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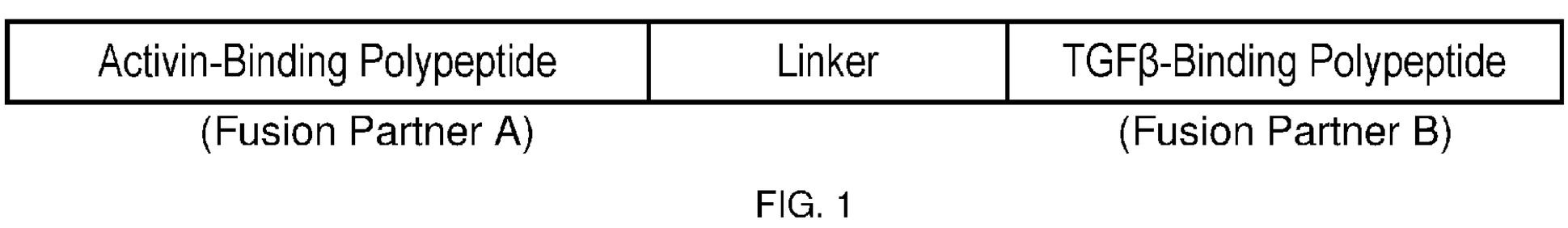


FIG. 1

(57) Abstract: This invention disclosure describes novel polypeptide antagonists capable of neutralizing multiple members of TGF-β family in a selective manner. Specifically, the multispecific polypeptide antagonists disclosed herein comprise at least one Activin-binding domain and at least one TGFβ-binding domain and therefore, are capable of neutralizing TGF-β and Activin as well as Activin-related ligands in parallel. Moreover, this invention disclosure also discloses bifunctional multispecific polypeptide antagonists designed to inhibit Activin, TGF-β and T-Cell immune checkpoint (i.e., PD1, PDL1 or CTLA4) in a simultaneous manner. Specifically, the bifunctional multispecific antagonists disclosed herein comprise at least one Activin-binding domain, at least one TGFβ-binding domain and at least one PD1-, PDL1- or CTLA4-binding domain. Also provided are pharmaceutical compositions of such multispecific or bifunctional multispecific polypeptide antagonists and their therapeutic uses for treating certain disease conditions, which involve overexpression of both TGF-β and Activin, such as fibrosis and cancer.

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NOVEL BIFUNCTIONAL MULTISPECIFIC ANTAGONISTS CAPABLE OF INHIBITING MULTIPLE LIGANDS OF TGF-BETA FAMILY AND USES THEREOF

Related Patent Applications

[001] This application claims benefit of U.S. Provisional Application No. 63/113,920, filed on November 15, 2020, and U.S. Provisional Application No. 63/109,814, filed on November 4, 2020, each incorporated in its entirety by reference herein.

Background Art

[002] The Transforming Growth Factor Beta (TGF-β) superfamily consists of the TGF-β proteins, Activins, Growth Differentiation Factors (GDFs), Bone Morphogenetic Proteins (BMPs), Glial-derived Neurotrophic Factors (GDNFs), Inhibins, Nodal, Lefty, and Mülllerian Inhibiting Substance (MIS). Ligands of the TGF-β superfamily form dimers that bind to heterodimeric receptor complexes consisting of type I and type II receptor subunits with serine/threonine kinase domains. Following ligand binding, the type II receptor phosphorylates and activates the type I receptor, initiating a Smad-dependent signaling cascade that induces or represses transcriptional activity.

[003] TGF-β (TGF-β1, TGF-β2 and TGF-β3) mediates Smad2/3 signaling through its binding and activation of the high-affinity receptors TGFβRII and TGFβRIIB on the cell surface. TGF-β plays a critical role in the regulation of a wide range of biology activities, including immune function, cell proliferation and differentiation, fibrogenesis, epithelial-mesenchymal transition, hematopoiesis, myogenesis and bone remodeling. Elevated TGF-β levels and consequently increased Smad2/3 signaling have been implicated in pathogenesis and progression of many disease conditions including cancer, fibrosis, anemia, bone metastasis, bone loss, pain, muscle loss, insulin resistance, chronic kidney disease, liver disease, and cardiovascular diseases.

[004] In addition, as a subset of TGF-β superfamily, Activins and related proteins (including Activin A, Activin B, Activin AB, GDF-8 and GDF-11) also mediate Smad2/3 signaling through binding and activation of their high-affinity receptors ActRIIA and ActRIIB on the cell surface. Activin and related proteins regulate a wide range of biology activities, including immune function, cell differentiation, myogenesis, fibrogenesis, bone remodeling, hematopoiesis, and reproductive physiology. Follistatin (FST), a secreted glycoprotein, binds to

the Activins and Activin-related ligands to negatively control their signaling activities. Overexpression of Activins and related ligands and increased Smad2/3 signaling have been implicated in pathogenesis and progression of many grievous conditions, such as cancer, fibrosis, anemia, bone metastasis, bone fragility, facture, muscle wasting disorders, cachexia, pulmonary hypertension, pain, insulin resistance, chronic kidney disease, liver disease, myocardial infarction and heart failure.

[005] TGF-β/Activin-Smad2/3 signaling pathway plays a central role in the pathogenesis and progression of fibrosis. A key mechanism underlying pathogenesis and progression of fibrosis is the increased TGF-β/Activin-Smad2/3 signaling, which lads to proliferation and activation of fibroblasts and consequently, overexpression of extracellular matrix components such as COL1A1, COL1A2, COL3A1, COL5A2, COL6A1 and COL6A3 in the disease tissue. Evidence indicates that TGF-β and Activin are both upregulated during fibrosis. When elevated, either TGF-β or Activin can cause fibroblast activation, leading to fibrosis. Since TGF-β and Activin are both elevated, it is important to inhibit not only TGF-β but also Activin in order to more effectively attenuate fibrosis.

[006] TGF-β/Activin-Smad2/3 signaling pathway also plays an important role in pathogenesis and progression of cancer in part due to its profound impact on tumor immune surveillance. TGF-β and Activin are highly overexpressed in various cancers. Overproduction of TGF-β and Activin in the cancer microenvironment results in activation of Smad2/3 signaling in regulatory T cells (Tregs) and causes their proliferation and activation. The increased activity of Tregs in turn causes inhibition of CD8+ cytotoxic T cells, thereby reducing the ability of CD8+ cytotoxic T cells to detect and eliminate cancer cells. Currently, a number of clinical trials in immune oncology are being focused on TGF-β inhibitor and T cell checkpoint inhibitor (such as anti-PD1 antibody and anti-CTLA4 antibody). However, it is important to note that TGF-β and Activin are both highly overexpressed in various cancers, and like elevated TGF-β, elevated Activin or Activin-related ