33 (or a humanized version thereof), anti-EGFR antibody mAb806 (or a humanized version thereof), anti-dPNAG antibody F598, or a fragment thereof. In some embodiments, the antigen-binding moiety comprises an antibody heavy chain with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the antibody heavy chain of trastuzumab, rituximab, brentuximab, cetuximab, panitumumab, GC33 (or a humanized version thereof), anti-EGFR antibody mAb806 (or a humanized version thereof), anti-dPNAG antibody F598, or a fragment thereof. In some embodiments, the antigen-binding moiety has an antibody light chain with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to the antibody light chain of trastuzumab, rituximab, brentuximab, cetuximab, panitumumab, GC33 (or a humanized version thereof), anti-EGFR antibody mAb806 (or a humanized version thereof), anti-dPNAG antibody F598, or a fragment thereof. The antigen-binding moiety is fused to an IL-2 agonist polypeptide. In some embodiments, the antigen-binding moiety comprises the six complementarity-determining regions (CDRs) of trastuzumab, rituximab, brentuximab, cetuximab, panitumumab, GC33, anti-EGFR antibody mAb806, or anti-dPNAG antibody F598.

[0085] A number of CDR delineations are known in the art and are encompassed herein. A person of skill in the art can readily determine a CDR for a given delineation based on the sequence of the heavy or light chain variable region. The “Kabat” CDRs are based on sequence variability and are the most commonly used (Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). “Chothia” CDRs refer to the location of the structural loops (Chothia & Lesk, *J. Mol. Biol.* (1987) 196:901-917). The “AbM” CDRs represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular’s AbM antibody modeling software. The “Contact” CDRs are based on an analysis of the available complex crystal structures. The residues from each of these CDRs are noted below in Table 1, in

reference to common antibody numbering schemes. Unless otherwise specified herein, amino acid numbers in antibodies refer to the Kabat numbering scheme as described in Kabat et al., *supra*, including when CDR delineations are made in reference to Kabat, Chothia, AbM, or Contact schemes. Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a framework region (FR) or CDR of the variable domain. For example, a heavy chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (e.g., residues 82a, 82b, and 82c, etc. according to Kabat) after heavy chain FR residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a “standard” Kabat numbered sequence.

Table 1. CDR Delineations According to Various Schemes

CDR	Kabat	AbM	Chothia	Contact
VL-CDR1	L24—L34	L24—L34	L26—L32	L30—L36
VL-CDR2	L50—L56	L50—L56	L50—L52	L46—L55
VL-CDR3	L89—L97	L89—L97	L91—L96	L89—L96
VH-CDR1 (Kabat nos.)	H31—H35B	H26—H35B	H26—H32	H30—H35B
VH-CDR1 (Chothia nos.)	H31—H35	H26—H35	H26—H32	H30—H35
VH-CDR2	H50—H65	H50—H58	H53—H55	H47—H58
VH-CDR3	H95—H102	H95—H102	H95—H101	H93—H101

[0086] In some embodiments, the CDRs are “extended CDRs,” and encompass a region that begins or terminates according to a different scheme. For example, an extended CDR can be as follows: L24—L36, L26—L34, or L26—L36 (VL-CDR1); L46—L52, L46—L56, or L50—L55 (VL-CDR2); L91—L97 (VL-CDR3); H47—H55, H47—H65, H50—H55, H53—H58, or H53—H65 (VH-CDR2); and/or H93—H102 (VH-CDR3).

[0087] In some embodiments, the antigen-binding moiety binds to PDL1, and comprises a light chain having an amino acid sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 45, or a fragment thereof, and a heavy chain having an amino acid sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%

identity to SEQ ID NO: 46, or a fragment thereof. In some embodiments, the antigen-binding domain comprises CDR1, CDR2, and CDR3 from SEQ ID NO: 45, and CDR1, CDR2, and CDR3 from SEQ ID NO: 46.

[0088] In some embodiments, the antigen-binding moiety binds to PD-1, and comprises a light chain having an amino acid sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 44, or a fragment thereof, and a heavy chain having an amino acid sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 47, or a fragment thereof. In some embodiments, the antigen-binding domain comprises CDR1, CDR2, and CDR3 from SEQ ID NO: 44, and CDR1, CDR2, and CDR3 from SEQ ID NO: 47.

[0089] In some embodiments, the antigen-binding moiety binds to PD-1, and comprises a light chain having an amino acid sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 48, or a fragment thereof, and a heavy chain having an amino acid sequence with at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 49, or a fragment thereof. In some embodiments, the antigen-binding domain comprises CDR1, CDR2, and CDR3 from SEQ ID NO: 48, and CDR1, CDR2, and CDR3 from SEQ ID NO: 49.

[0090] In some embodiments, the antigen-binding moiety comprises one, two, or three antigen-binding domains. For example, the antigen-binding moiety is bispecific and binds to two different antigens selected from the group consisting of CD3, HER2, HER3, EGFR, 5T4, FAP alpha, Trop-2, GPC3, VEGFR2, Claudin 18.2 and PD-L1. In some embodiments, the bispecific antigen-binding moiety binds to two different epitopes of HER2. In other embodiments, the antigen-binding moiety is bispecific and binds to two different antigens selected from PD-1, PD-L1, CTLA-4, CD47, CD3, TIM-3, LAG-3 and TIGIT.

2. Other Domains of Carrier Moieties

[0091] The carrier moieties may also comprise other domains that are not antigen-binding. For example, an antibody Fc domain (e.g., a human IgG₁, IgG₂, IgG₃, or IgG₄ Fc), a polymer (e.g., PEG), an albumin (e.g., a human albumin) or a fragment thereof, or a nanoparticle can be used.

[0092] By way of example, the cytokine agonist polypeptide (e.g., IL-2, IL-21, IL-5, or any cytokine disclosed herein) and its antagonist may be fused to an antibody Fc domain, forming an Fc fusion protein. In some embodiments, the cytokine agonist polypeptide is fused (directly or

through a peptide linker) to the C-terminus or N-terminus of one of the Fc domain polypeptide chains, and the cytokine mask is fused to the corresponding C-terminus or N-terminus of the other Fc domain polypeptide chain through a cleavable peptide linker, wherein the two Fc domain polypeptide chains contain mutations that allow the specific pairing of the two different Fc chains. In some embodiments, the Fc domain comprises the holes-into-holes mutations described above. In further embodiments, the Fc domain may comprise also the YTE and/or LALA mutations described above.

[0093] The carrier moiety of the prodrug may comprise an albumin (e.g., human serum albumin) or a fragment thereof. In some embodiments, the carrier moiety comprises an albumin fragment (e.g., a human serum albumin fragment) that is about 10 or more, 20 or more, 30 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, 100 or more, 120 or more, 140 or more, 160 or more, 180 or more, 200 or more, 250 or more, 300 or more, 350 or more, 400 or more, 450 or more, 500 or more, or 550 or more amino acids in length. In some embodiments, the albumin fragment is between about 10 amino acids and about 584 amino acids in length (such as between about 10 and about 20, about 20 and about 40, about 40 and about 80, about 80 and about 160, about 160 and about 250, about 250 and about 350, about 350 and about 450, or about 450 and about 550 amino acids in length). In some embodiments, the albumin fragment includes the Sudlow I domain or a fragment thereof, or the Sudlow II domain or the fragment thereof.

D. Linker Components of the Prodrugs

[0094] The cytokine agonist polypeptide may be fused to the carrier moiety with or without a peptide linker. The peptide linker is noncleavable. In some embodiments, the peptide linker is selected from SEQ ID NOs: 27-34. In particular embodiments, the peptide linker comprises the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO: 30).

[0095] The masking moiety may be fused to the cytokine moiety or to the carrier through a non-cleavable linker or without a peptide linker.

II. Pharmaceutical Compositions

[0096] Pharmaceutical compositions comprising the prodrugs and muteins (i.e., the active pharmaceutical ingredient or API) of the present disclosure may be prepared by mixing the API having the desired degree of purity with one or more optional pharmaceutically acceptable

excipients (*see, e.g., Remington's Pharmaceutical Sciences*, 16th Edition., Osol, A. Ed. (1980)) in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable excipients (or carriers) are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers containing, for example, phosphate, citrate, succinate, histidine, acetate, or another inorganic or organic acid or salt thereof; 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 sucrose, 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 polyethylene glycol (PEG).

[0097] Buffers are used to control the pH in a range which optimizes the therapeutic effectiveness, especially if stability is pH dependent. Buffers are preferably present at concentrations ranging from about 50 mM to about 250 mM. Suitable buffering agents for use with the present invention include both organic and inorganic acids and salts thereof, such as citrate, phosphate, succinate, tartrate, fumarate, gluconate, oxalate, lactate, and acetate. Additionally, buffers may comprise histidine and trimethylamine salts such as Tris.

[0098] Preservatives are added to retard microbial growth, and are typically present in a range from 0.2% - 1.0% (w/v). Suitable preservatives for use with the present invention include octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium halides (e.g., chloride, bromide, iodide), benzethonium chloride; thimerosal, phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol, 3-pentanol, and m-cresol.

[0099] Tonicity agents, sometimes known as “stabilizers” are present to adjust or maintain the tonicity of liquid in a composition. When used with large, charged biomolecules such as proteins and antibodies, they are often termed “stabilizers” because they can interact with the

charged groups of the amino acid side chains, thereby lessening the potential for inter- and intra-molecular interactions. Tonicity agents can be present in any amount between 0.1% to 25% by weight, or more preferably between 1% to 5% by weight, taking into account the relative amounts of the other ingredients. Preferred tonicity agents include polyhydric sugar alcohols, preferably trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol and mannitol.

[0100] Non-ionic surfactants or detergents (also known as “wetting agents”) are present to help solubilize the therapeutic agent as well as to protect the therapeutic protein against agitation-induced aggregation, which also permits the formulation to be exposed to shear surface stress without causing denaturation of the active therapeutic protein or antibody. Non-ionic surfactants are present in a range of about 0.05 mg/ml to about 1.0 mg/ml, preferably about 0.07 mg/ml to about 0.2 mg/ml.

[0101] Suitable non-ionic surfactants include polysorbates (20, 40, 60, 65, 80, etc.), polyoxamers (184, 188, etc.), PLURONIC[®] polyols, TRITON[®], polyoxyethylene sorbitan monoethers (TWEEN[®]-20, TWEEN[®]-80, etc.), laurmacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. Anionic detergents that can be used include sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents include benzalkonium chloride or benzethonium chloride.

[0102] The choice of pharmaceutical carrier, excipient or diluent may be selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions may additionally comprise any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s) or solubilizing agent(s).

[0103] There may be different composition/formulation requirements dependent on the different delivery systems. By way of example, pharmaceutical compositions useful in the present invention may be formulated to be administered using a mini-pump or by a mucosal route, for example, as a nasal spray or aerosol for inhalation or ingestible solution, or parenterally in which the composition is formulated by an injectable form, for delivery, by, for example, an intravenous, intramuscular or subcutaneous route.

[0104] In some embodiments, the pharmaceutical composition of the present disclosure is a lyophilized protein formulation. In other embodiments, the pharmaceutical composition may be an aqueous liquid formulation.

III. Methods of Treatment

[0105] The cytokine prodrug and fusion molecules can be used to treat a disease, depending on the antigen bound by the antigen-binding domain. In some embodiments, the cytokine prodrug or fusion molecule is used to treat cancer. In some embodiments, the cytokine prodrug or fusion molecule is used to treat an infection.

[0106] In some embodiments, a method of treating a disease (such as cancer, a parasitic infection, a viral infection, or a bacterial infection) in a subject comprises administering to the subject an effective amount of a cytokine prodrug or a fusion molecule.

[0107] In some embodiments, the cancer is a solid cancer. In some embodiments, the cancer is a blood cancer or a solid tumor. Exemplary cancers that may be treated include, but are not limited to, leukemia, lymphoma, kidney cancer, bladder cancer, urinary tract cancer, cervical cancer, brain cancer, head and neck cancer, skin cancer, uterine cancer, testicular cancer, esophageal cancer, liver cancer, colorectal cancer, stomach cancer, squamous cell carcinoma, prostate cancer, pancreatic cancer, lung cancer such as non-small cell lung cancer, cholangiocarcinoma, breast cancer, and ovarian cancer.

[0108] In some embodiments, the cytokine prodrug or fusion molecule is used to treat a viral infection. In some embodiments, the virus causing the viral infection is hepatitis C virus (HCV), hepatitis B virus (HBV), human immunodeficiency virus (HIV), or human papilloma virus (HPV). In some embodiments, the antigen-binding moiety binds to a viral antigen.

[0109] In some embodiments, the cytokine prodrug or fusion molecule is used to treat a bacterial infection such as sepsis. In some embodiments, the bacteria causing the bacterial infection is drug-resistant bacteria. In some embodiments, the antigen-binding moiety binds to a bacterial antigen.

[0110] Generally, dosages and routes of administration of the present pharmaceutical compositions are determined according to the size and conditions of the subject, according to standard pharmaceutical practice. In some embodiments, the pharmaceutical composition is administered to a subject through any route, including orally, transdermally, by inhalation,

intravenously, intra-arterially, intramuscularly, direct application to a wound site, application to a surgical site, intraperitoneally, by suppository, subcutaneously, intradermally, transcutaneously, by nebulization, intrapleurally, intraventricularly, intra-articularly, intraocularly, intracranially, or intraspinally. In some embodiments, the composition is administered to a subject intravenously.

[0111] In some embodiments, the dosage of the pharmaceutical composition is a single dose or a repeated dose. In some embodiments, the doses are given to a subject once per day, twice per day, three times per day, or four or more times per day. In some embodiments, about 1 or more (such as about 2, 3, 4, 5, 6, or 7 or more) doses are given in a week. In some embodiments, the pharmaceutical composition is administered weekly, once every 2 weeks, once every 3 weeks, once every 4 weeks, weekly for two weeks out of 3 weeks, or weekly for 3 weeks out of 4 weeks. In some embodiments, multiple doses are given over the course of days, weeks, months, or years. In some embodiments, a course of treatment is about 1 or more doses (such as about 2, 3, 4, 5, 7, 10, 15, or 20 or more doses).

[0112] Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. Exemplary methods and materials are described below, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure. In case of conflict, the present specification, including definitions, will control. Generally, nomenclature used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics, analytical chemistry, synthetic organic chemistry, medicinal and pharmaceutical chemistry, and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used in the art. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Throughout this specification and embodiments, the words "have" and "comprise," or variations such as "has," "having," "comprises," or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. It is understood that aspects and variations of the invention described herein include "consisting" and/or "consisting essentially

of” aspects and variations. All publications and other references mentioned herein are incorporated by reference in their entirety. Although a number of documents are cited herein, this citation does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

IV. Exemplary Embodiments

[0113] Further, particular embodiments of the present disclosure are described as follows. These embodiments are intended to illustrate the compositions and methods described in the present disclosure and are not intended to limit the scope of the present disclosure.

1. A prodrug comprising a cytokine moiety, a masking moiety, and a carrier moiety, wherein:
 - a) the masking moiety binds to the cytokine moiety and inhibits an intended biological activity of the cytokine;
 - b) the carrier moiety comprises an antigen binding moiety which binds to an antigen expressed on the surface of a cell; and
 - c) the masking moiety is linked directly or indirectly to the carrier moiety through a non-cleavable peptide linker or without a peptide linker;and wherein the activity of the prodrug is higher in stimulating a cell which expresses both the antigen targeted by the carrier moiety and the receptor(s) of the cytokine than its activity in stimulating a cell which expresses the receptor(s) of the cytokine but not the antigen targeted by the carrier moiety.
2. A prodrug comprising a cytokine moiety, a masking moiety, and a carrier moiety, wherein:
 - a) the masking moiety binds to the cytokine moiety and inhibits an intended biological activity of the cytokine;
 - b) the carrier moiety comprises an antigen binding moiety which binds to an antigen expressed on the surface of a cell; and
 - c) the masking moiety is linked directly or indirectly to the carrier moiety through a non-cleavable peptide linker or without a peptide linker;and wherein the prodrug is activated at a disease site where there are cells expressing both the antigen targeted by the carrier moiety and the receptor(s) of the cytokine, or a biological

activity of the prodrug is increased by at least 2 folds, at least 5 folds, or at least 10 folds at a disease site where there are cells expressing both the antigen targeted by the carrier moiety and the receptor(s) of the cytokine.

3. The prodrug of embodiment 1 or 2, wherein the receptor of the cytokine moiety comprises two or more subunits.
4. The prodrug of embodiment 1 or 2, wherein the carrier comprises an antigen-binding moiety, wherein the antigen is expressed on an immune cell.
5. The prodrug of embodiment 1 or 2, wherein the carrier moiety comprises an antigen-binding moiety, wherein the antigen is selected from PD-1, PD-L1, CTLA-4, TIGIT, TIM-3, LAG-3, CD25, CD16a, CD16b, NKG2D, NKP44, NKP30, CD19, CD20, CD38, and BCMA.
6. The prodrug of any of embodiments 1-5, wherein the cytokine moiety comprises a cytokine selected from an IL-2 agonist polypeptide, an IL-7 agonist polypeptide, an IL-9 agonist polypeptide, an IL-15 agonist polypeptide, and an IL-21 agonist polypeptide.
7. The prodrug of any of embodiments 1-5, wherein the cytokine is selected from an IL-1 α agonist polypeptide, an IL-1 β agonist polypeptide, an IL-4 agonist polypeptide, an IL-5 agonist polypeptide, an IL-6 agonist polypeptide, an IL-8 agonist polypeptide, an IL-10 agonist polypeptide, an IL-12 agonist polypeptide, an IL-17 agonist polypeptide, an IL-18 agonist polypeptide, an IL-22 agonist polypeptide, an IL-23 agonist polypeptide, an IL-31 agonist polypeptide, an IL-33 agonist polypeptide, an IL-36 agonist polypeptide, an Interferon-alpha agonist polypeptide, an interferon gamma agonist polypeptide, a 4-1BB ligand, an OX-40 ligand, and a CD-40 ligand.
8. The prodrug of any of embodiments 1-7, wherein the masking moiety is an extracellular domain (ECD) of a receptor of the cytokine.
9. The prodrug of any of embodiments 1-6, wherein the cytokine is an IL-7 agonist polypeptide; and wherein the masking moiety is the extracellular domain of IL-7 receptor α (IL-7R α ECD) or a functional analog thereof.
10. The prodrug of any of embodiments 1-6, wherein the cytokine is an IL-21 agonist polypeptide; and wherein the masking moiety is the extracellular domain of IL-21 receptor α (IL-21R α ECD) or a functional analog thereof.

11. The prodrug of any of embodiments 1-6, wherein the cytokine is an IL-2 agonist polypeptide or an IL-15 agonist polypeptide; and wherein the masking moiety is the extracellular domain of IL-2 receptor β (IL-2R β ECD).
12. The prodrug of any of embodiments 1-6, wherein the cytokine is an IL-21 agonist polypeptide; and wherein the masking moiety is a Fab, a single chain Fv (scFv) or a single domain antibody against IL-21.
13. The prodrug of any of embodiments 1-6, wherein the cytokine is an IL-2 agonist polypeptide; and wherein the masking moiety is a Fab, a single chain Fv (scFv), or a single domain antibody against IL-2.
14. The prodrug of any of embodiments 1-6, wherein the cytokine is an IL-15 agonist polypeptide; and wherein the masking moiety is a Fab, a single chain Fv (scFv), or a single domain antibody against IL-15.
15. The prodrug of any of embodiments 1-6, 11 and 14, wherein the cytokine moiety comprises an IL-15 agonist polypeptide, wherein the fusion molecule further comprises the sushi domain of IL-15 receptor α (IL-15R α sushi domain).
16. The prodrug of any of embodiment 10 or 12, wherein the IL-21 agonist polypeptide comprises an amino acid sequence as SEQ ID NO: 1, or at least 90% identical as that of SEQ ID NO: 1.
17. The prodrug of embodiment 10 or 16, wherein the masking moiety is IL-21R α -ECD or a functional analog thereof, which comprises an amino acid sequence selected from SEQ ID NO: 12, 63-72, and 73, or at least 90% identical as that of SEQ ID NO: 12.
18. The prodrug of embodiment 12 or 16, wherein the masking moiety is an scFv which binds to human IL-21; and wherein the scFv comprises an amino acid sequence of SEQ ID NO: 20 or 21.
19. The prodrug of embodiment 11 or 13, wherein the IL-2 agonist polypeptide comprises an amino acid sequence of SEQ ID NO: 6, or 61, or at least 95% identical as that of SEQ ID NO: 6, or 61.
20. The prodrug of embodiment 11 or 14, wherein the IL-15 agonist polypeptide comprises an amino acid sequence of SEQ ID NO: 7, or at least 95% identical as that of SEQ ID NO: 7.

21. The prodrug of embodiment 11, 19, or 20, wherein the masking moiety comprises the IL-2R β -ECD or a functional analog thereof; wherein the IL-2-R β -ECD comprises an amino acid sequence of SEQ ID NO: 11 or at least 95% identical as that of SEQ ID NO: 11.
22. The prodrug of any of embodiments 6, 13 or 19, wherein the masking moiety is an scFv which binds to IL-2, wherein the scFv inhibits or interferes with the interaction between IL-2 and IL-2R α , the interaction between IL-2 and IL-2R β , and/or the interaction between IL-2 and IL-2R γ .
23. The prodrug of any of embodiments 6, 14, 15 or 20, wherein the masking moiety is an scFv which binds to IL-15, wherein the scFv inhibits or interferes with the interaction between IL-15 and IL-2R β , and/or IL-2 and IL-2R γ .
24. The prodrug of any of embodiments 6, 12 or 16, wherein the masking moiety is an scFv which binds to IL-21, wherein the scFv inhibits or interferes with the interaction between IL-21 and IL-21R α , and/or IL-21 and IL-2R γ .
25. The prodrug of embodiment 6, wherein the masking moiety is an scFv which binds to a cytokine selected from IL-2, IL-7, IL-9, IL-15, or IL-21; wherein the scFv inhibits or interferes with the interaction between the cytokine and IL-2R γ ; and wherein the prodrug has a half-life in a non-human primate or a human that is at least 20 times, at least 50 times, at least 100 times, at least 150 times, or at least 200 times longer than that of the corresponding wild type cytokine.
26. A prodrug which comprises a carrier moiety, a cytokine moiety, and a masking moiety; wherein:
- a) the cytokine moiety is selected from an IL-2 agonist polypeptide, an IL-7 agonist polypeptide, an IL-9 agonist polypeptide, an IL-15 agonist polypeptide, or an IL-21 agonist polypeptide;
 - b) the masking moiety is an scFv which binds to the cytokine moiety;
 - c) the scFv inhibits or interferes with the interaction between the cytokine and IL-2R γ ; and
 - d) wherein the prodrug has a half-life in a non-human primate or a human that is at least 20 times, at least 50 times, at least 100 times, at least 150 times, or at least 200 times longer than that of the wild type cytokine.
27. The prodrug of any of embodiments 22-25, wherein the scFv binds to the cytokine with a K_D of 1-10 nM.

28. The prodrug of any of embodiments 22-25, wherein the scFv binds to the cytokine with a K_D of 10-100 nM.
29. The prodrug of any of embodiments 22-25, wherein the scFv binds to the cytokine with a K_D of 100-1000 nM.
30. The prodrug of embodiment 13 or 19, wherein the masking moiety is scFv which binds to IL-2, wherein the scFv comprises the same heavy chain and light chain CDRs as that of hybridoma 4E12B2D10.
31. The prodrug of embodiment 13 or 19, wherein the masking moiety is scFv which binds to IL-2, wherein the scFv comprises an amino acid sequence of SEQ ID NO: 22 or 23, or at least 95% identical as that of SEQ ID NO: 22 or 23.
32. The prodrug of embodiment 14 or 20, wherein the masking moiety is scFv which binds to IL-15, wherein the scFv comprises the same heavy chain and light chain CDRs as that of the IL-15 antibody 146B7, 146H5, or 404E4.
33. The prodrug of embodiment 14 or 20, wherein the masking moiety is scFv which binds to IL-15, wherein the scFv comprises an amino acid sequence of SEQ ID NO: 18 or 19.
34. The prodrug of any of the embodiments 1-32, wherein the prodrug does not contain a cleavable peptide linker.
35. The prodrug of embodiment 1, wherein the prodrug comprises two light chains with an amino acid sequence of SEQ ID NO: 44, and two heavy chain polypeptide chains whose amino acid sequences respectively comprise
- SEQ ID NOs: 35 and 36,
 - SEQ ID NOs: 37 and 36,
 - SEQ ID NOs: 37 and 38,
 - SEQ ID NOs: 39 and 41, or
 - SEQ ID NOs: 42 and 43.
36. The prodrug of embodiment 1, wherein the prodrug comprises two light chains with an amino acid sequence of SEQ ID NO: 50, and two heavy chain polypeptide chains whose amino acid sequences respectively comprise
- SEQ ID NOs: 51 and 54,
 - SEQ ID NOs: 51 and 55,
 - SEQ ID NOs: 51 and 56,

- SEQ ID NOs: 52 and 54,
SEQ ID NOs: 53 and 58,
SEQ ID NOs: 53 and 59, or
SEQ ID NOs: 52 and 57.
37. A pharmaceutical composition comprising the prodrug of any one of the embodiments 1-36 and a pharmaceutically acceptable excipient.
38. A polynucleotide or polynucleotides encoding the prodrug of any one of embodiments 1-36.
39. An expression vector or vectors comprising the polynucleotide or polynucleotides of embodiment 38.
40. A host cell comprising the vector(s) of embodiment 39.
41. A method of making the prodrug of any one of embodiments 1-36, comprising culturing the host cell of embodiment 46 under conditions that allow expression of the prodrug, wherein the host cell is a mammalian cell, and isolating the prodrug.
42. A method of treating a cancer, an autoimmune disease, or an infectious disease, or stimulating the immune system, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of embodiment 37.
43. A prodrug of any one of embodiments 1-36, for use in treating a cancer, an autoimmune disease or an infectious disease, or stimulating the immune system, in a patient in need thereof.
44. Use of a prodrug of any one of embodiments 1-36, for the manufacture of a medicament for treating a cancer, an autoimmune disease, or an infectious disease, or stimulating the immune system, in a patient in need thereof.
45. The method of embodiment 41, the prodrug for use of claim 42 or the fusion molecule for use of claim 43, or the use of claim 44, wherein the patient has HIV, HBV, HCV, or HPV infection; an autoimmune disease selected from lupus, type I diabetes, psoriasis, dermatomyositis, GvHD, or rheumatoid arthritis; or a cancer selected from the group consisting of breast cancer, lung cancer, pancreatic cancer, esophageal cancer, medullary thyroid cancer, ovarian cancer, uterine cancer, prostate cancer, testicular cancer, colorectal cancer, and stomach cancer.

46. A prodrug which comprises a carrier moiety, a cytokine moiety, and a masking moiety; wherein:

a) the cytokine moiety is selected from an IL-2 agonist polypeptide, an IL-7 agonist polypeptide, an IL-9 agonist polypeptide, an IL-15 agonist polypeptide, or an IL-21 agonist polypeptide;

b) the masking moiety is an scFv which binds to the cytokine moiety;

c) the scFv inhibits or interferes with the interaction between the cytokine and IL-2R γ ; and

d) wherein the prodrug has an area under curve (AUC) in a non-human primate or a human that is at least 20 times, at least 50 times, at least 100 times, at least 150 times, or at least 200 times longer than that of the wild type cytokine.

[0114] In order that this invention may be better understood, the following examples are set forth. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the invention in any manner.

EXAMPLES

[0115] The materials and methods for the experiments described in Examples 1 and 2 are as follows.

SEC-HPLC Analysis

[0116] SEC-HPLC was carried out using an Agilent 1100 Series of HPLC system with a TSKgel G3000SWXL column (7.8 mmID $\times$ 30cm, 5 μ m particle size) ordered from Tosoh Bioscience. A sample of up to 100 μ l was loaded. The column was run with a buffer containing 200 mM K₃PO₄, 250 mM KCl, pH 6.5. The flow rate was 0.5 ml/min. The column was run at room temperature.

Proteolytic Treatment

The proteases, human MMP2, human MMP9, mouse MMP2 and mouse MMP9 were purchased from R&D systems. The protease digestion was carried out by incubating 10 μ g-50 μ g of prodrugs with 1 μ g of human MMP2, human MMP9, mouse MMP2 or mouse MMP9 in the

HBS buffer (20 mM HEPES, 150 mM NaCl₂, pH 7.4) containing 2 mM CaCl₂ and 10 μ M ZnCl₂ at 37°C for 12 hours.

Cell-Based Activity Assay

[0117] The prodrugs prior to the protease digestion and the control samples were tested by the cell-based activity assay. Briefly, NK92 cells were grown in the RPMI-1640 medium supplemented with L-glutamine, 10% fetal bovine serum, 10% non-essential amino acids, 10% sodium pyruvate, and 55 μ M beta-mercaptoethanol. NK92 cells were non-adherent and maintained at 1×10^5 - 1×10^6 cells/ml in medium with 100 ng/ml of IL-2. Generally, cells were split twice per week. For bioassays, it was best to use cells no less than 48 hours after passage. IL-21 functional activity was determined by culturing NK92 cells at 5×10^4 cells/well with serial dilutions of the samples in the presence of a constant amount of IL-2 for 2 days. Supernatants were then assayed for interferon- γ by ELISA.

Mino IL-21 Viability Assay

[0118] The Mino cell viability assay is carried out following the protocol below:

- a) Perform serial dilutions of test articles in 50 μ L assay medium (RPMI 1640, 10% Fetal Bovine Serum, NEAA, sodium pyruvate, 55 μ M b-mercaptoethanol) in 96 well tissue culture plate.
- b) Add 20,000 Mino cells/well in 50 μ L assay medium.
- c) Culture for 3 or 5 days.
- d) Add 100 μ L/well Cell Titer Glo (Promega). Cell Titer-Glo provides a measure of cell viability by providing a quantitative assessment of ATP.
- e) Measure luminescence.

Ki67 Activation Assay with PBMC Primary Cells

[0119] Human PBMCs were stimulated with anti-CD3 antibody, OKT3 at 100 ng/mL for 2 days, followed by three-time washes, then were rested for 3 days in regular cell culture medium in 37°C, 5% CO₂ incubator. After that stimulated/rested PBMCs were seeded at 200K cells/well of 96-well plates and were treated with test articles as indicated at various concentrations for 5 days before subject to cell staining and flow cytometry analysis for Ki67 in PD-1⁺CD4⁺ and PD-1-CD4⁺ cell populations (all Abs used for cell staining were purchased from BD).

Example 1: Construction of Anti-PD-1 Antibody-IL-21 Prodrug Fusion Molecules

[0120] An anti-PD-1 antibody-based IL-21 prodrug was constructed with two identical light chains (with an amino acid sequence as shown in SEQ ID NO: 44). A first heavy chain polypeptide chain (with an amino acid sequence as shown in SEQ ID NO: 42) and a second heavy chain polypeptide chain (with an amino acid sequence as shown SEQ ID NO: 76). The molecule was transiently expressed and purified (lot# PW04-38).

[0121] A second PD-1 antibody-based IL-21 prodrug with the scFv as the masking moiety was also expressed and purified (Lot #PW05-68).

[0122] In addition, as a control, the anti-PD-1 antibody-IL-21 fusion molecule without the mask was also expressed and purified (Lot #PW05-67).

[0123] Further, a second control, the anti-PD-1 antibody-IL-21 mutein (R9ER76A) fusion molecule without the mask was also expressed and purified (Lot #PW09-02).

Example 2: Biological Activities of Anti-PD-1 Antibody-IL-21 Prodrug Fusion Molecules

[0124] The binding of the prodrug molecules and several control molecules to the Mino cells were tested by FACS. The results on **FIG. 2** show that both the PD-1 antibody and the Fc-IL-21 fusion molecule were able to bind to the Mino cells, indicating that the Mino cells express both the PD-1 and the receptors for IL-21. The results showed that both of the Fc-based IL-21 prodrug molecules had no binding to the cells, suggesting the IL-21 cytokine moieties have been masked by the corresponding masking moiety. However, the PD-1 antibody-based IL-21 prodrug molecules and fusion molecules were able to bind to the Mino cells.

[0125] Cell-based activity of the molecules were assessed using NK92 cells, a natural killer (NK) cell line. The results are shown in **FIG. 3**. The data show that without activation, the prodrug molecule with the IL-21 α ECD as the masking moiety (Lot# PW04-38) had minimum activity while the prodrug with an scFv as the masking moiety (Lot# PW05-68) had an activity ~1000 times lower than the one without the masking moiety (PW04-67). The data show that the bioassay activities of the prodrugs were significantly enhanced by the protease MMP2 treatment.

[0126] To test the tumor killing activity of the fusion molecules, Mino cells were used. Mino cells are a mantle cell lymphoma cell line that expresses both PD-1 and receptors for IL-21 (Harington et al., *Leuk Lymphoma* (2019) 60(10):2498-2507 and Gelebart et al., *Leukemia* (2009) 23:1836-1846). The Mino viability assay results are shown in **FIGs. 4A** and **4B**. Surprisingly, the anti-PD-1 antibody-based IL-21 prodrugs (Lots# PW04-38 and PW05-68) had

significant activities prior to activation, while the control molecule (PD-1 antibody-IL-21R9E/R76A fusion molecule, Lot# PW09-02) had no or little activity. The results demonstrate that the Anti-PD-1 IL-21 fusion molecule was activated through “cis-binding,” i.e., through binding to both the PD-1 and the IL-21 receptor(s). Cis-binding of the PD-1 antibody to the PD-1 antigen on the cell surface and the cytokine to its receptor on the same cell surface may have unraveled the masking effect of the masking moiety. It is therefore expected that prodrugs without cleavable peptide linker may be “activated” in a disease site such as a tumor because the local immune cells may express both the antigen targeted by the carrier and the receptor(s), which bind the cytokine moiety (e.g., IL-21).

Example 3: Construction of Anti-PD-1 Antibody-IL-15 Prodrug Fusion Molecules

[0127] A series of anti-PD-1 antibody-based IL-15 prodrugs were constructed, where the IL-15 moiety (i) was masked with an scFv 215 β , (ii) was masked an scFv 215 γ , (iii) had no mask (215 β Ref), or (iv) had mutations but no mask (PD1/IL15 mutein (M2)). The anti-PD-1 antibody in these prodrugs comprises two identical light chains with an amino acid sequence of SEQ ID NO: 44 and two identical heavy chains with an amino acid sequence of SEQ ID NO: 47.

[0128] The Fc-based prodrug 215 β is a heterodimer comprising amino acid sequence ID NOs: 16 and 17.

[0129] The anti-PD-1 antibody-based prodrug 215 γ comprises two identical light chains (SEQ ID NO: 44), a first heavy chain fusion polypeptide chain with an amino acid sequence of SEQ ID NO: 37 and a second heavy chain fusion polypeptide chain with an amino acid sequence of SEQ ID NO: 77.

[0130] 215 β Ref is an IL-15 mutein(D30N/E64Q/N65D)-Fc fusion molecule.

[0131] PD1/IL15 mutein (M2) is an anti-PD-1-antibody fused with an IL-15 mutein wherein the IL-15 agonist comprises mutations E46G, V49R, E64Q, D30N, and N1G.

[0132] All the samples were expressed by CHO cells and purified using a Protein A affinity chromatography followed by additional chromatography steps.

Example 4: Biological Activities of Anti-PD-1 Antibody-IL-15 Prodrug Fusion Molecules

[0133] The IL-15 prodrugs were assessed for their ability to stimulate Ki67 expression in PBMC cells obtained from human donors. **FIGs. 5A- 5C** show the results of Ki67 activation of the CD4⁺ T cells in PBMC after treatment. **FIG. 5A** shows the results of Ki67 activation of

CD4⁺ T cells without PD-1 expression. **FIG. 5B** shows the results of Ki67 activation of CD4⁺ T cells with PD-1 expression. **FIG. 5C** shows the EC₅₀ values of the testing articles with CD4⁺ T cells without and with PD-1 expression. It also showed the fold of changes of the EC₅₀ values between the CD4⁺ T cells without and with PD-1 expression. Surprisingly, the data showed that 215γ had significantly higher Ki67 activity with CD4⁺ cells expressing PD-1 than the ones without PD-1 expression, indicating that the prodrug 215γ was able to be activated without protease cleavage when it was acting with the cells expressing both the antigen PD-1 and the receptors for the cytokine IL-15.

Example 5: Anti-PD-1 Antibody-IL-2 Prodrug Fusion Molecules

[0134] An anti-PD-1 antibody-based IL-2 prodrugs was similarly constructed. The prodrug, PD-1/IL-2v*, comprises two identical light chains (SEQ ID NO: 44) and two heavy chain fusion polypeptides (SEQ ID NOs: 24 and 25, respectively). The IL-2 moiety is an IL-2 mutein, and the mask in the prodrug is an IL-2 receptor β extracellular domain. The IL-2 prodrug was assessed for its ability to stimulate Ki67 expression in PBMC cells obtained from human donors.

[0135] **FIGs. 6A** and **6B** show the results of Ki67 activation in the CD4⁺ T cells from PBMC after treatment with an anti-PD-1 antibody (PD-1), a negative control, or PD-1/IL-2v*. The negative control was an IgG1 antibody against human Claudin 18.2. All the samples were expressed by CHO cells and purified using a Protein A affinity chromatography followed by additional chromatography steps. **FIG. 6A** shows the results of Ki67 activation in CD4⁺ T cells without PD-1 expression. **FIG. 6B** shows the results of Ki67 activation in CD4⁺ T cells with PD-1 expression. Surprisingly, the data showed that the prodrug PD-1/IL2V* had significantly higher Ki67-inducing activity on CD4⁺ cells expressing PD-1 than on those without PD-1 expression. These results indicate that PD-1/IL-2v* was able to be activated without protease cleavage when it was acting on cells expressing both the antigen PD-1 and the receptors for the cytokine IL-2.

[0136] Collectively the above data indicate that the cytokine prodrugs were able to be activated at a site where there were cells were expressing both the receptors for the cytokines and the antigens targeted by the carrier moiety. It was surprising that the prodrugs with carriers having antigen-binding moieties were able to be activated without protease cleavage. While not wishing to be bound by theory, we expect that the antigen-binding domain of the carrier moiety targets

the prodrug molecules to the surface of the cells expressing the antigens and this allows the cytokine receptors on the cell surface to compete effectively with the mask moiety of the prodrug. This process culminates in protease cleavage-free activation of the prodrug via displacement of the masking moiety the cytokine receptors on the cell surface, as illustrated in **FIG. 7**.

[0137] Cells like exhausted Teff cells express both the antigen (e.g., PD-1) and the receptors for the cytokine (e.g., IL-2R β and IL-2R γ). Exhausted Teff cells are in general localized at tumor microenvironment but in the normal tissues. This differential distribution of the cells expressing the antigens and the cytokine receptors provides the disease site-specific activation of the prodrugs. Such target specificity would also result in enhanced safety for the cytokine therapeutics.

SEQUENCES

SEQ ID NO: 1 - human IL-21

QGQDRHMIRM RQLIDIVDQL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT
 GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLER FKSLLQKMIH
 QHLSSRTHGS EDS

SEQ ID NO: 2 - IL-21 Mutein A

QGQDRHMIRM RQLIDIVAQL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT
 GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLER FKSLLQKMIH
 QHLSSRTHGS EDS

SEQ ID NO: 3 - IL-21 Mutein B

QGQDRHMIRM RQLIDIVKQL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT
 GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLER FKSLLQKMIH
 QHLSSRTHGS EDS

SEQ ID NO: 4 - IL-21 Mutein C

QGQDRHMIRM RQLIDIVDQL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT
 GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLRR FKSLLQKMIH
 QHLSSRTHGS EDS

SEQ ID NO: 5 - IL-21 Mutein D

QGQDRHMIRM RQLIDIVDKL KNYVNDLVPE FLPAPEDVET NCEWSAFSCF QKAQLKSANT
 GNNERIINVS IKKLKRKPPS TNAGRRQKHR LTCPSCDSYE KKPPKEFLRR FKSLLQKMIH
 QHLSSRTHGS EDS

SEQ ID NO: 6 - Human IL-2

APTSSSTKKT QLQLEHLLLD LQMILNGINN YKNPKLTRML TFKFYMPKKA TELKHLQCLE
 EELKPLEEVL NLAQSKNFHL RPRDLISNIN VIVLELKGSE TTFMCEYADE TATIVEFLNR
 WITFCQSIIS TLT

SEQ ID NO: 7 - Human IL-15

NWVNVISDLK KIEDLIQSMH IDATLYTESD VHPSCKVTAM KCFLLELQVI SLESGDASIH
 DTVENLIILA NNSLSSNGNV TESGCKECEE LEEKNIKEFL QSFVHIVQMF INT

SEQ ID NO: 8 - Human IL-15 R α sushi domain

ITCPPPMSVE HADIWVKSYS LYSRERYICN SGFKRKAGTS SLTECVLNKA TNVAHWTPPS
 LKCIRDPAIV HQRPA

SEQ ID NO: 9 - Human IL-7

DCDIEGKD GK QYESVLMVSI DQLDSMKEI GSNCNNEFN FFKRHICDAN KEGMFLFRAA
 RKLQFLKMN STGDFDLHLL KVSEGTILL NCTGQVKGRK PAALGEAQPT KSLEENKSLK
 EQKKLNDLCF LKRLLEIKT CWNKILMGTK EH

SEQ ID NO: 10 - Human IL-9

QGCPTLAGIL DINFLINKMQ EDPASKCHCS ANVTSCCLCG IPSDNCTRPC FSERLSQMTN
 TTMQTRYPLI FSRVKKSVEV LKNNKCPYFS CEQPCNQTTA GNALTFLKSL LEIFQKEKMR
 GMRGKI

SEQ ID NO: 11 -IL-2R β ECD

AVNGTSQFTC FYNSTRANISC VWSQDQALQD TSCQVHAWPD RRRWNQTCLE LPVSQASWAC
 NLILGAPDSQ KLTTVDIVTL RVLCREGVRW RVMAIQDFKP FENLRLMAPI SLQVVHVETH
 RCNISWEISQ ASHYFERHLE FEARTLSPGH TWEEAPLLTL KQKQEWICLE TLTPDTQYEF
 QVRVKPLQGE FTTWSPWSQP LAFRTKPAAL GKDT

SEQ ID NO: 12 - IL-21R α ECD (source: uniprot.org/uniprot/Q9HBE5)
 CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
 SDYEDPAFYM LKGLQYELQ YRNRGDPWAV SPRRKLISVD SRSVSLLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 13 - Human IL-21R γ ECD
 LNTTILTPNG NEDTTADFFL TTMPDLSLV STLPLPEVQC FVFNVEYMNC TWNSSSEPQP
 TNLTLHYWYK NSDNDKVQKC SHYLFSEEIT SGCQLQKKEI HLYQTFVVLQ QDPREPRRQA
 TQMLKLQNLV IPWAPENLTL HKLSESQLEL NWNRRFLNHC LEHLVQYRTD WDHWSWTEQSV
 DYRHKFSLPS VDGQKRYTFR VRSRFPNPLCG SAQHWSSEWSH PIHWGSNTSK ENPFLFALEA

SEQ ID NO: 14 - IL-7 α receptor ECD (Source: <https://www.uniprot.org/uniprot/P16871>)
 ESGYAQNGDL EDAELDDYSF SCYSQLEVNG SQHSLTCAFE DPDVNITNLE FEICGALVEV
 KCLNFRKLQE IYFIETKKFL LIGKSNICVK VGEKSLTCKK IDLTTIVKPE APFDLSVVYR
 EGANDFVVT FNTSHLQKKYV KVLMDHVAYR QEKDENKWTN VNLSSTKLTL LQRKLQPAAM
 YEIKVRSIPD HYFKGFWSEW SPSYYFRTPE INNSSGEMD

SEQ ID NO: 15 - IL-9 α receptor ECD (source:)
 SVTGEGQGPR SRTFTCLTNN ILRIDCHWSA PELGQGSSPW LLFTSNQAPG GTHKCILRGS
 ECTVVLPEEA VLVPDSNFTI TFHHCMMSGRE QVSLVDPEYL PRRHVKLDPD SDLQSNISSG
 HCILTWSISP ALEPMTTLLS YELAFKKQEE AWEQAQHRDH IVGVTWLILE AFELDPGFIH
 EARLRVQMAT LEDDVVEER YTGQWSEWSQ PVCFQAPQRQ GPLIPPWGW

SEQ ID NO: 16 Fc-scFv2 against IL-15
 DKTHTCPPCP APEAAGGPSV FLFPPKPKDT LYITREPEVT CVVVDVSHED PEVKFNWYVD
 GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK
 GQPREPQVCT LPPSREEMTK NQVSLSCAVK GFYPSDIAVE WESNGQPENN YKTTTPVLDS
 DGSFFLVSKL TVDKSRWQQG NVFSCSVME ALHNHYTQKS LSLSPGAGGG GSVHMPGLFL
 GPRQARVVNG GGGGSGGGGS EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK
 PGQAPRLLIY GASRRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ RYGSSHTFGQ
 GTKLEISGGG GSGGGGSGGG GSEVQLVQSG AEVKKPGESL KISCKVSGYF FTTYWIGWVR
 QMPGKGLEYM GIIYPGDSDT RYSPSFQGV TISADKSIST AYLQWSSLKA SDTAMYYCAR
 GGNWNCFDYW GQGTLVTVSS

SEQ ID NO: 17 Fc-IL-15 N65D
 DKTHTCPPCP APEAAGGPSV FLFPPKPKDT LYITREPEVT CVVVDVSHED PEVKFNWYVD
 GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK
 GQPREPQVYT LPPCREEMTK NQVSLWCLVK GFYPSDIAVE WESNGQPENN YKTTTPVLDS
 DGSFFLYSKL TVDKSRWQQG NVFSCSVME ALHNHYTQKS LSLSPGAGGG GSGGGGSGGG
 GSITCPPPMS VEHADIVVKS YSLYSRERYI CNSGFKRKAG TSSLTECVLN KATNVAHWT
 PSLKCIIRGGG GSGGGGSGGG SAAGGGGSGG GSGGGGGSNW VNVISDLKKI EDLIQSMHID
 ATLYTESDVH PSCKVTAMKC FLLELQVISL ESGDASIHDT VEDLIILANN SLSSNGNVTE
 SGCKECEELE EKNIKEFLQS FVHIVQMFN TS

SEQ ID NO: 18 - Anti-IL-15 scFv1 (*italic: VH and VL*)

EVQLVQSGAE VKKPGESLKI SCKVSGYFFT TYWIGWVRQM PGKGLEYMGI IYPGDSSTRY
 SPSFQGGQVTI SADKSISTAY LQWSSLKASD TAMYYCARGG NWNCFDYWGQ GTLVTVSSGG
 GSGGGGSGG GSGGIVLTQS PGTLSLSPGE RATLSCRASQ SVSSSYLAWY QQKPGQAPRL
 LIYGASRRAT GIPDRFSGSG SGTDFTLTIS RLEPEDFAVY YCQRYGSSHT FGQGTKLEIS

SEQ ID NO: 19 - Anti-IL-15 scFv2 (*italic: VL and VH*)

EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASRRATGIP
 DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ RYGSSHTFGQ GTKLEISGGG GSGGGGSGGG
 GSEVQLVQSG AEVKKPGESL KISCKVSGYF FTTYWIGWVR QMPGKGLEYM GIIYPGDSST
 RYSPSFQGGQV TISADKSIS TAYLQWSSLK ASDTAMYYCA RGGNWNCFDY WGQGLTVTVSS

SEQ ID NO: 20 - Anti-IL-21 scFv1 (*italic: VH and VL*)

QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAF IWYDGS DKYY
 ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDG DSSDWYGDY FGMDVWGQGT
 TVTVSSGGGG SGGGGSGGGG SEIVLTQSPG TSLSPGERA TLSCRASQSV SSSYLAWYQQ
 KPGQAPRLLI YGASSRATGI PDRFSGSGSG TDFTLTISRLE EPEDFAVYYC QQYGSWTFGQ
 GTKVEIK

SEQ ID NO: 21 - Anti-IL-21 scFv2 (*italic: VL and VH*)

EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASSRATGIP
 DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSWTFGQG TKVEIKGGGG SGGGGSGGGG
 SQVQLVESGG GVVQPGRSLR LSCAASGFTF SSYGMHWVRQ APGKLEWVA FIWYDGS DKY
 YADSVKGRFT ISRDNSKNTL YLQMNSLRAE DTAVYYCARD GDSSDWYGDY YFGMDVWGQG
 TTVTVSS

SEQ ID NO: 22 - Anti-IL-2 scFv1 (underlined: HCDR1-3 and LCDR1-3;
italic: VH and VL)

QVQLVQSGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPIFGTANY
AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARVD RYYNWNYFLG SFDYWGQGT
VTVSSGGGGG GGGGSGGGG SYVLTQPPSV SVAPGKTARI TCGGNNIRSK SVHWYQQKPG
QAPVVVIYYD SDRPSGIPER ISGSNSGNTA TLTISRVEAG DEADYFCQVW DSSSDHHVFG
 GGTKLTVL

SEQ ID NO: 23 - Anti-IL-2 scFv2 (underlined: LCDR1-3 and HCDR1-3;
italic: VL and VH)

SYVLTQPPSV SVAPGKTARI TCGGNNIRSK SVHWYQQKPG QAPVVVIYYD SDRPSGIPER
ISGSNSGNTA TLTISRVEAG DEADYFCQVW DSSSDHHVFG GGTKLTVLGG GGSGGGSGGG
GSQVQLVQSG AEVKKPGSSV KVSCKASGGT FSSYAIWVR QAPGQGLEWM GGIIPIFGTA
NYAQKFQGRV TITADESTST AYMELSSLRS EDTAVYYCAR VDRYYNWNFY LGSFDYWGQG
 TLTVTVSS

SEQ ID NO: 24 - PD1-HC - IL-2V (CX3.58.1)

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGS KRY
 ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGT LVT VSSASTKGPS
 VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
 VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPKP
 KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
 VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPCQEE MTKNQVSLWC
 LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
 MHEALHNHYT QKSLSLSLGK GGGSGGGGGS GGGGSAPASS STKKTQLQLE HLLLDLQML

NGINNYKNPK LTSMLTAKFA MPKKATELKH LQCLEEALKP LEEVLNLAQS KNFHLRPRDL
ISNINVIVLE LKGSETTFMC EYADETATIV EFLNRWITFS QSIISTLT

SEQ ID NO: 25 - PD1-HC - IL-2R β -ECD (CX3.58.3)

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTILVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTPEVTCVVVDVSD QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VCTLPSSQEE MTKNQVSLSC
AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLV SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGK GGGSGGPLGV RGGGGSGGGG SAVNGTSQFT CFYNSRANIS
CVWSQDQALQ DTSCQVHAWP DRRRWNTCE LLPVSQASWA CNLILGAPDS QKLTTVDIVT
LRVLCREGRV WRVMAIQDFK PFENLRLMAP ISLQVVHVET HRCNISWEIS QASHYFERHL
EFEARTLSPG HTWEEAPLLT LKQKQEWICL ETLTPDTQYE FQVRVKPLQG EFTTWSWPSQ
PLAFRTKPAA LGKDT

SEQ ID NO: 26 - PD1-HC - IL-21R α ECD WITH NON-CLEAVABLE PEPTIDE LINKER

MGVKVLEFALI CIAVAEAQVQ LVESGGGVVQ PGRSLRLDCK ASGITFSNSG MHWVRQAPGK
GLEWVAVIY DGSKRYYADS VKGRFTISRDN SKNTLFLQM NSLRAEDTAV YYCATNDYDW
GQGTILVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV
HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP
APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK
PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT
LPSSQEEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTTPVLDS DGSFFLYSRL
TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LLSLSLGAGGG GSGGGGSAAG GGGSGGGGSC
PDLVCYTDYL QTVICILEMW NLHPSTLTLT WQDQYEELKD EATSCSLHRS AHNATHATYT
CHMDVFHFMA DDIFSVNITD QSGNYSQECG SFLLAESIKP APPFNVTVTF SGQYNISWRS
DYEDPAFYML KGKLQYELQY RNRGDPWAVS PRRKLISVDS RSVSLPLEF RKDSSYELQV
RAGPMPGSSY QGTWSEWSDP VIFQTQSEEL KE

SEQ ID NO: 27-34 Peptide Linker

(GGGS)_n (SEQ ID NO: 27), wherein n = 1, 2, 3, and 4

GGGS (SEQ ID NO: 28)

GGGSGGGG (SEQ ID NO: 29)

GGGSGGGSGGGG (SEQ ID NO: 30)

GGGSGGGGSXXGGGSGGGG (SEQ ID NO: 31), X = A or N

GGGSGGGSGGGGSXXGGGSGGGG (SEQ ID NO: 32), X = A or N

GGGSGGGSGGGGSXXGGGSGGGSGGGG (SEQ ID NO: 33), X = A or N

GGGSGGGGXGGGYGGGS (SEQ ID NO: 34), X = S, A or N, and Y = A or N

SEQ ID NO: 35 - PD1-HC - IL-2V

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTILVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTPEVTCVVVDVSD QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLA (GGGS)_{n1}X₁X₂ (GGGS)_{n2}APX_{aa3}SSSTKKTQL QLEHLLLDLQ
MILNGINNYK NPX_{aa35}LTRMLTX_{aa42}KFX_{aa45}M PKKATELKH LQCLEEELKP

LEEVLNX_{aa72}X_{aa73}QSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW
ITFX_{aa125}QSIIS TLT

wherein Xaa3 is N or A; wherein Xaa125 is A or S; wherein Xaa35 is selected from K and N; wherein Xaa42 is selected from A, G, S, T, Q, E, N, D, R, and K; wherein Xaa45 is selected from A, G, S, T, Q, E, N, D, R, and K; wherein Xaa72 is selected from A, G, S, T, Q, E, N, D, R, and K; wherein Xaa73 is selected from A and T; wherein $n_1 = 0, 1, 2$, or 3; $n_2 = 0, 1, 2$, or 3; and X_1 is an amino acid Alanine or deleted; and X_2 is an amino acid Alanine or deleted.

SEQ ID NO: 36 - PD1-HC - IL-2R β -ECD

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNV DH KPSNTKV DDKR VESKYGPPCP PCPAPEFLGG PSVFLFPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA (GGGS)_{n1}X₁X₂ (GGGS)_{n2}AV NGTSQFTCFY NSRANISCVW
SQDGALQDTS CQVHAWPDRR RWNQTCELLP VSQASWACNL ILGAPDSQKL TTVDIVTLRV
LCREGVRWRV MAIQDFKPF E NLRLMAPISL QVVHVETHRC NISWEISQAS HYFERHLEFE
ARTLSPGHTW EEAPLLTLKQ KQEWICLET L TPDTQYEFQV RVKPLQGEFT TWSPWSQPLA
FRTPKPAALGK DT

Wherein $n_1 = 0, 1, 2$, or 3; $n_2 = 0, 1, 2$, or 3; X_1 is an amino acid Alanine or deleted; X_2 is an amino acid Alanine or deleted.

SEQ ID NO: 37 - PD1-HC with - SUSHI - IL-15V

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNV DH KPSNTKV DDKR VESKYGPPCP PCPAPEFLGG PSVFLFPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA GGGSGGGGS GGGGSITCPP PMSVEHADIW VKSYSLYSRE
RYICNSGFKR KAGTSSLTEC VLNKATNVAH WTPSLK CIR GGGSGGGSG GGGSAAGGGG
SGGGSGGGG SNWVNVISDL KKIEDLIQSM HIDATLYTES DVHPCKVTA MKCFLLELQV
ISLES GDASI HDTVEDLIIL ANNSLSSNGN VTESGCKECE ELEEKNIKEF LQSFVHIVQM
FINTS

SEQ ID NO: 38 - PD1-HC - SCFV2 AGAINST IL-15

QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTTLVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNV DH KPSNTKV DDKR VESKYGPPCP PCPAPEFLGG PSVFLFPKP
KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA (GGGS)_{n1}X₁X₂ (GGGS)_{n2}EI VLTQSPGTLS LSPGERATLS
CRASQSVSSS YLAWYQQKPG QAPRLLIYGA SRRATGIPDR FSGSGSGTDF TLTISRLEPE

DFAVYYCQRY GSSHTFGQGT KLEISGGGGS GGGGSGGGGS EVQLVQSGAE VKKPGESLKI
 SCKVSGYFFT TYWIGWVRQM PGKGLEYMGI IYPGDS TRY SPSFQGVVTI SADKSISTAY
 LQWSSLKASD TAMYYCARGG NWNCFDYWGQ GTLTVTVSS

Wherein $n_1 = 0, 1, 2, \text{ or } 3$; $n_2 = 0, 1, 2, \text{ or } 3$; X_1 is an amino acid Alanine or deleted; and X_2 is an amino acid Alanine or deleted.

SEQ ID NO: 39 - PD1-HC - IL-21

MGVKVLFALI CIAVAEAQVQ LVESGGGVVQ PGRSLRLDCK ASGITFSNSG MHWVRQAPGK
 GLEWVAVIY DGSKRYIADS VKGRFTISR DSKNTLFLQM NSLRAEDTAV YYCATNDDYW
 GQGT LVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSKV
 HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP
 APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK
 PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT
 LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTTPVLDS DGSFFLYSRL
 TVDKSRWQEG NVFSCSV MHE ALHNHYTQKS LSLSLGAGGG GSGGGGSGGG GSQGDHRMI
 RMRQLIDIVD QLKNYVNDLV PEFLPAPEDV ETNCEWSAFS CFQKAQLKSA NTGNNERIIN
 VSIKKLKRKP PSTNAGRRQK HRLTCPSCDS YEKKPPKEFL ERFKSLLQKM IHQHLSSRTH
 GSEDS

SEQ ID NO: 40 - PD1-HC - IL-21R α ECD WITH CLEAVABLE PEPTIDE LINKER

MGVKVLFALICIAVAEA
 QVQLVESGGG VVQPGRLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYI
 ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGT LVT VSSASTKGPS
 VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
 VVTVPSSSLG TKTYTCNV D KPSNTKVDK R VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
 KDTLMISRTPEVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
 VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
 LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
 MHEALHNHYT QKSLSLSLGA GGGGSGGGGS GPLGVRGGGG SCPDLVCYTD YLQTVICILE
 MWNLHPSTLT LTWQDQYEEL KDEATSCSLH RSAHNATHAT YTCHMDVFHF MADDIFSVNI
 TDQSGNYSQE CGSFLLAESI KPAPPFNVTV TFSGQYNISW RSDYEDPAFY MLKGKLQYEL
 QYRNRGDPWA VSPRRKLISV DSRVSLLPL EFRKDSSYEL QVRAGPMPGS SYQGTWSEWS
 DPVIFQTQSE ELKE

SEQ ID NO: 41 -PD1-HC - SCFV2 AGAINST IL-21

MGVKVLFALI CIAVAEAQVQ LVESGGGVV QPGRSLRLDC KASGITFSNS GMHWVRQAPG
 KGLEWVAVIY YDGSKRYIAD SVKGRFTIS RDNSKNTLFL QMNSLRAEDT AVYYCATNDD
 YWGQGT LVTV SSASTKGPSV FPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT
 SGVHTFPAVL QSSGLYSLSS VVTVPSSSL GTKTYTCNV D HKPSNTKVDK R VESKYGPPC
 PPCPAPEFLG GPSVFLFPPK PKDTLMISR TPEVTCVVVD VSQEDPEVQF NWYVDGVEVH
 NAKTKPREEQ FNSTYRVVSV LTVLHQDWL NGKEYKCKVS NKGLPSSIEK TISKAKGQPR
 EPQVYTLPPS QEEMTKNQVS LTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDS DGS
 FFLYSRLTVD KSRWQEGNVF SCSVMHEAL HNHYTQKSLS LSLGAGGGGS GGGGSAAGGG
 GSGGGGSEIV LTQSPGTL SL SPGERATLS CRASQSVSSS YLAWYQQKPG QAPRLLIYGA
 SSRATGIPDR FSGSGGTDF TLTISRLEP EDFAVYYCQQ YGSWTFGQGT KVEIKGGGGS
 GGGGSGGGGS QVQLVESGGG VVQPGRLR LS CAASGFTF SSYGMHWVRQ APGKGLEWVA
 FIWYDGS D KY YADSVKGRFT ISRDNSKNT LYLQMNSLRA EDTAVYYCAR DGDSSDWYGD
 YYFGMDVWGQ GTTVTVSS

SEQ ID NO: 42 - PD1-HC with knob mutations - IL-21

QVQLVESGGG VVQPGRLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRY
 ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLLV VSSASTKGPS
 VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
 VVTVPSSSLG TKTYTCNV DH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
 KDTLMISRTPEVTCVVVDV QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
 VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPCQEE MTKNQVSLWC
 LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
 MHEALHNHYT QKSLSLGLGA GGGSGGGGS GGGSGGGQDR HMIRMRQLID IVDQLKNYVN
 DLVPEFLPAP EDVETNCEWS AFSCFQKAQL KSANTGNNER IINVSIIKKL RKPPSTNAGR
 RQKHRLTTPS CDSYEKKPPK EFLERFKSL QKMIHQHLSS RTHGSEDS

SEQ ID NO: 43 - PD1-HC with hole mutations - IL-21Rα ECD

QVQLVESGGG VVQPGRLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRY
 ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLLV VSSASTKGPS
 VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
 VVTVPSSSLG TKTYTCNV DH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
 KDTLMISRTPEVTCVVVDV QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
 VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VCTLPPSQEE MTKNQVSLSC
 AVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLV SRLTVDKSRW QEGNVFSCSV
 MHEALHNHYT QKSLSLGLGA GGGSGGGGS AAGGGSGGG GSCPDLCVYT DYLQTVICIL
 EMWNLHPSTL TLTWQDQYEE LKDEATSCSL HRSAHNATHA TYTCHMDVFH FMADDIFSVN
 ITDQSGNYSQ ECGSFLLAES IKPAPPFNVV VTFSGQYNIS WRSYEDPAF YMLKGKLQYE
 LQYRNRGDPW AVSPRRKLIS VDSRSVSLP LFRKDSSEY LQVRAGPMPG SSYQGTWSEW
 SDPVI FQTQS EELKE

SEQ ID NO: 44 - PD1-LC

EIVLTQSPATLSLSPGERAT LSCRASQSVS SYLAWYQQKPGQAPRLLIYD ASNRATGIPA
 RFGSGSGTDFTLTISLEPEDFAVYYCQSSNWPRTEFGGTKVEIKRTVAAPSVFIFPP
 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSLT
 LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGE

SEQ ID NO: 45 - Anti-PDL1 atezolizumab LC

DIQMTQSPSSLSASVGDRVTITCRASQDVS TAVAWYQQKPGKAPKLLIYS ASFLYSGVPS
 RFGSGSGTDFTLTISLQPEDFATYYCQQLYHPATFGGTKVEIKRTVAAPSVFIFPP
 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSLT
 LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGE

SEQ ID NO: 46 - Anti-PDL1 atezolizumab HC

EVQLVESGGGLVQPGGSLRLSCAASGFTFS DSWIHWVRQA PGKGLEWVAV ISPYGGSTYY
 ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARRH WPGGFDYWGQ GTLVTVSSAS
 TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
 YSLSSVTVTPSSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS
 VFLFPPPKPD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYAST
 YRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKA KGQPREPQVY TLPPSREEMT
 KNQVSLTCLV KGFYPSDI AVEWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
 GNVFSCSVMH EALHNHYTQKSLSLSPGK

SEQ ID NO: 47 - Anti-PD-1 Nivolumab HC

QVQLVESGGG VVQPGRLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRY
 ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLLV VSSASTKGPS
 VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
 VVTVPSSSLG TKTYTCNV DH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP

KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLGLGK

SEQ ID NO: 48 - Anti-PD-1 Pembrolizumab LC

EIVLTQSPAT LSLSPGERAT LSCRASKGVS TSGYSYLHWY QQKPGQAPRL LIYLASYLES
GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRDLP TFGGGTKVEI KRTVAAPSVF
IFPPSDEQLK SGTASVCLL NNFYPREAV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS
STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC

SEQ ID NO: 49 - Anti-PD-1 Pembrolizumab HC

QVQLVQSGVE VKKPGASVKV SCKASGYTFT NYYMYWVRQA PGQGLEWMGG INPSNGGTNF
NEKFKNRVTL TTDSSTTTAY MELKSLQFDD TAVYYCARRD YRFDMGFDYW GQGTTVTVSS
ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV
FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY
RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK
NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTTPVLDS DGSFFLYSRL TVDKSRWQEG
NVFSCSVME ALHNHYTQKS LSLSLGK

SEQ ID NO: 50 - CTLA-4 antibody Ipilimumab LC

EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP
PSDEQLKSGT ASVVCLLNNF YPREAVQWK VDNALQSGNS QESVTEQDSK DSTYSLSTL
TLKADYEKH KVIYACEVTHQ GLSSPVTKSF NRGEC

SEQ ID NO: 51 - CTLA-4 antibody Ipilimumab HC- IL2v

QVQLVESGGG VVQPGRLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNMKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
YSLSSVVTVP SSSLTGTQYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSVMH EALHNHYTQK SLSLSPGA (GGGS)_{n1}X₁X₂ (GGGS)_{n2}APX_{aa3} SSSTKKTQLQ
LEHLLLDLQM ILNGINNYKN PX_{aa35}LTRMLTX_{aa42}KFX_{aa45}M PKKATELKLHQL CLEELKPLE
EVLNX_{aa72}X_{aa73}QSKNFHLRPR DLISNINVIV LELKGSETTF MCEYADETATI VEFLNRWITF
X_{aa125}QSIIST LT

wherein Xaa3 is N or A; wherein Xaa125 is A or S; wherein Xaa35 is selected from K and N; wherein Xaa42 is selected from A, G, S, T, Q, E, N, D, R, and K; wherein Xaa45 is selected from A, G, S, T, Q, E, N, D, R, and K; wherein Xaa72 is selected from A, G, S, T, Q, E, N, D, R, and K; wherein Xaa73 is selected from A and T; wherein n₁ = 0, 1, 2, or 3; n₂ = 0, 1, 2, or 3; and X₁ is an amino acid Alanine or deleted; and X₂ is an amino acid Alanine or deleted.

SEQ ID NO: 52 - CTLA-4 antibody Ipilimumab HC- IL15v

QVQLVESGGG VVQPGRLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNMKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL

YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
 VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
 YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
 KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
 GNVFSCSVMH EALHNHYTQK SLSLSPGAGG GSGGGGSGG GGSITCPPPM SVEHADIWVK
 SYLSYSRERY ICNSGFKRKA GTSSLTECVL NKATNVAHWT TPSLKCIRGG GSGGGGSGGG
 GSAAAGGGGSG GSGGGGSGSN WVNVISDLKK IEDLIQSMHI DATLYTESDV HPSCKVTAMK
 CFLLELQVIS LESGDASIHD TVEDLIILAN NSLSSNGNVT ESGCKECEEL EEKNIKEFLQ
 SFVHIVQMFI NTS

SEQ ID NO: 53 - CTLA-4 antibody Ipilimumab HC- IL-21

QVQLVESGGG VVQPGRSLR LSCAASGFTF SSYTMHWVRQ APGKGLEWVT FISYDGNKYY
 ADSVKGRFTI SRDNSKNTL YLQMNSLRAE DTAIYYCART GWLGPFDYWG QGTLVTVSSAS
 TKGPSVFPLA PSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFAVLQSSGL
 YSLSSVVTVP SSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGPS
 VFLFPPKPKD TLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNST
 YRVVSVLTVL HQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDELT
 KNQVSLTCLV KGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQQ
 GNVFSCSVMH EALHNHYTQ KSLSLSPGA (GGGS)_{n1}X₁X₂ (GGGS)_{n2}QGQDRHMIRM RQLI
 DIVDQLKNYV NDLVPEFLP APEDVETNCE WSAFSCFQKA QLKSANTGNN ERIINVISIKKL
 KRKPPSTNAG RRQKHRLTC PSCDSYEKKP PKEFLERFKS LLQKMIHQHL SSRTHGSEDS
 Wherein n₁ = 0, 1, 2, or 3; n₂ = 0, 1, 2, or 3; X₁ is an amino acid
 Alanine or deleted; and X₂ is an amino acid Alanine or deleted.

SEQ ID NO: 54 - CTLA-4 antibody Ipilimumab HC- IL-2Rβ-ECD

QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
 ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFYDWGQ GTLVTVSSAS
 TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
 YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
 VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
 YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
 KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
 GNVFSCSVMH EALHNHYTQK SLSLSPGA (GGGS)_{n1}X₁X₂ (GGGS)_{n2} AVNG TSQFTCFYNS
 RANISCVWSQ DGALQDTSCQ VHAWPDRRRW NQTCCELLPVS QASWACNLIL GAPDSQKLTT
 VDIVTLRVLC REGVRWRVMA IQDFKPFENL RLMAPISLQV VHVETHRCNI SWEISQASHY
 FERHLEFEAR TLSPGHTWEE APLLTCLKQKQ EWICLETLP DTQYEFQVRV KPLQGEFTTW
 SPWSQPLAFR TKPAALGKDT
 Wherein n₁ = 0, 1, 2, or 3; n₂ = 0, 1, 2, or 3; X₁ is an amino acid
 Alanine or deleted; and X₂ is an amino acid Alanine or deleted.

SEQ ID NO: 55 - CTLA-4 antibody Ipilimumab HC- scFv1 against IL-2 (in the scFV, underlined: HCDR1-3 and LCDR1-3; italic: VH and VL)

QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
 ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFYDWGQ GTLVTVSSAS
 TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
 YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
 VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
 YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
 KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
 GNVFSCSVMH EALHNHYTQK SLSLSPGA (GGGS)_{n1}X₁X₂ (GGGS)_{n2}QVQ LVQSGAEVKK
 PGSSVKVSCK ASGGTFSSYA ISWVRQAPGQ GLEWMGGIIP IFGTANYAQK FQGRVTITAD
 ESTSTAYMEL SSLRSEDVAV YYCARVDRIY NWNYFLGSFD YWGQGLTVTV SSGGGGSGGG

GSGGGGSSYV LTQPPSVSVA PGKTARITCG GNNIRSKSVH WYQKPGQAP VVVIYYDSDR
PSGIPERISG SNSGNTATLTISRVEAGDEADYFCQVWDSSSDHHVFGGGTKLTVL;

wherein $n_1 = 0, 1, 2, \text{ or } 3$; $n_2 = 0, 1, 2, \text{ or } 3$; X_1 is an amino acid Alanine or deleted; and X_2 is an amino acid Alanine or deleted.

SEQ ID NO: 56 - CTLA-4 antibody Ipilimumab HC- scFv2 against IL-2
 (underlined: LCDR1-3 and HCDR1-3; italic: VL and VH)

QVQLVESGGG VVQPGRLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
 ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
 TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
 YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
 VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
 YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
 KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTPPVLD SDGSFFLYSK LTVDKSRWQQ
 GNVFSCSVMH EALHNHYTQK SLSLSPGA(GGGGS) _{n_1} X_1 X_2 (GGGS) _{n_2} SYVL TQPPSVSVAP
GKTARITCGG NNIRSKSVHW YQKPGQAPV VVIYYDSDRP SGIPERISGS NSGNTATLTI
SRVEAGDEAD YFCQVWDSSS DHHVFGGGTK LTVLGGGGSG GGSGGGGSQ VQLVQSGAEV
KKPGSSVKVS CKASGGTFSS YALSWVRQAP GQGLEWMGGI IPIFGTANYA QKFQGRVTIT
ADESTSTAYM ELSSLRSED AVYYCARVDR YNNWNYFLGS FDYWGQGLV TVSS;

Wherein $n_1 = 0, 1, 2, \text{ or } 3$; $n_2 = 0, 1, 2, \text{ or } 3$; X_1 is an amino acid Alanine or deleted; and X_2 is an amino acid Alanine or deleted.

SEQ ID NO: 57 - CTLA-4 antibody Ipilimumab HC- scFv2 against IL-15

QVQLVESGGG VVQPGRLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
 ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
 TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
 YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
 VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
 YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
 KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTPPVLD SDGSFFLYSK LTVDKSRWQQ
 GNVFSCSVMH EALHNHYTQK SLSLSPGA(GGGGS) _{n_1} X_1 X_2 (GGGS) _{n_2} EIVL TQSPGTLTSL
 PGERATLSCR ASQSVSSSYL AWYQKPGQA PRLLIYGASR RATGIPDRFS GSGSGTDFTL
 TISRLPEDEF AVYYCQRYGS SHTFGQGTKL EISGGGGSGG GSGGGGSEV QLVQSGAEVK
 KPGESLKISC KVSQYFFTTY WIGWVRQMPG KGLEYMGIY PGSDTRYSP SFQGQVTISA
 DKSISTAYLQ WSSLKASDTA MYCARGGNW NCFDYWGQGT LTVSS

Wherein $n_1 = 0, 1, 2, \text{ or } 3$; $n_2 = 0, 1, 2, \text{ or } 3$; X_1 is an amino acid Alanine or deleted; and X_2 is an amino acid Alanine or deleted.

SEQ ID NO: 58 - CTLA-4 antibody Ipilimumab HC- IL-21R α -ECD

QVQLVESGGG VVQPGRLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
 ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
 TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
 YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
 VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
 YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
 KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTPPVLD SDGSFFLYSK LTVDKSRWQQ
 GNVFSCSVMH EALHNHYTQK SLSLSPGAGG GSGGGGSAA GGGSGGGGS CPDLVCYTDY
 LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY TCHMDVFHFM
 ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR SDYEDPAFYM
 LKGLQYELQ YRNRGDPWAV SPRRKLISVD SRSVSLPLE FRKDSSYELQ VRAGPMPGSS
 YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 59 - CTLA-4 antibody Ipilimumab HC- scFv2 against IL-21
 QVQLVESGGG VVQPGRLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNKYY
 ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
 TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
 YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
 VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
 YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
 KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
 GNVFSCSVMH EALHNHYTQK SLSLSPGAGG GSGGGGSAA GGGSGGGGS EIVLTQSPGT
 LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASSRATGIP DRFSGSGSGT
 DFTLTISRLE PEDFAVYYCQ QYGSWTFGQG TKVEIKGGG SGGSGGGG SQVQLVESGG
 GVVQPGRLR LSCAASGFTF SSYGMHWVRQ APGKGLEWVA FIWYDGSQYK YADSVKGRFT
 ISRDNKNTL YLQMNSLRAE DTAVYYCARD GDSSDWYGDY YFGMDVW-GQGTITVTSS

SEQ ID NO: 60 - 4E12B2D10 anti-IL2 HC variable domain (underlined:
 HCDR1-3)
 EVQLQQSGAE LVRPGASVKL SCTASGFNIK DDYLHWVRQR PEQGLEWIGR IDPANGNTKY
 APKFQDKATI TADTSSNTAY LQLSILTS E AVYYCAARF GYFYGSSFYA VAYWGQTSV
 TVSS

SEQ ID NO: 61 - 4E12B2D10 anti-IL2 LC variable domain (underlined:
 LCDR1-3)
 QIVLTQSPAI MSASPGEKVT MTCSASSSVS YMHYQQKSG TSPKRWIYDT SKLASGVPAR
 FSGSGSGTSY SLTISSMEAE DAATYYCQOW SSNPYTFGGGTKLEIK

SEQ ID NO: 62 - IL-2 agonist polypeptide
 APX_{aa3}SSSTK KTQLQLEHLL LDLQMILNGI NNYKNPX_{aa35}LTRMLTX_{aa42}KFX_{aa45}MPKKATEL
 KHLQCLEEEL KPLEEVLNX_{aa72}X_{aa73}QSKNFH LRPRDLISNI NVIVLELKGSE TTFMCEYADE
 TATIVEFLNR WITFX_{aa125}QS IISTLT

wherein Xaa3 is N or A; wherein Xaa125 is C, A or S; wherein Xaa35 is selected from K and N; wherein Xaa42 is selected from A, G, S, T, Q, E, N, D, R, and K; wherein Xaa45 is selected from A, G, S, T, Q, E, N, D, R, and K; wherein Xaa72 is selected from A, G, S, T, Q, E, N, D, R, and K; and wherein Xaa73 is selected from A and T.

SEQ ID NO: 63 - IL-21 receptor alpha ECD mutant ver1 (mutations underlined)
 CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
 SDYEDPAFYM LKGLQYELQ YRNRGDGSGV SPRRKLISVD SRSVSLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 64 - IL-21 receptor alpha ECD mutant ver2 (mutations underlined)
 CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
 SDYEDPAFYM LKGLQYELQ YRNRGDNASV SPRRKLISVD SRSVSLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 65 - IL-21 receptor alpha ECD mutant ver3 (mutations underlined)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
 SDYEDPAFYM LKGKLQYELQ YRNRGDNGSV SPRRKLISSVD SRSVSLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 66 - IL-21 receptor alpha ECD mutant ver4 (mutations underlined)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLNR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
 SDYEDPAFYM LKGKLQYELQ YRNRGDNASV SPRRKLISSVD SRSVSLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 67 - IL-21 receptor alpha ECD mutant ver5 (mutations underlined)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
 SDYEDPAFYM LKGKLQYELQ YRNRGDPSAV SPRRKLISSVD SRSVSLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 68 - IL-21 receptor alpha ECD mutant ver6 (mutations underlined)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
 SDYEDPAFYM LKGKLQYELQ YRNRGDPSGV SPRRKLISSVD SRSVSLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 69 - IL-21 receptor alpha ECD mutant ver7 (mutations underlined)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
SAYEDPAFYM LKGKLQYELQ YRNRGDGSGV SPRRKLISSVD SRSVSLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 70 - IL-21 receptor alpha ECD mutant ver8 (mutations underlined)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
SIYEDPAFYM LKGKLQYELQ YRNRGDGSGV SPRRKLISSVD SRSVSLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 71 - IL-21 receptor alpha ECD mutant ver9 (mutations underlined)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
SWYEDPAFYM LKGKLQYELQ YRNRGDGSGV SPRRKLISSVD SRSVSLPLE FRKDSSYELQ
 VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 72 - IL-21 receptor alpha ECD mutant ver10 (mutations underlined)

CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
 TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR

SFYEDPAFYM LKGKLQYELQ YRNRGDGSGV SPRRKLISSVD SRSVSLPLE FRKDSSYELQ
VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 73 - IL-21 receptor alpha ECD mutant ver11
CPDLVCYTDY LQTVICILEM WNLHPSTLTL TWQDQYEELK DEATSCSLHR SAHNATHATY
TCHMDVFHFM ADDIFSVNIT DQSGNYSQEC GSFLLAESIK PAPPFNVTVT FSGQYNISWR
SYEDPAFYM LKGKLQYELQ YRNRGDGSGV SPRRKLISSVD SRSVSLPLE FRKDSSYELQ
VRAGPMPGSS YQGTWSEWSD PVIFQTQSEE LKE

SEQ ID NO: 74 - PD1-HC with hole mutations - IL-21R α ECD
QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLLV VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDRK VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTPEVTCVVVDVSD QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VCTLPPSQEE MTKNQVSLSC
AVKGFYPSDI AVEWESNGQP ENNYKTTTPPV LDSDGSFFLV SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA GGGSGGGGS GPLGVRGGGG SCPDLVCYTD YLQTVICILE
MWNLHPSTLT LTWQDQYEEL KDEATSCSLH RSAHNATHAT YTCHMDVFHF MADDIFSVNI
TDQSGNYSQE CGSFLLAESI KPAPPFNVTV TFSGQYNISW RSDYEDPAFY MLKGKLQYEL
QYRNRGDPWA VSPRRKLISV DSRVSLPL EFRKDSSYEL QVRAGPMPGS SYQGTWSEWS
DPVIFQTQSE ELKE

SEQ ID NO: 75 - PD1-HC fusion polypeptide with scFv2 against IL-15
QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLLV VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDRK VESKYGPPCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTPEVTCVVVDVSD QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHEALHNHYT QKSLSLSLGA GGGSGGGGS GPLGVRGGGG SGGGGSEIVL TQSPGTLTSL
PGERATLSCR ASQSVSSSYL AWYQQKPGQA PRLIIYGASR RATGIPDRFS GSGSGTDFTL
TISRLEPEDF AVYYCQRYGS SHTFGQGTKL EISGGGGSGG GSGGGGSEVQLVQSGAEVK
KPGESLKISC KVSIFYFTTY WIGWVRQMPG KGLEYMGIY PGDSSTRYSP SFQGQVTISA
DKSISTAYLQ WSSLKASDTA MYYCARGGNW NCFDYWGQGT LTVTVSS

SEQ ID NO: 76 - Anti-IL-15 antibody 146B7 HC CDR1 (protein sequence)
TYWIG

SEQ ID NO: 77 - Anti-IL-15 antibody 146B7 HC CDR2 (protein sequence)
IIYPGDSSTR YSPSFQG

SEQ ID NO: 78 - Anti-IL-15 antibody 146B7 HC CDR3 (protein sequence)
GNWNCFDY

SEQ ID NO: 79 - Anti-IL-15 antibody 146B7 LC CDR1 (protein sequence)
RASQSVSSSY LA

SEQ ID NO: 80 - Anti-IL-15 antibody 146B7 LC CDR2 (protein sequence)
GASRRAT

SEQ ID NO: 81 - Anti-IL-15 antibody 146B7 LC CDR3 (protein sequence)
QRYGSSHT

SEQ ID NO: 82 - Anti-IL-15 antibody 146B7 HC CDR3 ver2 (protein sequence)
GNWNSFDY

SEQ ID NO: 83 - Anti-IL-15 antibody 146B7 HC variable domain
(underlined: HCDR1-3)
EVQLVQSGAE VKKPGESLKI SCKVSGYFFT TYWIGWVRQM PGKGLEYMGI IYPGDS DTRY
SPSFQGGQVTI SADKSISTAY LQWSSLKASD TAMYICARGG NWNCFDYWGQ GTLVTVSS

SEQ ID NO: 84 - Anti-IL-15 antibody 146B7 LC variable domain
(underlined: LCDR1-3)
EIVLTQSPGT LSLSPGREAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASRRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ RYGSSHTFGQ GTKLEISRTV AAPSVFIFP

CLAIMS

1. A prodrug comprising a cytokine moiety, a masking moiety, and a carrier moiety, wherein:
 - a) the masking moiety binds to the cytokine moiety and inhibits a biological activity of the cytokine;
 - b) the carrier moiety comprises an antigen-binding moiety, wherein the antigen-binding moiety binds to an antigen expressed on the surface of a target cell; and
 - c) the masking moiety is linked directly or indirectly to the carrier moiety through a non-cleavable peptide linker or without a peptide linker.
2. The prodrug of claim 1, wherein the prodrug is activated by cells that express on the cell surface both the antigen and a receptor for the cytokine moiety, optionally wherein the biological activity of the prodrug is increased by at least 2, 5, or 10 folds at a disease site comprising the cells as compared to a site not comprising the cells.
3. The prodrug of claim 1 or 2, wherein the receptor for the cytokine moiety comprises two or more subunits.
4. The prodrug of any one of the preceding claims, wherein the antigen is selected from PD-1, PD-L1, CTLA-4, TIGIT, TIM-3, LAG-3, CD25, CD16a, CD16b, NKG2D, NKP44, NKP30, CD19, CD20, CD30, CD38, BCMA, and signal regulatory protein alpha (SIRP alpha).
5. The prodrug of any one of the preceding claims, wherein the cytokine moiety comprises a an IL-2 agonist polypeptide, an IL-7 agonist polypeptide, an IL-9 agonist polypeptide, an IL-15 agonist polypeptide, an IL-21 agonist polypeptide, an IL-1 α agonist polypeptide, an IL-1 β agonist polypeptide, an IL-4 agonist polypeptide, an IL-5 agonist polypeptide, an IL-6 agonist polypeptide, an IL-8 agonist polypeptide, an IL-10 agonist polypeptide, an IL-12 agonist polypeptide, an IL-17 agonist polypeptide, an IL-18 agonist polypeptide, an IL-22 agonist polypeptide, an IL-23 agonist polypeptide, an IL-31 agonist polypeptide, an IL-33 agonist polypeptide, an IL-36 agonist polypeptide, an interferon-alpha agonist polypeptide, an interferon gamma agonist polypeptide, a 4-1BB ligand, an OX-40 ligand, or a CD-40 ligand.

6. The prodrug of any one of the preceding claims, wherein the masking moiety comprises an ECD of a receptor of the cytokine, or an antigen-binding domain that specifically binds the cytokine.

7. The prodrug of any one of the preceding claims, wherein

i) the cytokine moiety comprises an IL-7 agonist polypeptide and the masking moiety comprises an extracellular domain (ECD) of IL-7 receptor α (IL-7R α ECD) or a functional analog thereof,

ii) the cytokine moiety comprises an IL-21 agonist polypeptide and the masking moiety comprises an ECD of IL-21 receptor α (IL-21R α ECD) or a functional analog thereof,

iii) the cytokine moiety comprises an IL-2 agonist polypeptide or an IL-15 agonist polypeptide and the masking moiety comprises an ECD of IL-2 receptor β (IL-2R β ECD) or a functional analog thereof,

iv) the cytokine moiety comprises an IL-21 agonist polypeptide and the masking moiety comprises a Fab, a single chain Fv (scFv), or a single domain antibody against IL-21,

v) the cytokine moiety comprise an IL-2 agonist polypeptide and the masking moiety comprises a Fab, an scFv, or a single domain antibody against IL-2,

vi) the cytokine moiety comprises an IL-15 agonist polypeptide and the masking moiety comprises a Fab, an scFv, or a single domain antibody against IL-15, or

vii) the cytokine moiety comprises an IL-15 agonist polypeptide and the masking moiety comprises a sushi domain of IL-15 receptor α (IL-15R α sushi domain).

8. The prodrug of any one of claims 5-7, wherein the cytokine moiety comprises an IL-2 agonist polypeptide comprising SEQ ID NO: 6 or 62, or an amino acid sequence at least 95% identical thereto.

9. The prodrug of any one of claims 5-7, wherein the cytokine moiety comprises an IL-15 agonist polypeptide comprising SEQ ID NO: 7, or an amino acid sequence at least 95% identical thereto.

10. The prodrug of any one of claims 5-9, wherein the cytokine moiety comprises an IL-2 or IL-15 agonist polypeptide and the masking moiety comprises an IL-2R β ECD or a functional analog thereof, optionally wherein the IL-2R β ECD comprises SEQ ID NO: 11, or an amino acid sequence at least 95% identical thereto.

11. The prodrug of any one of claims 5-9, wherein the cytokine moiety comprises an IL-2 agonist polypeptide and the masking moiety comprises an scFv against IL-2 and optionally inhibits or interferes with the interaction between the IL-2 cytokine moiety and one or more of IL-2R α , IL-2R β , and IL-2R γ , optionally wherein the scFv comprises

the HCDR1-3 and LCDR1-3, or the heavy and light chain variable domains, of antibody 4E12B2D10, Anti-IL-2 scFv1, or Anti-IL-2 scFv2, or

an amino acid sequence comprising SEQ ID NO: 22, SEQ ID NO: 23, or SEQ ID NOs: 60 and 61, or an amino acid sequence at least 95% identical thereto.

12. The prodrug of any one of any one of claims 5-9, wherein the cytokine moiety comprises an IL-15 agonist polypeptide and the masking moiety comprises an scFv against IL-15 and optionally inhibits or interferes with the interaction between the IL-15 cytokine moiety and one or more of IL-15R α , IL-2R β , and IL-2R γ , optionally wherein the scFv comprises

the HCDR1-3 and LCDR1-3, or the heavy and light chain variable domains, of antibody 146B7, Anti-IL-15 scFv1, or Anti-IL-15 scFv2, or

an amino acid sequence comprising SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NOs: 83 and 84, or an amino acid sequence at least 95% identical thereto.

13. The prodrug of any one of claims 5-7, wherein the cytokine moiety comprises an IL-21 agonist polypeptide comprising any one of SEQ ID NOs: 1-5, or an amino acid sequence at least 95% identical thereto.

14. The prodrug of any one of claims 5-7 or 13, wherein the cytokine moiety comprises an IL-21 agonist polypeptide and the masking moiety comprises an IL-21R α ECD or a functional analog thereof, or an IL-21R γ ECD or a functional analog thereof, optionally wherein the

masking moiety comprises SEQ ID NO: 12, 13, or any one of SEQ ID NOs: 63-73, or an amino acid sequence at least 95% identical thereto.

15. The prodrug of any one of claims 5-7 or 13, wherein the cytokine moiety comprises an IL-21 agonist polypeptide and the masking moiety comprises an scFv against human IL-21 and optionally inhibits or interferes with the interaction between the IL-21 cytokine moiety and IL-21R α and/or IL-21R γ , optionally wherein the scFv comprises

the HCDR1-3 and LCDR1-3, or the heavy and light chain variable domains, of Anti-IL-21 scFv1, or Anti-IL-21 scFv2, or

an amino acid sequence comprising SEQ ID NO: 20 or 21, or an amino acid sequence at least 95% identical thereto.

16. The prodrug of any one of the preceding claims, wherein the masking moiety comprises an scFv against a cytokine selected from IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 and optionally inhibits or interferes with the interaction between the cytokine and IL-2R γ , or

an ECD of a receptor α or γ of a cytokine selected from IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21.

17. The prodrug of any one of the preceding claims, wherein the prodrug comprises an anti-PD-1 antibody moiety, wherein the antibody moiety comprises two light chains comprising SEQ ID NO: 44, and two heavy chains comprising respectively:

SEQ ID NOs: 24 and 25,

SEQ ID NOs: 24 and 26 or 74,

SEQ ID NOs: 35 and 36,

SEQ ID NOs: 37 and 36,

SEQ ID NOs: 37 and 38 or 75,

SEQ ID NOs: 39 and 41 or 74, or

SEQ ID NOs: 42 and 43 or 74.

18. The prodrug of any one of the preceding claims, wherein the prodrug comprises an anti-CTLA4 antibody moiety, wherein the antibody moiety comprises two light chains comprising SEQ ID NO: 50, and two heavy chains comprising respectively:

SEQ ID NOs: 51 and 54,
SEQ ID NOs: 51 and 55,
SEQ ID NOs: 51 and 56,
SEQ ID NOs: 52 and 54,
SEQ ID NOs: 53 and 58,
SEQ ID NOs: 53 and 59, or
SEQ ID NOs: 52 and 57.

19. A pharmaceutical composition comprising the prodrug of any one of claims 1-18 and a pharmaceutically acceptable excipient.

20. A polynucleotide or polynucleotides encoding the prodrug of any one of claims 1-18.

21. An expression vector or vectors comprising the polynucleotide or polynucleotides of claim 20.

22. A host cell comprising the vector(s) of claim 21, optionally wherein the host cell is a mammalian cell.

23. A method of making the prodrug of any one of claims 1-18, comprising
a) culturing the host cell of claim 22 under conditions that allow expression of the prodrug wherein the host cell is a mammalian cell; and
b) isolating the prodrug from the cell culture.

24. A method of treating a cancer, an autoimmune disease, or an infectious disease, or stimulating the immune system in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a prodrug of any one of claims 1-18 or the pharmaceutical composition of claim 19.

25. A prodrug of any one of claims 1-18 or the pharmaceutical composition of claim 19 for use in treating a cancer, an autoimmune disease or an infectious disease, or stimulating the immune system, in a patient in need thereof.

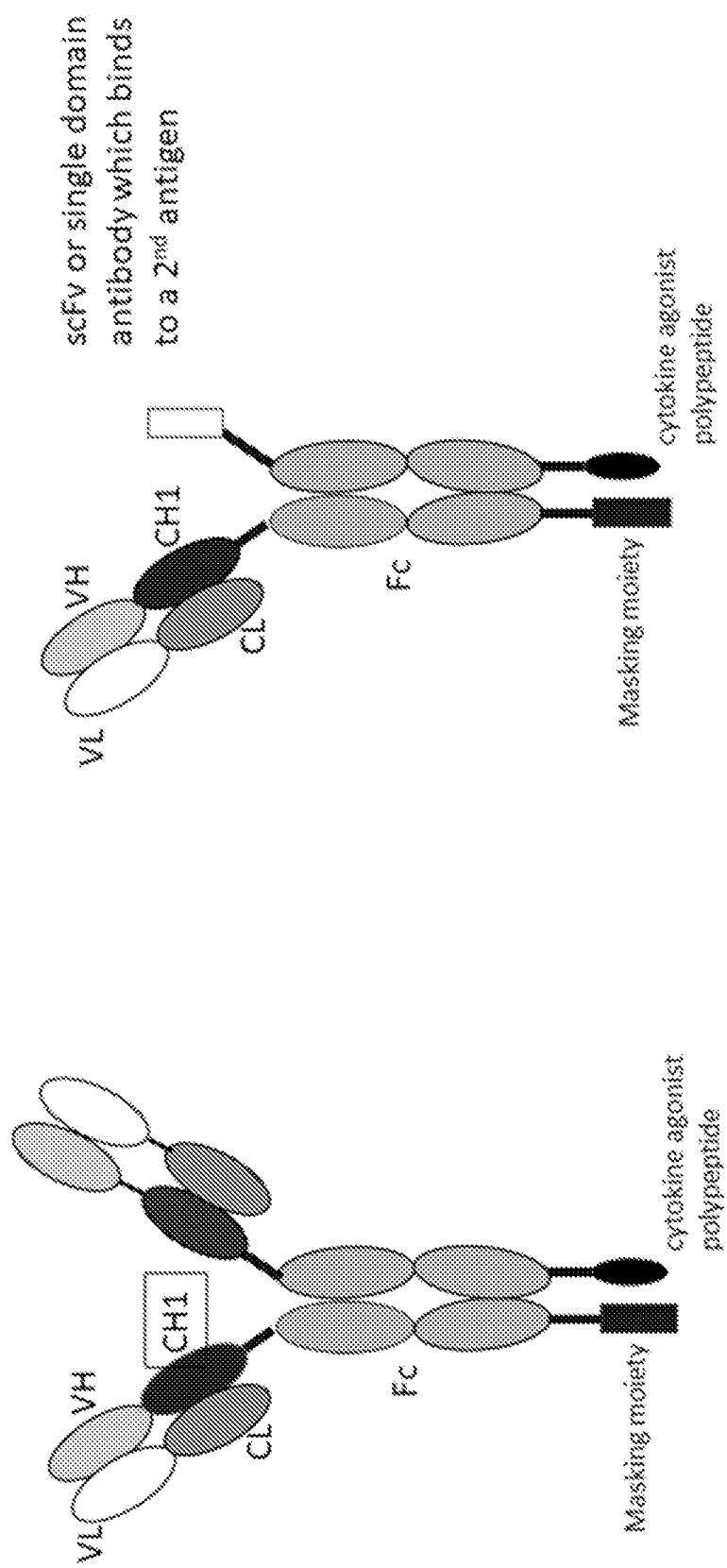
26. Use of a prodrug of any one of claims 1-18 for the manufacture of a medicament for treating a cancer, an autoimmune disease, or an infectious disease, or stimulating the immune system, in a patient in need thereof.

27. The method of claim 24, the prodrug or pharmaceutical composition for use of claim 25, or the use of claim 26, wherein the patient has

an HIV, HBV, HCV, or HPV infection,

an autoimmune disease selected from lupus, type I diabetes, psoriasis, dermatomyositis, GvHD, or rheumatoid arthritis, or

a cancer selected from the group consisting of breast cancer, lung cancer, pancreatic cancer, esophageal cancer, medullary thyroid cancer, ovarian cancer, uterine cancer, prostate cancer, testicular cancer, colorectal cancer, or stomach cancer.



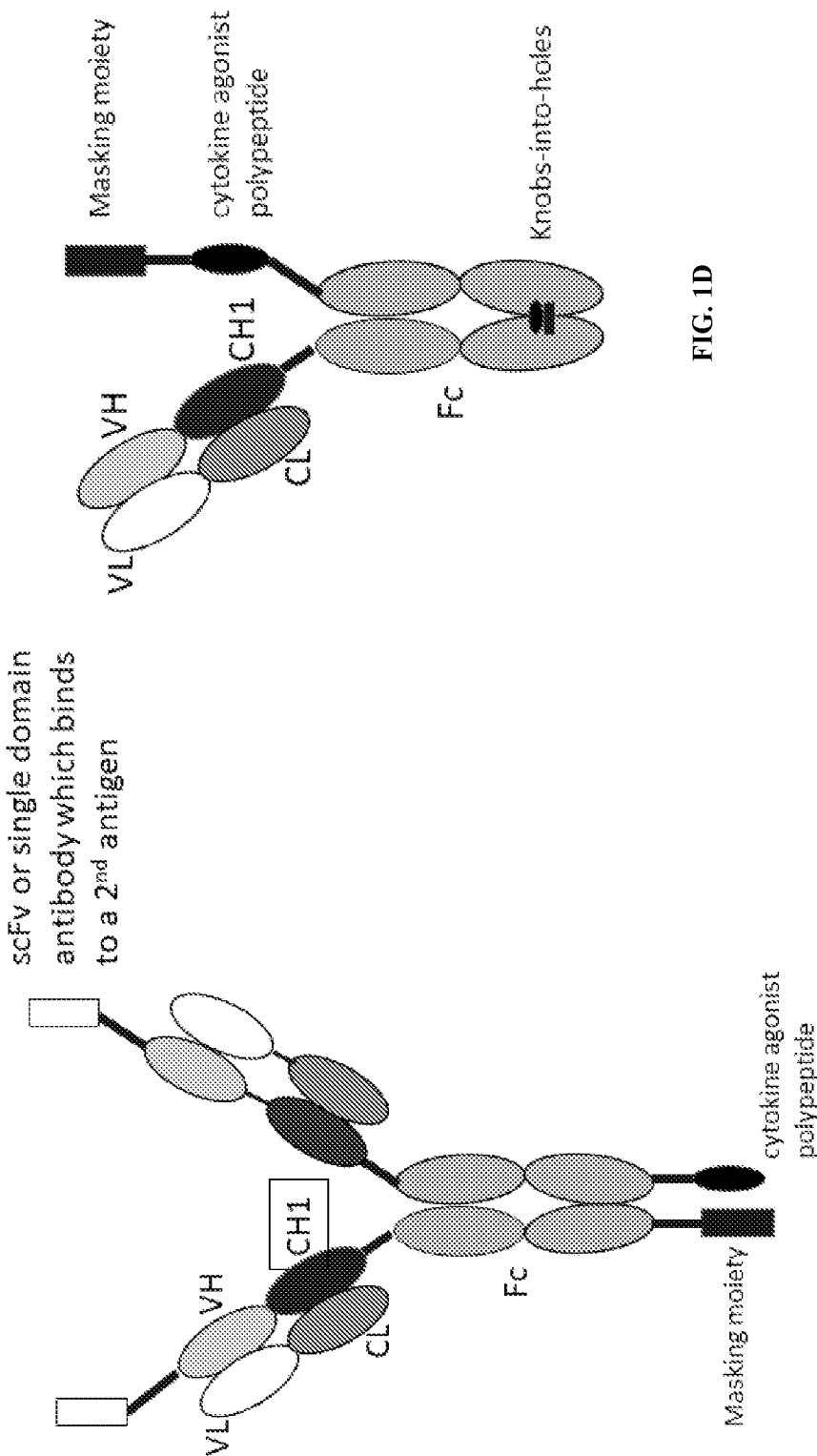


FIG. 1D

FIG. 1C

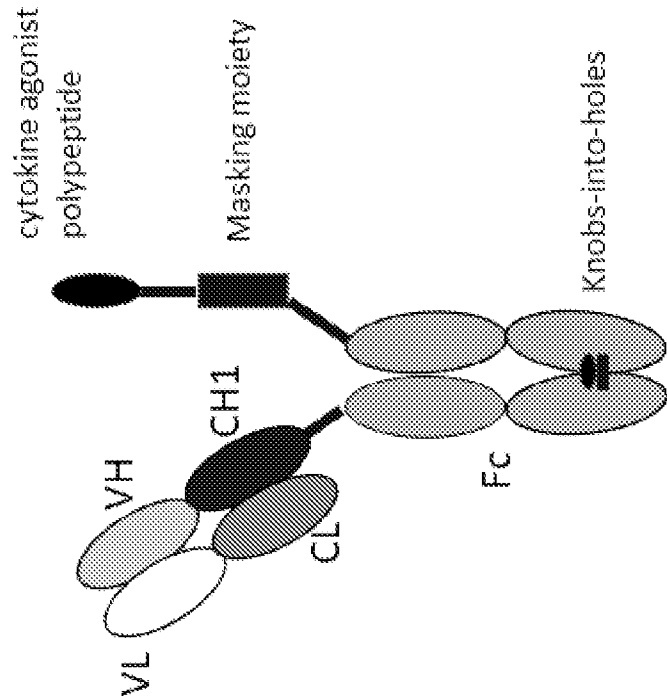


FIG. 1E

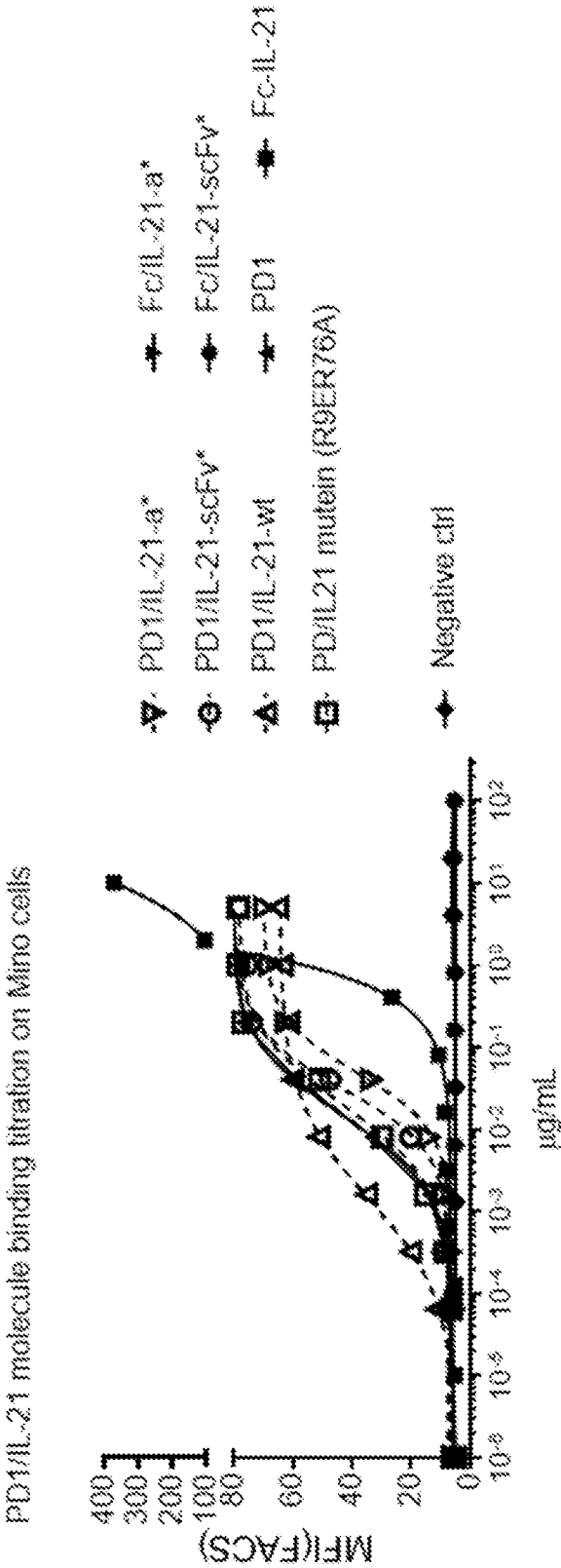


FIG. 2

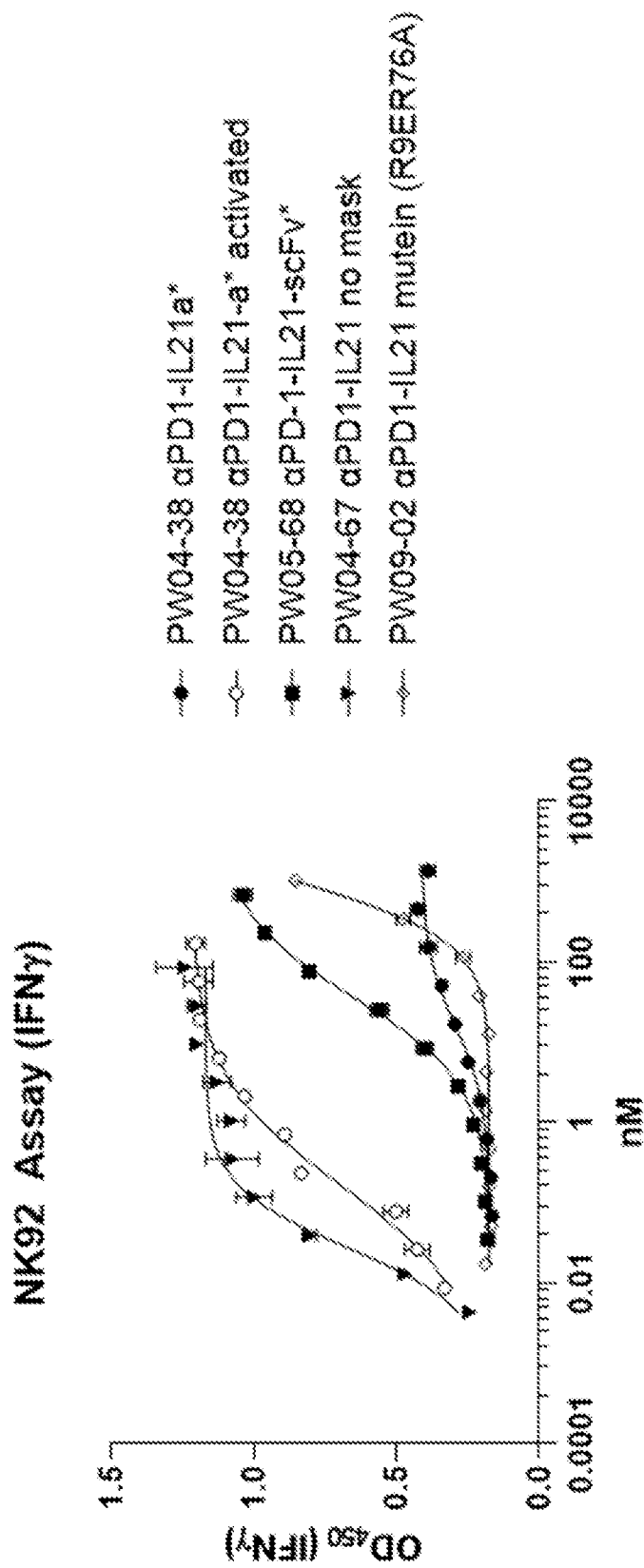


FIG. 3

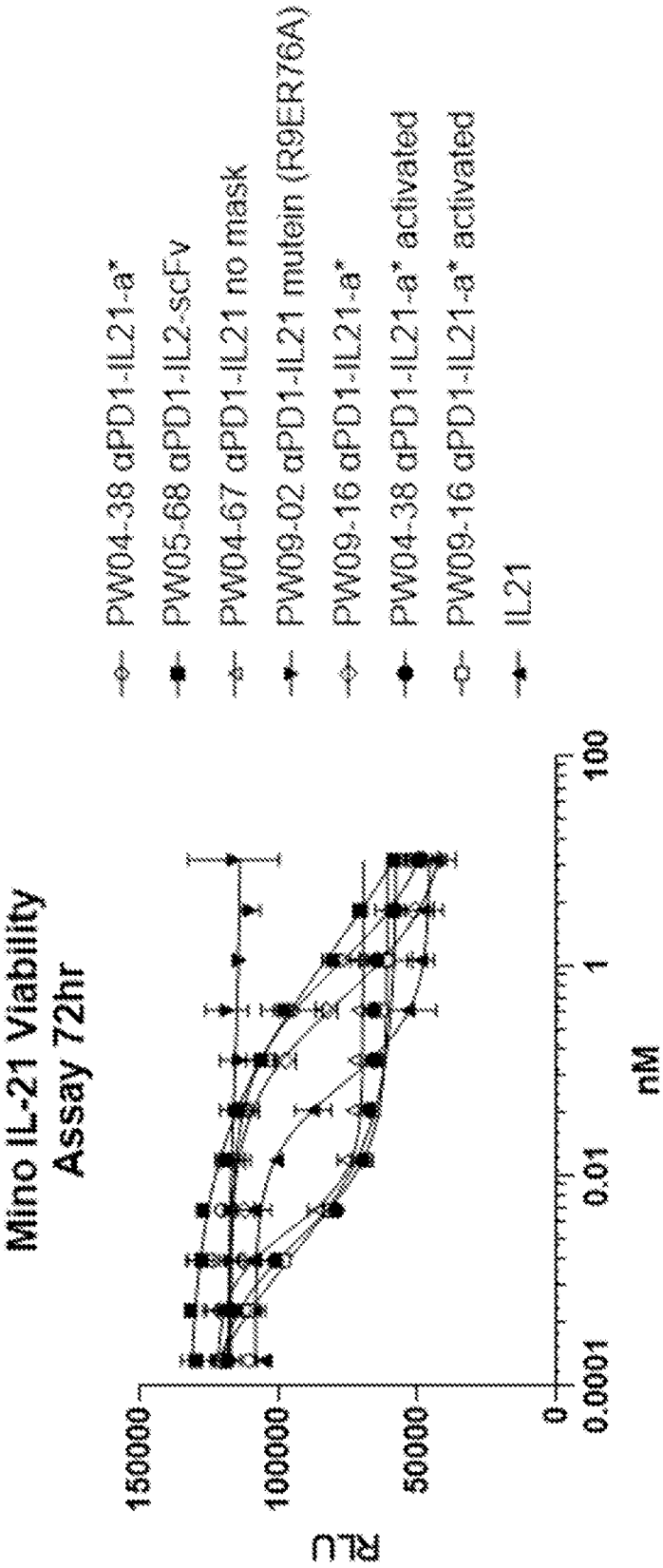


FIG. 4A

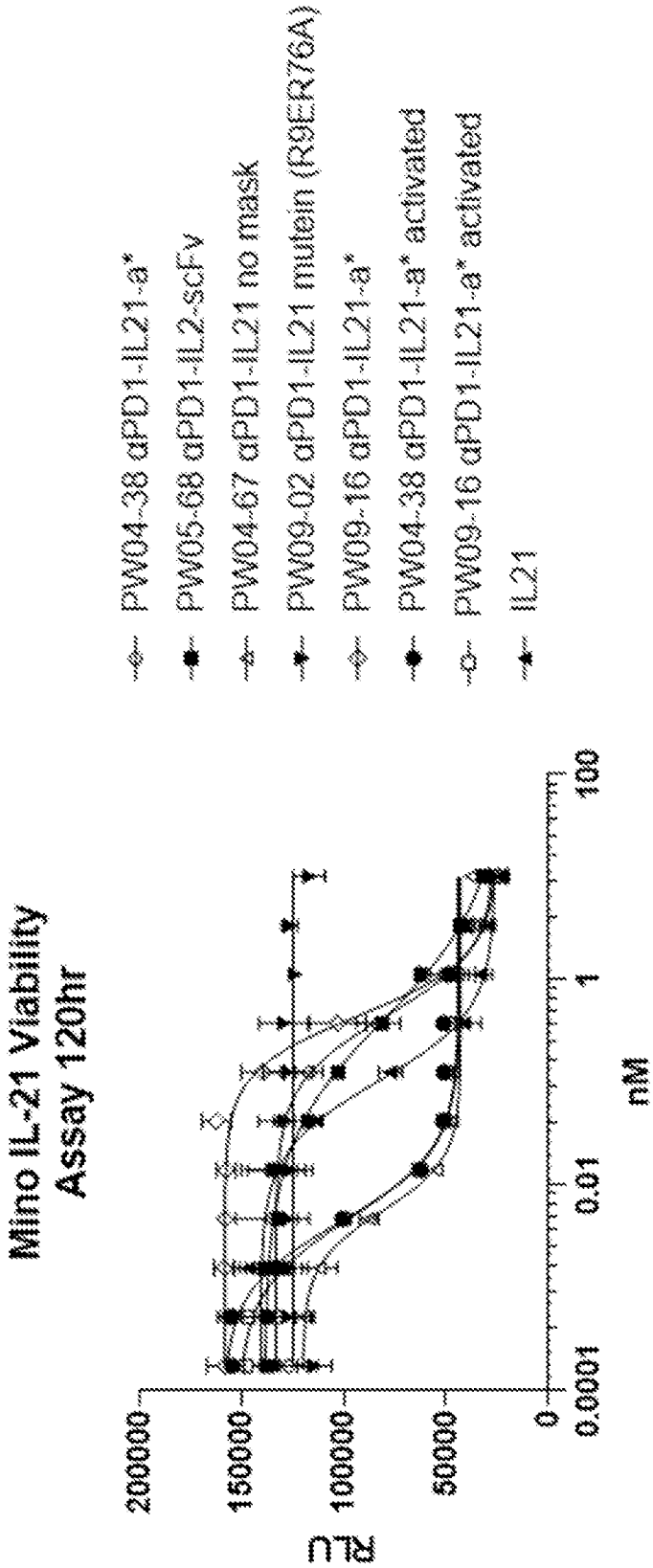


FIG. 4B

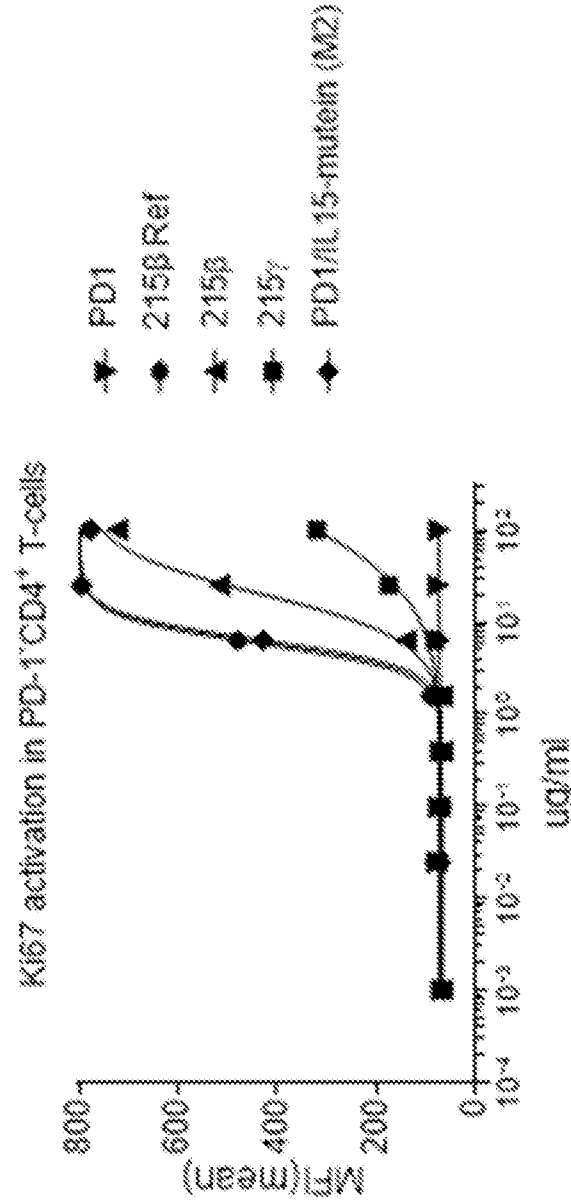


FIG. 5A

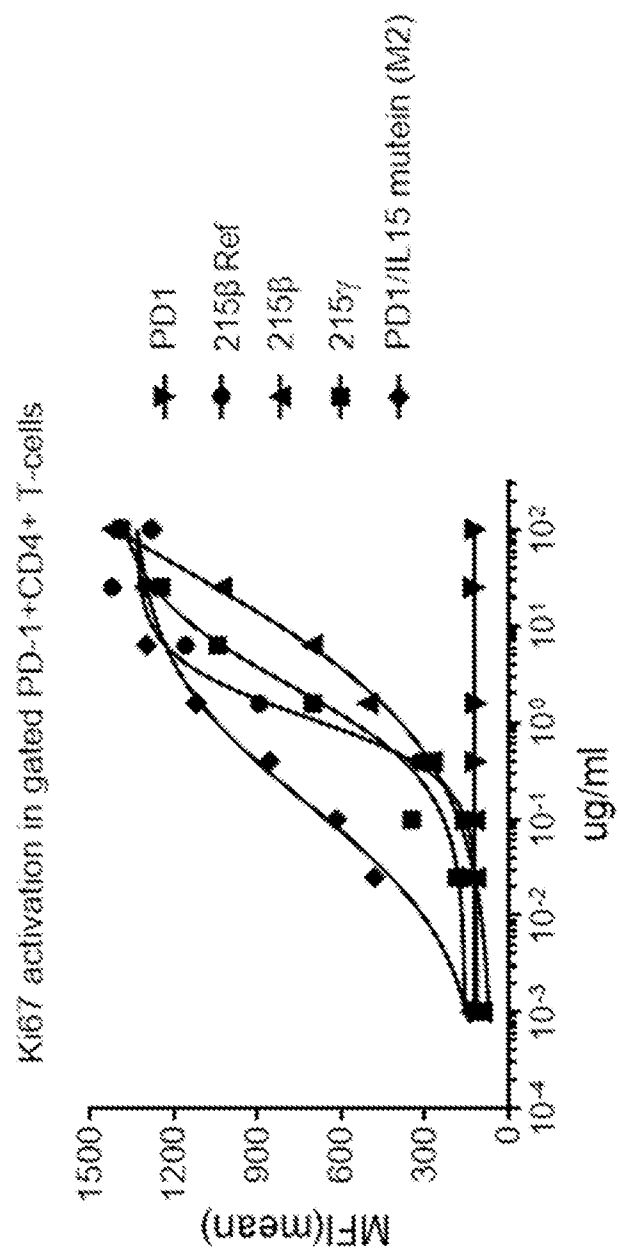


FIG. 5B

	PD-1+ T cell (EC ₅₀ µg/mL)	PD-1- T cells (EC ₅₀ µg/mL)	Potency Fold Change (EC ₅₀ PD-1- / EC ₅₀ PD-1+)
PD-1	>10,000	>10,000	N/A
215β Ref	1.12	5.72	5 x ↑
215β	38.48	20	2 x ↓
215γ	2.47	195	79 x ↑
PD1/IL15 mutein (M2)	0.14	6.25	44 x ↑

FIG. 5C

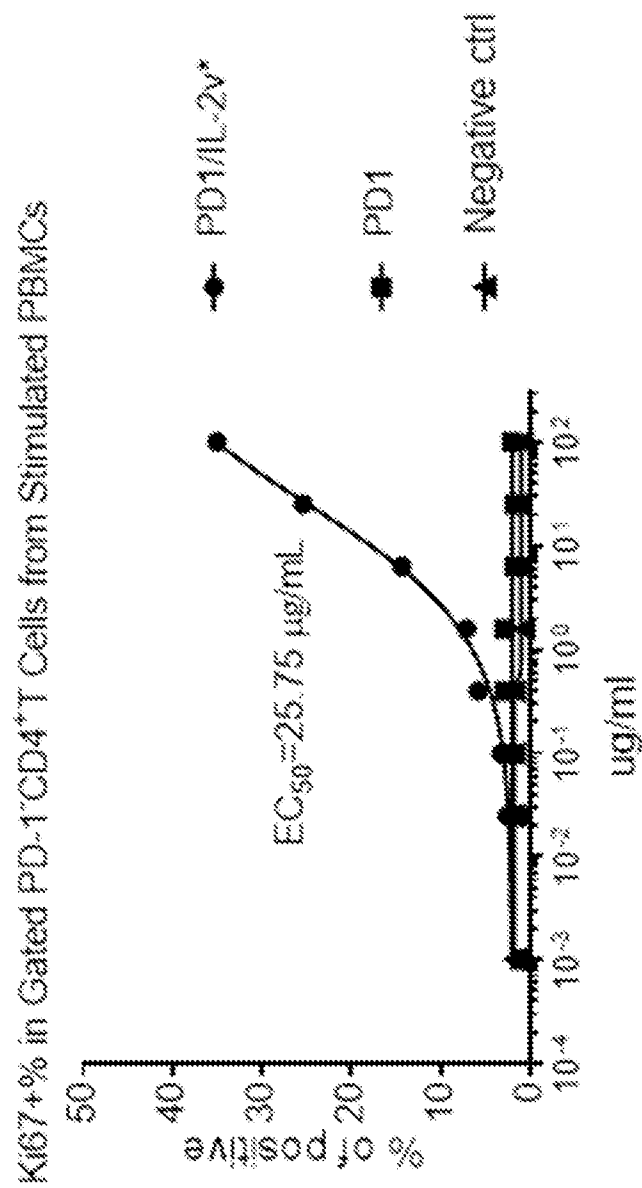


FIG. 6A

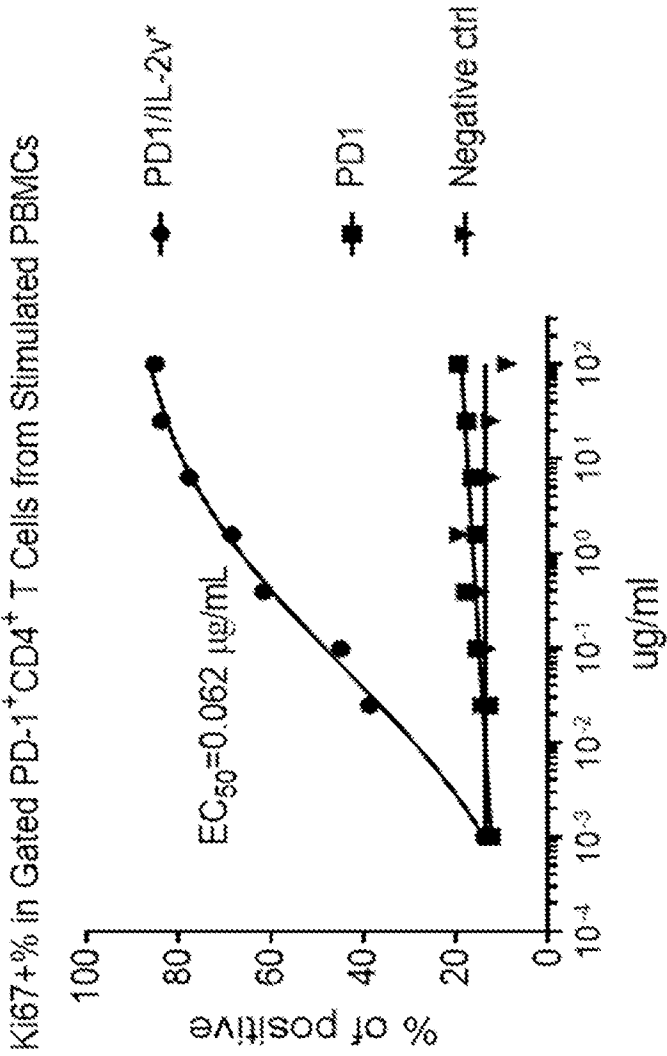


FIG. 6B

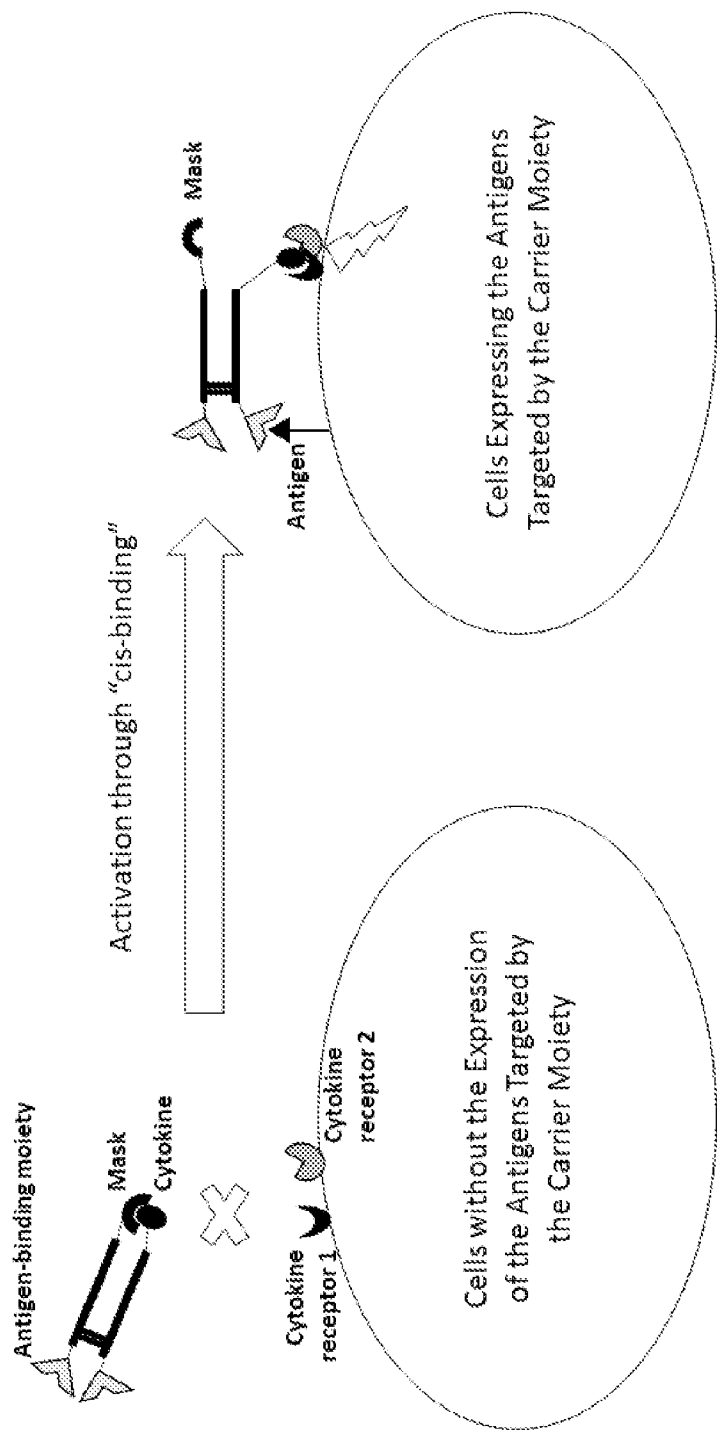


FIG. 7

SEQUENCE LISTING

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<120> NOVEL MASKED CYTOKINES AND METHODS OF USE THEREOF

<130> 025471.W0008

<140>

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<150> 63/126,393

<151> 2020-12-16

<150> 63/029,473

<151> 2020-05-23

<150> 63/027,138

<151> 2020-05-19

<150> 62/959,973

<151> 2020-01-11

<160> 84

<170> PatentIn version 3.5

<210> 1

<211> 133

<212> PRT

<213> Homo sapiens

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Gln	Gly	Gln	Asp	Arg	His	Met	Ile	Arg	Met	Arg	Gln	Leu	Ile	Asp	Ile
1				5					10					15	

Val	Asp	Gln	Leu	Lys	Asn	Tyr	Val	Asn	Asp	Leu	Val	Pro	Glu	Phe	Leu
			20					25					30		

Pro	Ala	Pro	Glu	Asp	Val	Glu	Thr	Asn	Cys	Glu	Trp	Ser	Ala	Phe	Ser
		35					40					45			

Cys	Phe	Gln	Lys	Ala	Gln	Leu	Lys	Ser	Ala	Asn	Thr	Gly	Asn	Asn	Glu
	50					55					60				

Arg	Ile	Ile	Asn	Val	Ser	Ile	Lys	Lys	Leu	Lys	Arg	Lys	Pro	Pro	Ser
65					70					75					80

Thr	Asn	Ala	Gly	Arg	Arg	Gln	Lys	His	Arg	Leu	Thr	Cys	Pro	Ser	Cys
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

85

90

95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
 100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
 115 120 125

Gly Ser Glu Asp Ser
 130

<210> 2

<211> 133

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 2

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
 1 5 10 15

Val Ala Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
 20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
 35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
 50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
 65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
 85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
 100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 3

<211> 133

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 3

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Lys Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 4
<211> 133
<212> PRT
<213> Artificial Sequence

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

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Arg Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 5
<211> 133
<212> PRT
<213> Artificial Sequence

<220>

<221> source

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

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Lys Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Arg Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 6

<211> 133

<212> PRT

<213> Homo sapiens

<400> 6

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His
1 5 10 15

Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys
20 25 30

Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys
35 40 45

Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys
50 55 60

Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu
65 70 75 80

Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu
85 90 95

Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala
100 105 110

Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile
115 120 125

Ile Ser Thr Leu Thr
130

<210> 7
<211> 113
<212> PRT
<213> Homo sapiens

<400> 7
Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr

<210> 8
<211> 75
<212> PRT
<213> Homo sapiens

<400> 8
Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala
65 70 75

<210> 9
<211> 152
<212> PRT
<213> Homo sapiens

<400> 9
Asp Cys Asp Ile Glu Gly Lys Asp Gly Lys Gln Tyr Glu Ser Val Leu
1 5 10 15

Met Val Ser Ile Asp Gln Leu Leu Asp Ser Met Lys Glu Ile Gly Ser
20 25 30

Asn Cys Leu Asn Asn Glu Phe Asn Phe Phe Lys Arg His Ile Cys Asp

35

40

45

Ala Asn Lys Glu Gly Met Phe Leu Phe Arg Ala Ala Arg Lys Leu Arg
 50 55 60

Gln Phe Leu Lys Met Asn Ser Thr Gly Asp Phe Asp Leu His Leu Leu
 65 70 75 80

Lys Val Ser Glu Gly Thr Thr Ile Leu Leu Asn Cys Thr Gly Gln Val
 85 90 95

Lys Gly Arg Lys Pro Ala Ala Leu Gly Glu Ala Gln Pro Thr Lys Ser
 100 105 110

Leu Glu Glu Asn Lys Ser Leu Lys Glu Gln Lys Lys Leu Asn Asp Leu
 115 120 125

Cys Phe Leu Lys Arg Leu Leu Gln Glu Ile Lys Thr Cys Trp Asn Lys
 130 135 140

Ile Leu Met Gly Thr Lys Glu His
 145 150

<210> 10

<211> 126

<212> PRT

<213> Homo sapiens

<400> 10

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

Asn Lys Met Gln Glu Asp Pro Ala Ser Lys Cys His Cys Ser Ala Asn
 20 25 30

Val Thr Ser Cys Leu Cys Leu Gly Ile Pro Ser Asp Asn Cys Thr Arg
 35 40 45

Pro Cys Phe Ser Glu Arg Leu Ser Gln Met Thr Asn Thr Thr Met Gln
 50 55 60

Thr Arg Tyr Pro Leu Ile Phe Ser Arg Val Lys Lys Ser Val Glu Val

65

70

75

80

Leu Lys Asn Asn Lys Cys Pro Tyr Phe Ser Cys Glu Gln Pro Cys Asn
 85 90 95

Gln Thr Thr Ala Gly Asn Ala Leu Thr Phe Leu Lys Ser Leu Leu Glu
 100 105 110

Ile Phe Gln Lys Glu Lys Met Arg Gly Met Arg Gly Lys Ile
 115 120 125

<210> 11

<211> 214

<212> PRT

<213> Homo sapiens

<400> 11

Ala Val Asn Gly Thr Ser Gln Phe Thr Cys Phe Tyr Asn Ser Arg Ala
 1 5 10 15

Asn Ile Ser Cys Val Trp Ser Gln Asp Gly Ala Leu Gln Asp Thr Ser
 20 25 30

Cys Gln Val His Ala Trp Pro Asp Arg Arg Arg Trp Asn Gln Thr Cys
 35 40 45

Glu Leu Leu Pro Val Ser Gln Ala Ser Trp Ala Cys Asn Leu Ile Leu
 50 55 60

Gly Ala Pro Asp Ser Gln Lys Leu Thr Thr Val Asp Ile Val Thr Leu
 65 70 75 80

Arg Val Leu Cys Arg Glu Gly Val Arg Trp Arg Val Met Ala Ile Gln
 85 90 95

Asp Phe Lys Pro Phe Glu Asn Leu Arg Leu Met Ala Pro Ile Ser Leu
 100 105 110

Gln Val Val His Val Glu Thr His Arg Cys Asn Ile Ser Trp Glu Ile
 115 120 125

Ser Gln Ala Ser His Tyr Phe Glu Arg His Leu Glu Phe Glu Ala Arg

130

135

140

Thr Leu Ser Pro Gly His Thr Trp Glu Glu Ala Pro Leu Leu Thr Leu
 145 150 155 160

Lys Gln Lys Gln Glu Trp Ile Cys Leu Glu Thr Leu Thr Pro Asp Thr
 165 170 175

Gln Tyr Glu Phe Gln Val Arg Val Lys Pro Leu Gln Gly Glu Phe Thr
 180 185 190

Thr Trp Ser Pro Trp Ser Gln Pro Leu Ala Phe Arg Thr Lys Pro Ala
 195 200 205

Ala Leu Gly Lys Asp Thr
 210

<210> 12

<211> 213

<212> PRT

<213> Homo sapiens

<400> 12

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
 1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
 20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
 35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
 50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
 65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
 85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser

100

105

110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
 115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
 130 135 140

Gly Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp
 145 150 155 160

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
 165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
 180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
 195 200 205

Glu Glu Leu Lys Glu
 210

<210> 13

<211> 240

<212> PRT

<213> Homo sapiens

<400> 13

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

Asp Phe Phe Leu Thr Thr Met Pro Thr Asp Ser Leu Ser Val Ser Thr
 20 25 30

Leu Pro Leu Pro Glu Val Gln Cys Phe Val Phe Asn Val Glu Tyr Met
 35 40 45

Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro Gln Pro Thr Asn Leu Thr
 50 55 60

Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn Asp Lys Val Gln Lys Cys

65

70

75

80

Ser His Tyr Leu Phe Ser Glu Glu Ile Thr Ser Gly Cys Gln Leu Gln
 85 90 95

Lys Lys Glu Ile His Leu Tyr Gln Thr Phe Val Val Gln Leu Gln Asp
 100 105 110

Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln Met Leu Lys Leu Gln Asn
 115 120 125

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

Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn Arg Phe Leu Asn His Cys
 145 150 155 160

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

Glu Gln Ser Val Asp Tyr Arg His Lys Phe Ser Leu Pro Ser Val Asp
 180 185 190

Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg Ser Arg Phe Asn Pro Leu
 195 200 205

Cys Gly Ser Ala Gln His Trp Ser Glu Trp Ser His Pro Ile His Trp
 210 215 220

Gly Ser Asn Thr Ser Lys Glu Asn Pro Phe Leu Phe Ala Leu Glu Ala
 225 230 235 240

<210> 14

<211> 219

<212> PRT

<213> Homo sapiens

<400> 14

Glu Ser Gly Tyr Ala Gln Asn Gly Asp Leu Glu Asp Ala Glu Leu Asp
 1 5 10 15

Asp Tyr Ser Phe Ser Cys Tyr Ser Gln Leu Glu Val Asn Gly Ser Gln

20

25

30

His Ser Leu Thr Cys Ala Phe Glu Asp Pro Asp Val Asn Ile Thr Asn
 35 40 45

Leu Glu Phe Glu Ile Cys Gly Ala Leu Val Glu Val Lys Cys Leu Asn
 50 55 60

Phe Arg Lys Leu Gln Glu Ile Tyr Phe Ile Glu Thr Lys Lys Phe Leu
 65 70 75 80

Leu Ile Gly Lys Ser Asn Ile Cys Val Lys Val Gly Glu Lys Ser Leu
 85 90 95

Thr Cys Lys Lys Ile Asp Leu Thr Thr Ile Val Lys Pro Glu Ala Pro
 100 105 110

Phe Asp Leu Ser Val Val Tyr Arg Glu Gly Ala Asn Asp Phe Val Val
 115 120 125

Thr Phe Asn Thr Ser His Leu Gln Lys Lys Tyr Val Lys Val Leu Met
 130 135 140

His Asp Val Ala Tyr Arg Gln Glu Lys Asp Glu Asn Lys Trp Thr His
 145 150 155 160

Val Asn Leu Ser Ser Thr Lys Leu Thr Leu Leu Gln Arg Lys Leu Gln
 165 170 175

Pro Ala Ala Met Tyr Glu Ile Lys Val Arg Ser Ile Pro Asp His Tyr
 180 185 190

Phe Lys Gly Phe Trp Ser Glu Trp Ser Pro Ser Tyr Tyr Phe Arg Thr
 195 200 205

Pro Glu Ile Asn Asn Ser Ser Gly Glu Met Asp
 210 215

<210> 15

<211> 230

<212> PRT

<213> Homo sapiens

<400> 15

Ser Val Thr Gly Glu Gly Gln Gly Pro Arg Ser Arg Thr Phe Thr Cys
1 5 10 15

Leu Thr Asn Asn Ile Leu Arg Ile Asp Cys His Trp Ser Ala Pro Glu
20 25 30

Leu Gly Gln Gly Ser Ser Pro Trp Leu Leu Phe Thr Ser Asn Gln Ala
35 40 45

Pro Gly Gly Thr His Lys Cys Ile Leu Arg Gly Ser Glu Cys Thr Val
50 55 60

Val Leu Pro Pro Glu Ala Val Leu Val Pro Ser Asp Asn Phe Thr Ile
65 70 75 80

Thr Phe His His Cys Met Ser Gly Arg Glu Gln Val Ser Leu Val Asp
85 90 95

Pro Glu Tyr Leu Pro Arg Arg His Val Lys Leu Asp Pro Pro Ser Asp
100 105 110

Leu Gln Ser Asn Ile Ser Ser Gly His Cys Ile Leu Thr Trp Ser Ile
115 120 125

Ser Pro Ala Leu Glu Pro Met Thr Thr Leu Leu Ser Tyr Glu Leu Ala
130 135 140

Phe Lys Lys Gln Glu Glu Ala Trp Glu Gln Ala Gln His Arg Asp His
145 150 155 160

Ile Val Gly Val Thr Trp Leu Ile Leu Glu Ala Phe Glu Leu Asp Pro
165 170 175

Gly Phe Ile His Glu Ala Arg Leu Arg Val Gln Met Ala Thr Leu Glu
180 185 190

Asp Asp Val Val Glu Glu Glu Arg Tyr Thr Gly Gln Trp Ser Glu Trp
195 200 205

Ser Gln Pro Val Cys Phe Gln Ala Pro Gln Arg Gln Gly Pro Leu Ile
210 215 220

Pro Pro Trp Gly Trp Pro
225 230

<210> 16
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<213> Artificial Sequence

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

<400> 16
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr
20 25 30

Ile Thr Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

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

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

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

Cys Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

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

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

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

Pro Gly Ala Gly Gly Gly Gly Ser Val His Met Pro Leu Gly Phe Leu
225 230 235 240

Gly Pro Arg Gln Ala Arg Val Val Asn Gly Gly Gly Gly Gly Ser Gly
245 250 255

Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
260 265 270

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

Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
290 295 300

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Arg Arg Ala Thr Gly Ile Pro
305 310 315 320

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
325 330 335

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Tyr
340 345 350

Gly Ser Ser His Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Ser Gly
355 360 365

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val
370 375 380

Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu
385 390 395 400

Lys Ile Ser Cys Lys Val Ser Gly Tyr Phe Phe Thr Thr Tyr Trp Ile
405 410 415

Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Tyr Met Gly Ile
420 425 430

Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln Gly
435 440 445

Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln
450 455 460

Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg
465 470 475 480

Gly Gly Asn Trp Asn Cys Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
485 490 495

Thr Val Ser Ser
500

<210> 17

<211> 452

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 17

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr
20 25 30

Ile Thr Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

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

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

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

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

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

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

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

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

Pro Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly

225					230						235				240
Gly	Ser	Ile	Thr	Cys	Pro	Pro	Pro	Met	Ser	Val	Glu	His	Ala	Asp	Ile
				245					250					255	
Trp	Val	Lys	Ser	Tyr	Ser	Leu	Tyr	Ser	Arg	Glu	Arg	Tyr	Ile	Cys	Asn
			260					265					270		
Ser	Gly	Phe	Lys	Arg	Lys	Ala	Gly	Thr	Ser	Ser	Leu	Thr	Glu	Cys	Val
		275					280					285			
Leu	Asn	Lys	Ala	Thr	Asn	Val	Ala	His	Trp	Thr	Thr	Pro	Ser	Leu	Lys
	290					295					300				
Cys	Ile	Arg	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
305					310					315					320
Ser	Ala	Ala	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
			325					330						335	
Gly	Ser	Asn	Trp	Val	Asn	Val	Ile	Ser	Asp	Leu	Lys	Lys	Ile	Glu	Asp
		340						345					350		
Leu	Ile	Gln	Ser	Met	His	Ile	Asp	Ala	Thr	Leu	Tyr	Thr	Glu	Ser	Asp
	355						360					365			
Val	His	Pro	Ser	Cys	Lys	Val	Thr	Ala	Met	Lys	Cys	Phe	Leu	Leu	Glu
	370					375					380				
Leu	Gln	Val	Ile	Ser	Leu	Glu	Ser	Gly	Asp	Ala	Ser	Ile	His	Asp	Thr
385					390				395						400
Val	Glu	Asp	Leu	Ile	Ile	Leu	Ala	Asn	Asn	Ser	Leu	Ser	Ser	Asn	Gly
			405					410						415	
Asn	Val	Thr	Glu	Ser	Gly	Cys	Lys	Glu	Cys	Glu	Glu	Leu	Glu	Glu	Lys
		420						425					430		
Asn	Ile	Lys	Glu	Phe	Leu	Gln	Ser	Phe	Val	His	Ile	Val	Gln	Met	Phe
	435					440						445			

Ile Asn Thr Ser
450

<210> 18

<211> 240

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 18

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

Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Tyr Phe Phe Thr Thr Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Tyr Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Asn Trp Asn Cys Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Gly Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
130 135 140

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
145 150 155 160

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
165 170 175

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Arg Arg Ala Thr Gly Ile
180 185 190

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
195 200 205

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg
210 215 220

Tyr Gly Ser Ser His Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Ser
225 230 235 240

<210> 19

<211> 240

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 19

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Arg Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Tyr Gly Ser Ser His

85

90

95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Ser Gly Gly Gly Gly Ser
 100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Gln
 115 120 125

Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys
 130 135 140

Lys Val Ser Gly Tyr Phe Phe Thr Thr Tyr Trp Ile Gly Trp Val Arg
 145 150 155 160

Gln Met Pro Gly Lys Gly Leu Glu Tyr Met Gly Ile Ile Tyr Pro Gly
 165 170 175

Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile
 180 185 190

Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu
 195 200 205

Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Asn Trp
 210 215 220

Asn Cys Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 225 230 235 240

<210> 20

<211> 247

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 20

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Phe Ile Trp Tyr Asp Gly Ser Asp Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Asp Ser Ser Asp Trp Tyr Gly Asp Tyr Tyr Phe Gly
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val
130 135 140

Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
145 150 155 160

Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
165 170 175

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly
180 185 190

Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly
195 200 205

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp
210 215 220

Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Trp Thr Phe Gly Gln
225 230 235 240

Gly Thr Lys Val Glu Ile Lys
245

<210> 21

<211> 247

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 21

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Trp Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser
115 120 125

Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala
130 135 140

Ala Ser Gly Phe Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln

145		150		155		160									
Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ala	Phe	Ile	Trp	Tyr	Asp	Gly
				165					170					175	
Ser	Asp	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser
			180					185					190		
Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg
		195					200					205			
Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Gly	Asp	Ser	Ser
	210					215					220				
Asp	Trp	Tyr	Gly	Asp	Tyr	Tyr	Phe	Gly	Met	Asp	Val	Trp	Gly	Gln	Gly
225					230					235					240
Thr	Thr	Val	Thr	Val	Ser	Ser									
				245											

<210> 22
 <211> 248
 <212> PRT
 <213> Artificial Sequence

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

<400> 22
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

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

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Asp Arg Tyr Tyr Asn Trp Asn Tyr Phe Leu Gly Ser Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu
130 135 140

Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys Thr Ala Arg Ile
145 150 155 160

Thr Cys Gly Gly Asn Asn Ile Arg Ser Lys Ser Val His Trp Tyr Gln
165 170 175

Gln Lys Pro Gly Gln Ala Pro Val Val Val Ile Tyr Tyr Asp Ser Asp
180 185 190

Arg Pro Ser Gly Ile Pro Glu Arg Ile Ser Gly Ser Asn Ser Gly Asn
195 200 205

Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp
210 215 220

Tyr Phe Cys Gln Val Trp Asp Ser Ser Ser Asp His His Val Phe Gly
225 230 235 240

Gly Gly Thr Lys Leu Thr Val Leu
245

<210> 23

<211> 248

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 23

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Arg Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Val Val Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Ile Ser Gly Ser
50 55 60

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

Asp Glu Ala Asp Tyr Phe Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly
100 105 110

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val
115 120 125

Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser
130 135 140

Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr Ala Ile Ser Trp Val
145 150 155 160

Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Gly Ile Ile Pro
165 170 175

Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr
180 185 190

Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser

195

200

205

Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Val Asp Arg
 210 215 220

Tyr Tyr Asn Trp Asn Tyr Phe Leu Gly Ser Phe Asp Tyr Trp Gly Gln
 225 230 235 240

Gly Thr Leu Val Thr Val Ser Ser
 245

<210> 24

<211> 588

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 24

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

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Gln Glu Glu Met Thr
340 345 350

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

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Leu Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly
435 440 445

Gly Ser Gly Gly Gly Gly Ser Ala Pro Ala Ser Ser Ser Thr Lys Lys
450 455 460

Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu
465 470 475 480

Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Ser Met Leu Thr
485 490 495

Ala Lys Phe Ala Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln
500 505 510

Cys Leu Glu Glu Ala Leu Lys Pro Leu Glu Glu Val Leu Asn Leu Ala
515 520 525

Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile
530 535 540

Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys
545 550 555 560

Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp
565 570 575

Ile Thr Phe Ser Gln Ser Ile Ile Ser Thr Leu Thr
580 585

<210> 25
<211> 675
<212> PRT
<213> Artificial Sequence

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

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

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Gln Glu Glu Met Thr

340

345

350

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

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val
 385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
 405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 420 425 430

Ser Leu Ser Leu Ser Leu Gly Lys Gly Gly Gly Gly Ser Gly Pro Leu
 435 440 445

Gly Val Arg Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Val Asn
 450 455 460

Gly Thr Ser Gln Phe Thr Cys Phe Tyr Asn Ser Arg Ala Asn Ile Ser
 465 470 475 480

Cys Val Trp Ser Gln Asp Gly Ala Leu Gln Asp Thr Ser Cys Gln Val
 485 490 495

His Ala Trp Pro Asp Arg Arg Arg Trp Asn Gln Thr Cys Glu Leu Leu
 500 505 510

Pro Val Ser Gln Ala Ser Trp Ala Cys Asn Leu Ile Leu Gly Ala Pro
 515 520 525

Asp Ser Gln Lys Leu Thr Thr Val Asp Ile Val Thr Leu Arg Val Leu
 530 535 540

Cys Arg Glu Gly Val Arg Trp Arg Val Met Ala Ile Gln Asp Phe Lys
 545 550 555 560

Pro Phe Glu Asn Leu Arg Leu Met Ala Pro Ile Ser Leu Gln Val Val
565 570 575

His Val Glu Thr His Arg Cys Asn Ile Ser Trp Glu Ile Ser Gln Ala
580 585 590

Ser His Tyr Phe Glu Arg His Leu Glu Phe Glu Ala Arg Thr Leu Ser
595 600 605

Pro Gly His Thr Trp Glu Glu Ala Pro Leu Leu Thr Leu Lys Gln Lys
610 615 620

Gln Glu Trp Ile Cys Leu Glu Thr Leu Thr Pro Asp Thr Gln Tyr Glu
625 630 635 640

Phe Gln Val Arg Val Lys Pro Leu Gln Gly Glu Phe Thr Thr Trp Ser
645 650 655

Pro Trp Ser Gln Pro Leu Ala Phe Arg Thr Lys Pro Ala Ala Leu Gly
660 665 670

Lys Asp Thr
675

<210> 26

<211> 692

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 26

Met Gly Val Lys Val Leu Phe Ala Leu Ile Cys Ile Ala Val Ala Glu
1 5 10 15

Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly
20 25 30

Arg Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn
35 40 45

Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
50 55 60

Val Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser
65 70 75 80

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
85 90 95

Phe Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
100 105 110

Cys Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
115 120 125

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
130 135 140

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
145 150 155 160

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
165 170 175

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
180 185 190

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
195 200 205

Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
210 215 220

Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
225 230 235 240

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

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
260 265 270

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
275 280 285

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
290 295 300

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
305 310 315 320

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
325 330 335

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
340 345 350

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
355 360 365

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
370 375 380

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
385 390 395 400

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
405 410 415

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
420 425 430

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
435 440 445

Lys Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly
450 455 460

Gly Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys
465 470 475 480

Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys Ile
485 490 495

Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp Gln
500 505 510

Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu His
515 520 525

Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met Asp
530 535 540

Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr Asp
545 550 555 560

Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala Glu
565 570 575

Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser Gly
580 585 590

Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe Tyr
595 600 605

Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg Gly
610 615 620

Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp Ser
625 630 635 640

Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser Tyr
645 650 655

Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln Gly
660 665 670

Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser Glu
675 680 685

Glu Leu Lys Glu
690

<210> 27
<211> 20
<212> PRT
<213> Artificial Sequence

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

<220>
<221> SITE
<222> (1)..(20)
<223> /note="This sequence may encompass 1-4 'Gly Gly Gly Gly Ser' repeating units"

<400> 27
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> 28
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 28
Gly Gly Gly Gly Ser
1 5

<210> 29
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 29
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 30
<211> 15
<212> PRT
<213> Artificial Sequence

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

<400> 30
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 31
<211> 22
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(12)
<223> /replace="N"

<220>
<221> SITE
<222> (1)..(22)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 31
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Gly Ser
20

<210> 32

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

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

<220>
<221> VARIANT
<222> (16)..(17)
<223> /replace="N"

<220>
<221> SITE
<222> (1)..(27)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 32
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
1 5 10 15

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

<210> 33
<211> 32
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (16)..(17)
<223> /replace="N"

<220>
<221> SITE
<222> (1)..(32)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 33
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
1 5 10 15

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

<210> 34
<211> 20
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (10)..(10)
<223> /replace="A" or "N"

<220>
<221> VARIANT
<222> (15)..(15)
<223> /replace="N"

<220>
<221> SITE
<222> (1)..(20)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 34
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> 35
<211> 604
<212> PRT
<213> Artificial Sequence

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

polypeptide"

<220>

<221> SITE

<222> (440)..(454)

<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>

<221> VARIANT

<222> (455)..(455)

<223> /replace=" "

<220>

<221> VARIANT

<222> (456)..(456)

<223> /replace=" "

<220>

<221> SITE

<222> (457)..(471)

<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>

<221> VARIANT

<222> (474)..(474)

<223> /replace="A"

<220>

<221> VARIANT

<222> (506)..(506)

<223> /replace="N"

<220>

<221> VARIANT

<222> (513)..(513)

<223> /replace="G" or "S" or "T" or "Q" or "E" or "N" or
"D" or "R" or "K"

<220>

<221> VARIANT

<222> (516)..(516)

<223> /replace="G" or "S" or "T" or "Q" or "E" or "N" or
"D" or "R" or "K"

<220>

<221> VARIANT

<222> (543)..(543)

<223> /replace="G" or "S" or "T" or "Q" or "E" or "N" or
"D" or "R" or "K"

<220>

<221> VARIANT
<222> (544)..(544)
<223> /replace="T"

<220>
<221> VARIANT
<222> (596)..(596)
<223> /replace="S"

<220>
<221> SITE
<222> (1)..(604)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 35
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr

145		150		155		160
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr		165		170		175
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys		180		185		190
Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp		195		200		205
Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala		210		215		220
Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro		225		230		235
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val		245		250		255
Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val		260		265		270
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln		275		280		285
Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln		290		295		300
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly		305		310		315
Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro		325		330		335
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr		340		345		350
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser		355		360		365

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Leu Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly
435 440 445

Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly Gly
450 455 460

Gly Ser Gly Gly Gly Gly Ser Ala Pro Asn Ser Ser Ser Thr Lys Lys
465 470 475 480

Thr Gln Leu Gln Leu Glu His Leu Leu Leu Asp Leu Gln Met Ile Leu
485 490 495

Asn Gly Ile Asn Asn Tyr Lys Asn Pro Lys Leu Thr Arg Met Leu Thr
500 505 510

Ala Lys Phe Ala Met Pro Lys Lys Ala Thr Glu Leu Lys His Leu Gln
515 520 525

Cys Leu Glu Glu Glu Leu Lys Pro Leu Glu Glu Val Leu Asn Ala Ala
530 535 540

Gln Ser Lys Asn Phe His Leu Arg Pro Arg Asp Leu Ile Ser Asn Ile
545 550 555 560

Asn Val Ile Val Leu Glu Leu Lys Gly Ser Glu Thr Thr Phe Met Cys
565 570 575

Glu Tyr Ala Asp Glu Thr Ala Thr Ile Val Glu Phe Leu Asn Arg Trp

580

585

590

Ile Thr Phe Ala Gln Ser Ile Ile Ser Thr Leu Thr
595 600

<210> 36

<211> 686

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<220>

<221> SITE

<222> (441)..(455)

<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser' repeating units"

<220>

<221> VARIANT

<222> (456)..(456)

<223> /replace=" "

<220>

<221> VARIANT

<222> (457)..(457)

<223> /replace=" "

<220>

<221> SITE

<222> (458)..(472)

<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser' repeating units"

<220>

<221> SITE

<222> (1)..(686)

<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 36

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

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
340 345 350

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

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly
435 440 445

Gly Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly
450 455 460

Gly Gly Ser Gly Gly Gly Gly Ser Ala Val Asn Gly Thr Ser Gln Phe
465 470 475 480

Thr Cys Phe Tyr Asn Ser Arg Ala Asn Ile Ser Cys Val Trp Ser Gln
485 490 495

Asp Gly Ala Leu Gln Asp Thr Ser Cys Gln Val His Ala Trp Pro Asp
500 505 510

Arg Arg Arg Trp Asn Gln Thr Cys Glu Leu Leu Pro Val Ser Gln Ala
515 520 525

Ser Trp Ala Cys Asn Leu Ile Leu Gly Ala Pro Asp Ser Gln Lys Leu
530 535 540

Thr Thr Val Asp Ile Val Thr Leu Arg Val Leu Cys Arg Glu Gly Val
545 550 555 560

Arg Trp Arg Val Met Ala Ile Gln Asp Phe Lys Pro Phe Glu Asn Leu
565 570 575

Arg Leu Met Ala Pro Ile Ser Leu Gln Val Val His Val Glu Thr His
580 585 590

Arg Cys Asn Ile Ser Trp Glu Ile Ser Gln Ala Ser His Tyr Phe Glu
595 600 605

Arg His Leu Glu Phe Glu Ala Arg Thr Leu Ser Pro Gly His Thr Trp
610 615 620

Glu Glu Ala Pro Leu Leu Thr Leu Lys Gln Lys Gln Glu Trp Ile Cys
625 630 635 640

Leu Glu Thr Leu Thr Pro Asp Thr Gln Tyr Glu Phe Gln Val Arg Val
645 650 655

Lys Pro Leu Gln Gly Glu Phe Thr Thr Trp Ser Pro Trp Ser Gln Pro
660 665 670

Leu Ala Phe Arg Thr Lys Pro Ala Ala Leu Gly Lys Asp Thr
675 680 685

<210> 37

<211> 665

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 37

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

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
340 345 350

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

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

370

375

380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
 405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 420 425 430

Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly
 435 440 445

Gly Ser Gly Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro Met Ser Val
 450 455 460

Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu
 465 470 475 480

Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Ser Ser
 485 490 495

Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr
 500 505 510

Thr Pro Ser Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Gly Gly Gly
 515 520 525

Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly Gly
 530 535 540

Gly Ser Gly Gly Gly Gly Ser Asn Trp Val Asn Val Ile Ser Asp Leu
 545 550 555 560

Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu
 565 570 575

Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys
 580 585 590

Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala
595 600 605

Ser Ile His Asp Thr Val Glu Asp Leu Ile Ile Leu Ala Asn Asn Ser
610 615 620

Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu
625 630 635 640

Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His
645 650 655

Ile Val Gln Met Phe Ile Asn Thr Ser
660 665

<210> 38
<211> 712
<212> PRT
<213> Artificial Sequence

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

<220>
<221> SITE
<222> (441)..(455)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>
<221> VARIANT
<222> (456)..(456)
<223> /replace=" "

<220>
<221> VARIANT
<222> (457)..(457)
<223> /replace=" "

<220>
<221> SITE
<222> (458)..(472)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>

<221> SITE

<222> (1)..(712)

<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 38

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

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
340 345 350

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

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly
435 440 445

Gly Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly
450 455 460

Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro
465 470 475 480

Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg
485 490 495

Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys
500 505 510

Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Arg Arg Ala
515 520 525

Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
530 535 540

Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr
545 550 555 560

Cys Gln Arg Tyr Gly Ser Ser His Thr Phe Gly Gln Gly Thr Lys Leu
565 570 575

Glu Ile Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
580 585 590

Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro
595 600 605

Gly Glu Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Tyr Phe Phe Thr
610 615 620

Thr Tyr Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu
625 630 635 640

Tyr Met Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro
645 650 655

Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr
660 665 670

Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr
675 680 685

Tyr Cys Ala Arg Gly Gly Asn Trp Asn Cys Phe Asp Tyr Trp Gly Gln
690 695 700

Gly Thr Leu Val Thr Val Ser Ser
705 710

<210> 39

<211> 605

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 39

Met Gly Val Lys Val Leu Phe Ala Leu Ile Cys Ile Ala Val Ala Glu
1 5 10 15

Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly
20 25 30

Arg Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn
35 40 45

Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
50 55 60

Val Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser

65					70					75					80
Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu
				85					90				95		
Phe	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr
			100					105					110		
Cys	Ala	Thr	Asn	Asp	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val
		115					120					125			
Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys
	130					135					140				
Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys
145					150					155					160
Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu
				165					170					175	
Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu
			180					185						190	
Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr
		195					200					205			
Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val
	210					215					220				
Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro
225					230					235					240
Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
				245					250					255	
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
			260					265					270		
Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr
		275					280					285			

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
290 295 300

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
305 310 315 320

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
325 330 335

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
340 345 350

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
355 360 365

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
370 375 380

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
385 390 395 400

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
405 410 415

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
420 425 430

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
435 440 445

Lys Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly
450 455 460

Gly Gly Ser Gly Gly Gly Gly Ser Gln Gly Gln Asp Arg His Met Ile
465 470 475 480

Arg Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val
485 490 495

Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp Val Glu Thr

500

505

510

Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys
 515 520 525

Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys
 530 535 540

Lys Leu Lys Arg Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys
 545 550 555 560

His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro
 565 570 575

Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His
 580 585 590

Gln His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
 595 600 605

<210> 40

<211> 691

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 40

Met Gly Val Lys Val Leu Phe Ala Leu Ile Cys Ile Ala Val Ala Glu
 1 5 10 15

Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly
 20 25 30

Arg Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn
 35 40 45

Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
 50 55 60

Val Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser
65 70 75 80

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
85 90 95

Phe Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
100 105 110

Cys Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
115 120 125

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
130 135 140

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
145 150 155 160

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
165 170 175

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
180 185 190

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
195 200 205

Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
210 215 220

Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
225 230 235 240

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

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
260 265 270

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
275 280 285

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
290 295 300

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
305 310 315 320

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
325 330 335

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
340 345 350

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
355 360 365

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
370 375 380

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
385 390 395 400

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
405 410 415

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
420 425 430

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
435 440 445

Lys Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly
450 455 460

Gly Gly Ser Gly Pro Leu Gly Val Arg Gly Gly Gly Gly Ser Cys Pro
465 470 475 480

Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys Ile Leu
485 490 495

Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp Gln Asp
500 505 510

Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu His Arg
515 520 525

Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met Asp Val
530 535 540

Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr Asp Gln
545 550 555 560

Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala Glu Ser
565 570 575

Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser Gly Gln
580 585 590

Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe Tyr Met
595 600 605

Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg Gly Asp
610 615 620

Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp Ser Arg
625 630 635 640

Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser Tyr Glu
645 650 655

Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln Gly Thr
660 665 670

Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser Glu Glu
675 680 685

Leu Lys Glu
690

<210> 41
<211> 726

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 41

Met Gly Val Lys Val Leu Phe Ala Leu Ile Cys Ile Ala Val Ala Glu
1 5 10 15

Ala Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly
20 25 30

Arg Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn
35 40 45

Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
50 55 60

Val Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser
65 70 75 80

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
85 90 95

Phe Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
100 105 110

Cys Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
115 120 125

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
130 135 140

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
145 150 155 160

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
165 170 175

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu

180

185

190

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
 195 200 205

Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
 210 215 220

Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
 225 230 235 240

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

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 260 265 270

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
 275 280 285

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 290 295 300

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 305 310 315 320

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 325 330 335

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 340 345 350

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
 355 360 365

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 370 375 380

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 385 390 395 400

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
405 410 415

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
420 425 430

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
435 440 445

Lys Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly
450 455 460

Gly Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
465 470 475 480

Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu
485 490 495

Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
500 505 510

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
515 520 525

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
530 535 540

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
545 550 555 560

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Trp Thr Phe
565 570 575

Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly
580 585 590

Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly
595 600 605

Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala

610

615

620

Ser Gly Phe Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala
 625 630 635 640

Pro Gly Lys Gly Leu Glu Trp Val Ala Phe Ile Trp Tyr Asp Gly Ser
 645 650 655

Asp Lys Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
 660 665 670

Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
 675 680 685

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Gly Asp Ser Ser Asp
 690 695 700

Trp Tyr Gly Asp Tyr Tyr Phe Gly Met Asp Val Trp Gly Gln Gly Thr
 705 710 715 720

Thr Val Thr Val Ser Ser
 725

<210> 42

<211> 588

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 42

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

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Gln Glu Glu Met Thr
340 345 350

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

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly
435 440 445

Gly Ser Gly Gly Gly Gly Ser Gln Gly Gln Asp Arg His Met Ile Arg
450 455 460

Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn
465 470 475 480

Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp Val Glu Thr Asn
485 490 495

Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser
500 505 510

Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys
515 520 525

Leu Lys Arg Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His
530 535 540

Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys
545 550 555 560

Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln
565 570 575

His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
580 585

<210> 43

<211> 675

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 43

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

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

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

275

280

285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
 305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 325 330 335

Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
 340 345 350

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

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val
 385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
 405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 420 425 430

Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly
 435 440 445

Gly Ser Ala Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro
 450 455 460

Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys Ile Leu
 465 470 475 480

Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp Gln Asp
 485 490 495

Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu His Arg
500 505 510

Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met Asp Val
515 520 525

Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr Asp Gln
530 535 540

Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala Glu Ser
545 550 555 560

Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser Gly Gln
565 570 575

Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe Tyr Met
580 585 590

Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg Gly Asp
595 600 605

Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp Ser Arg
610 615 620

Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser Tyr Glu
625 630 635 640

Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln Gly Thr
645 650 655

Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser Glu Glu
660 665 670

Leu Lys Glu
675

<210> 44

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 44

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

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

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser Asn Trp Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 45

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 45

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 46

<211> 448

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 46

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
20 25 30

Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 47

<211> 440

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 47

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

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

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

245

250

255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
 260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 275 280 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
 305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
 340 345 350

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

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
 405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 420 425 430

Ser Leu Ser Leu Ser Leu Gly Lys
 435 440

<210> 48
 <211> 218
 <212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 48

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser
 20 25 30

Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
 35 40 45

Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ala
 50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
 85 90 95

Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
 100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 49

<211> 447

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 49

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe
50 55 60

Lys Asn Arg Val Thr Leu Thr Thr Asp Ser Ser Thr Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala

130

135

140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205

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

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
 225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
 260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 275 280 285

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

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
 325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 50

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 50

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

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

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Phe Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 51
<211> 613
<212> PRT
<213> Artificial Sequence

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

<220>
<221> SITE
<222> (449)..(463)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>
<221> VARIANT
<222> (464)..(464)
<223> /replace=" "

<220>
<221> VARIANT
<222> (465)..(465)
<223> /replace=" "

<220>
<221> SITE
<222> (466)..(480)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>
<221> VARIANT
<222> (483)..(483)
<223> /replace="A"

<220>
<221> VARIANT
<222> (515)..(515)
<223> /replace="N"

<220>
<221> VARIANT
<222> (522)..(522)
<223> /replace="G" or "S" or "T" or "Q" or "E" or "N" or
"D" or "R" or "K"

<220>
<221> VARIANT
<222> (525)..(525)
<223> /replace="G" or "S" or "T" or "Q" or "E" or "N" or
"D" or "R" or "K"

<220>
<221> VARIANT
<222> (552)..(552)
<223> /replace="G" or "S" or "T" or "Q" or "E" or "N" or
"D" or "R" or "K"

<220>
<221> VARIANT
<222> (553)..(553)
<223> /replace="T"

<220>
<221> VARIANT
<222> (605)..(605)
<223> /replace="S"

<220>

<221> SITE

<222> (1)..(613)

<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 51

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser

180

185

190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
 210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
 225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
 260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
 325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
 355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
 385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
450 455 460

Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
465 470 475 480

Ala Pro Asn Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His
485 490 495

Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys
500 505 510

Asn Pro Lys Leu Thr Arg Met Leu Thr Ala Lys Phe Ala Met Pro Lys
515 520 525

Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys
530 535 540

Pro Leu Glu Glu Val Leu Asn Ala Ala Gln Ser Lys Asn Phe His Leu
545 550 555 560

Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu
565 570 575

Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala
580 585 590

Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Ala Gln Ser Ile
595 600 605

Ile Ser Thr Leu Thr

610

<210> 52

<211> 673

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 52

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ile
450 455 460

Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys
465 470 475 480

Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe
485 490 495

Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys
500 505 510

Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
515 520 525

Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ala
530 535 540

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn
545 550 555 560

Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln
565 570 575

Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro
580 585 590

Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val
595 600 605

Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asp
610 615 620

Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr
625 630 635 640

Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys
645 650 655

Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr
660 665 670

Ser

<210> 53
<211> 613
<212> PRT
<213> Artificial Sequence

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

<220>
<221> SITE
<222> (449)..(463)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>
<221> VARIANT
<222> (464)..(464)
<223> /replace=" "

<220>
<221> VARIANT
<222> (465)..(465)
<223> /replace=" "

<220>
<221> SITE
<222> (466)..(480)

<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>

<221> SITE

<222> (1)..(613)

<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 53

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

Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
		20						25					30		

Thr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			

Thr	Phe	Ile	Ser	Tyr	Asp	Gly	Asn	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75				80	

Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys
			85						90					95	

Ala	Arg	Thr	Gly	Trp	Leu	Gly	Pro	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		

Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
		115					120					125			

Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
	130					135					140				

Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
145				150						155					160

Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
				165					170					175	

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp

385		390		395		400									
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser
				405					410					415	
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			420					425					430		
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Ala
		435					440					445			
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala
	450					455					460				
Ala	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
465					470					475					480
Gln	Gly	Gln	Asp	Arg	His	Met	Ile	Arg	Met	Arg	Gln	Leu	Ile	Asp	Ile
				485					490					495	
Val	Asp	Gln	Leu	Lys	Asn	Tyr	Val	Asn	Asp	Leu	Val	Pro	Glu	Phe	Leu
			500					505					510		
Pro	Ala	Pro	Glu	Asp	Val	Glu	Thr	Asn	Cys	Glu	Trp	Ser	Ala	Phe	Ser
		515					520					525			
Cys	Phe	Gln	Lys	Ala	Gln	Leu	Lys	Ser	Ala	Asn	Thr	Gly	Asn	Asn	Glu
	530					535					540				
Arg	Ile	Ile	Asn	Val	Ser	Ile	Lys	Lys	Leu	Lys	Arg	Lys	Pro	Pro	Ser
545					550					555					560
Thr	Asn	Ala	Gly	Arg	Arg	Gln	Lys	His	Arg	Leu	Thr	Cys	Pro	Ser	Cys
				565					570					575	
Asp	Ser	Tyr	Glu	Lys	Lys	Pro	Pro	Lys	Glu	Phe	Leu	Glu	Arg	Phe	Lys
			580					585					590		
Ser	Leu	Leu	Gln	Lys	Met	Ile	His	Gln	His	Leu	Ser	Ser	Arg	Thr	His
		595					600					605			

Gly Ser Glu Asp Ser
610

<210> 54
<211> 694
<212> PRT
<213> Artificial Sequence

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

<220>
<221> SITE
<222> (449)..(463)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>
<221> VARIANT
<222> (464)..(464)
<223> /replace=" "

<220>
<221> VARIANT
<222> (465)..(465)
<223> /replace=" "

<220>
<221> SITE
<222> (466)..(480)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>
<221> SITE
<222> (1)..(694)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 54
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
450 455 460

Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
465 470 475 480

Ala Val Asn Gly Thr Ser Gln Phe Thr Cys Phe Tyr Asn Ser Arg Ala
485 490 495

Asn Ile Ser Cys Val Trp Ser Gln Asp Gly Ala Leu Gln Asp Thr Ser
500 505 510

Cys Gln Val His Ala Trp Pro Asp Arg Arg Arg Trp Asn Gln Thr Cys
515 520 525

Glu Leu Leu Pro Val Ser Gln Ala Ser Trp Ala Cys Asn Leu Ile Leu
530 535 540

Gly Ala Pro Asp Ser Gln Lys Leu Thr Thr Val Asp Ile Val Thr Leu
545 550 555 560

Arg Val Leu Cys Arg Glu Gly Val Arg Trp Arg Val Met Ala Ile Gln
565 570 575

Asp Phe Lys Pro Phe Glu Asn Leu Arg Leu Met Ala Pro Ile Ser Leu
580 585 590

Gln Val Val His Val Glu Thr His Arg Cys Asn Ile Ser Trp Glu Ile
595 600 605

Ser Gln Ala Ser His Tyr Phe Glu Arg His Leu Glu Phe Glu Ala Arg
610 615 620

Thr Leu Ser Pro Gly His Thr Trp Glu Glu Ala Pro Leu Leu Thr Leu
625 630 635 640

Lys Gln Lys Gln Glu Trp Ile Cys Leu Glu Thr Leu Thr Pro Asp Thr
645 650 655

Gln Tyr Glu Phe Gln Val Arg Val Lys Pro Leu Gln Gly Glu Phe Thr
660 665 670

Thr Trp Ser Pro Trp Ser Gln Pro Leu Ala Phe Arg Thr Lys Pro Ala
675 680 685

Ala Leu Gly Lys Asp Thr
690

<210> 55
<211> 728
<212> PRT
<213> Artificial Sequence

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

<220>
<221> SITE
<222> (449)..(463)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>
<221> VARIANT
<222> (464)..(464)
<223> /replace=" "

<220>
<221> VARIANT
<222> (465)..(465)
<223> /replace=" "

<220>
<221> SITE
<222> (466)..(480)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>
<221> SITE
<222> (1)..(728)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 55
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg

245

250

255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
 260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
 325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
 355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
 385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
 405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
 435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
 450 455 460

Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
465 470 475 480

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
485 490 495

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
500 505 510

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
515 520 525

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
530 535 540

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
545 550 555 560

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
565 570 575

Ala Arg Val Asp Arg Tyr Tyr Asn Trp Asn Tyr Phe Leu Gly Ser Phe
580 585 590

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
595 600 605

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu
610 615 620

Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys Thr Ala Arg Ile
625 630 635 640

Thr Cys Gly Gly Asn Asn Ile Arg Ser Lys Ser Val His Trp Tyr Gln
645 650 655

Gln Lys Pro Gly Gln Ala Pro Val Val Val Ile Tyr Tyr Asp Ser Asp
660 665 670

Arg Pro Ser Gly Ile Pro Glu Arg Ile Ser Gly Ser Asn Ser Gly Asn

675

680

685

Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp
 690 695 700

Tyr Phe Cys Gln Val Trp Asp Ser Ser Ser Asp His His Val Phe Gly
 705 710 715 720

Gly Gly Thr Lys Leu Thr Val Leu
 725

<210> 56

<211> 728

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<220>

<221> SITE

<222> (449)..(463)

<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser' repeating units"

<220>

<221> VARIANT

<222> (464)..(464)

<223> /replace=" "

<220>

<221> VARIANT

<222> (465)..(465)

<223> /replace=" "

<220>

<221> SITE

<222> (466)..(480)

<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser' repeating units"

<220>

<221> SITE

<222> (1)..(728)

<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 56

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
450 455 460

Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
465 470 475 480

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
485 490 495

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Arg Ser Lys Ser Val
500 505 510

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Val Val Ile Tyr
515 520 525

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Ile Ser Gly Ser
530 535 540

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
545 550 555 560

Asp Glu Ala Asp Tyr Phe Cys Gln Val Trp Asp Ser Ser Ser Asp His
565 570 575

His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly
580 585 590

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val
595 600 605

Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser
610 615 620

Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr Ala Ile Ser Trp Val
625 630 635 640

Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Gly Ile Ile Pro
645 650 655

Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr
660 665 670

Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser
675 680 685

Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Val Asp Arg
690 695 700

Tyr Tyr Asn Trp Asn Tyr Phe Leu Gly Ser Phe Asp Tyr Trp Gly Gln
705 710 715 720

Gly Thr Leu Val Thr Val Ser Ser
725

<210> 57
<211> 720
<212> PRT
<213> Artificial Sequence

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

<220>
<221> SITE
<222> (449)..(463)
<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser'
repeating units"

<220>
<221> VARIANT
<222> (464)..(464)
<223> /replace=" "

<220>
<221> VARIANT
<222> (465)..(465)
<223> /replace=" "

<220>
<221> SITE
<222> (466)..(480)

<223> /note="This region may encompass 0-3 'Gly Gly Gly Gly Ser' repeating units"

<220>

<221> SITE

<222> (1)..(720)

<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 57

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp

385					390						395					400
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	
				405					410					415		
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	
			420					425					430			
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Ala	
		435					440					445				
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ala	
	450					455					460					
Ala	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	
465					470					475					480	
Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Gly	Thr	Leu	Ser	Leu	Ser	Pro	Gly	
				485					490					495		
Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Ser	
			500					505					510			
Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	
		515					520					525				
Ile	Tyr	Gly	Ala	Ser	Arg	Arg	Ala	Thr	Gly	Ile	Pro	Asp	Arg	Phe	Ser	
	530					535					540					
Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Arg	Leu	Glu	
545					550					555					560	
Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Arg	Tyr	Gly	Ser	Ser	His	
				565					570					575		
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Ser	Gly	Gly	Gly	Gly	Ser	
			580					585					590			
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Val	Gln	Leu	Val	Gln	
	595						600					605				

Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys
610 615 620

Lys Val Ser Gly Tyr Phe Phe Thr Thr Tyr Trp Ile Gly Trp Val Arg
625 630 635 640

Gln Met Pro Gly Lys Gly Leu Glu Tyr Met Gly Ile Ile Tyr Pro Gly
645 650 655

Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile
660 665 670

Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu
675 680 685

Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Asn Trp
690 695 700

Asn Cys Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
705 710 715 720

<210> 58

<211> 683

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 58

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly
450 455 460

Ser Gly Gly Gly Gly Ser Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr
465 470 475 480

Leu Gln Thr Val Ile Cys Ile Leu Glu Met Trp Asn Leu His Pro Ser
485 490 495

Thr Leu Thr Leu Thr Trp Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu
500 505 510

Ala Thr Ser Cys Ser Leu His Arg Ser Ala His Asn Ala Thr His Ala
515 520 525

Thr Tyr Thr Cys His Met Asp Val Phe His Phe Met Ala Asp Asp Ile
530 535 540

Phe Ser Val Asn Ile Thr Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys
545 550 555 560

Gly Ser Phe Leu Leu Ala Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn
565 570 575

Val Thr Val Thr Phe Ser Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp
580 585 590

Tyr Glu Asp Pro Ala Phe Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu
595 600 605

Leu Gln Tyr Arg Asn Arg Gly Asp Pro Trp Ala Val Ser Pro Arg Arg
610 615 620

Lys Leu Ile Ser Val Asp Ser Arg Ser Val Ser Leu Leu Pro Leu Glu
625 630 635 640

Phe Arg Lys Asp Ser Ser Tyr Glu Leu Gln Val Arg Ala Gly Pro Met
645 650 655

Pro Gly Ser Ser Tyr Gln Gly Thr Trp Ser Glu Trp Ser Asp Pro Val
660 665 670

Ile Phe Gln Thr Gln Ser Glu Glu Leu Lys Glu
675 680

<210> 59

<211> 717

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 59

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

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

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser

405

410

415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ala
 435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ala Gly Gly Gly Gly
 450 455 460

Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr
 465 470 475 480

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
 485 490 495

Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
 500 505 510

Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly
 515 520 525

Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
 530 535 540

Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln
 545 550 555 560

Gln Tyr Gly Ser Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 565 570 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
 580 585 590

Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser
 595 600 605

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Gly
 610 615 620

Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
625 630 635 640

Phe Ile Trp Tyr Asp Gly Ser Asp Lys Tyr Tyr Ala Asp Ser Val Lys
645 650 655

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
660 665 670

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
675 680 685

Arg Asp Gly Asp Ser Ser Asp Trp Tyr Gly Asp Tyr Tyr Phe Gly Met
690 695 700

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
705 710 715

<210> 60
<211> 124
<212> PRT
<213> Artificial Sequence

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

<400> 60
Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Leu His Trp Val Arg Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Ala Pro Lys Phe
50 55 60

Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ser Ile Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Arg Phe Gly Tyr Phe Tyr Gly Ser Ser Phe Tyr Ala Val Ala
100 105 110

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 61

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 61

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

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Tyr Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 62

<211> 133
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="A"

<220>
<221> VARIANT
<222> (35)..(35)
<223> /replace="N"

<220>
<221> VARIANT
<222> (42)..(42)
<223> /replace="G" or "S" or "T" or "Q" or "E" or "N" or "D" or "R" or "K"

<220>
<221> VARIANT
<222> (45)..(45)
<223> /replace="G" or "S" or "T" or "Q" or "E" or "N" or "D" or "R" or "K"

<220>
<221> VARIANT
<222> (72)..(72)
<223> /replace="G" or "S" or "T" or "Q" or "E" or "N" or "D" or "R" or "K"

<220>
<221> VARIANT
<222> (73)..(73)
<223> /replace="T"

<220>
<221> VARIANT
<222> (125)..(125)
<223> /replace="A" or "S"

<220>
<221> SITE
<222> (1)..(133)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 62

Ala Pro Asn Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His
1 5 10 15

Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys
20 25 30

Asn Pro Lys Leu Thr Arg Met Leu Thr Ala Lys Phe Ala Met Pro Lys
35 40 45

Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Glu Leu Lys
50 55 60

Pro Leu Glu Glu Val Leu Asn Ala Ala Gln Ser Lys Asn Phe His Leu
65 70 75 80

Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu
85 90 95

Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala
100 105 110

Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile
115 120 125

Ile Ser Thr Leu Thr
130

<210> 63

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 63

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp

20

25

30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
 35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
 50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
 65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
 85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
 100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
 115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
 130 135 140

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

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
 165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
 180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
 195 200 205

Glu Glu Leu Lys Glu
 210

<210> 64

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 64

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
 20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
 35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
 50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
 85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
 100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
 115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
 130 135 140

Gly Asp Asn Ala Ser Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp
145 150 155 160

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
 165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
 180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
195 200 205

Glu Glu Leu Lys Glu
210

<210> 65

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 65

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg

130

135

140

Gly Asp Asn Gly Ser Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp
 145 150 155 160

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
 165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
 180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
 195 200 205

Glu Glu Leu Lys Glu
 210

<210> 66

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 66

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
 1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
 20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
 35 40 45

Asn Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
 50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
 65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
130 135 140

Gly Asp Asn Ala Ser Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp
145 150 155 160

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
195 200 205

Glu Glu Leu Lys Glu
210

<210> 67

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 67

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
130 135 140

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

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
195 200 205

Glu Glu Leu Lys Glu
210

<210> 68

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 68

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
130 135 140

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

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
195 200 205

Glu Glu Leu Lys Glu
210

<210> 69

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 69

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Ala Tyr Glu Asp Pro Ala Phe
115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
130 135 140

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

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
195 200 205

Glu Glu Leu Lys Glu
210

<210> 70

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 70

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Ile Tyr Glu Asp Pro Ala Phe
115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
130 135 140

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

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
195 200 205

Glu Glu Leu Lys Glu
210

<210> 71

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 71

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu

35

40

45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Trp Tyr Glu Asp Pro Ala Phe
115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
130 135 140

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

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
195 200 205

Glu Glu Leu Lys Glu
210

<210> 72

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 72

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Phe Tyr Glu Asp Pro Ala Phe
115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
130 135 140

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

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
165 170 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
180 185 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
195 200 205

Glu Glu Leu Lys Glu
210

<210> 73

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 73

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Tyr Tyr Glu Asp Pro Ala Phe
115 120 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
130 135 140

Gly Asp Gly Ser Gly Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
340 345 350

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

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val
385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Leu Gly Ala Gly Gly Gly Gly Ser Gly Gly Gly
435 440 445

Gly Ser Gly Pro Leu Gly Val Arg Gly Gly Gly Gly Ser Cys Pro Asp
450 455 460

Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys Ile Leu Glu
465 470 475 480

Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp Gln Asp Gln
485 490 495

Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu His Arg Ser
500 505 510

Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met Asp Val Phe
515 520 525

His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr Asp Gln Ser
530 535 540

Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala Glu Ser Ile
545 550 555 560

Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser Gly Gln Tyr
565 570 575

Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe Tyr Met Leu
580 585 590

Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg Gly Asp Pro
595 600 605

Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp Ser Arg Ser
610 615 620

Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser Tyr Glu Leu
625 630 635 640

Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln Gly Thr Trp
645 650 655

Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser Glu Glu Leu
660 665 670

Lys Glu

<210> 75

<211> 706

<212> PRT

<213> Artificial Sequence

<220>

<221> source

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

<400> 75

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

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

225		230		235		240									
Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val
				245					250					255	
Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val
			260					265					270		
Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln
		275					280					285			
Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln
	290						295				300				
Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly
305					310					315					320
Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro
				325					330					335	
Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr
			340					345					350		
Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser
		355					360					365			
Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr
	370					375					380				
Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr
385					390					395					400
Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe
				405					410					415	
Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys
			420					425					430		
Ser	Leu	Ser	Leu	Ser	Leu	Gly	Ala	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly
		435					440					445			

Gly Ser Gly Pro Leu Gly Val Arg Gly Gly Gly Gly Ser Gly Gly Gly
450 455 460

Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser
465 470 475 480

Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser
485 490 495

Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg
500 505 510

Leu Leu Ile Tyr Gly Ala Ser Arg Arg Ala Thr Gly Ile Pro Asp Arg
515 520 525

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg
530 535 540

Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Tyr Gly Ser
545 550 555 560

Ser His Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Ser Gly Gly Gly
565 570 575

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
580 585 590

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile
595 600 605

Ser Cys Lys Val Ser Gly Tyr Phe Phe Thr Thr Tyr Trp Ile Gly Trp
610 615 620

Val Arg Gln Met Pro Gly Lys Gly Leu Glu Tyr Met Gly Ile Ile Tyr
625 630 635 640

Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val
645 650 655

Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser

660

665

670

Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly
675 680 685

Asn Trp Asn Cys Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
690 695 700

Ser Ser
705

<210> 76
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 76
Thr Tyr Trp Ile Gly
1 5

<210> 77
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 77
Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 78
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 78
Gly Asn Trp Asn Cys Phe Asp Tyr
1 5

<210> 79
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 79
Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 80
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 80
Gly Ala Ser Arg Arg Ala Thr
1 5

<210> 81
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 81
Gln Arg Tyr Gly Ser Ser His Thr
1 5

<210> 82
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 82
Gly Asn Trp Asn Ser Phe Asp Tyr
1 5

<210> 83
<211> 118
<212> PRT
<213> Artificial Sequence

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

<400> 83
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Tyr Phe Phe Thr Thr Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Tyr Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Asn Trp Asn Cys Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 84
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 84
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Arg Glu Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Arg Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Tyr Gly Ser Ser His
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Ser Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro
115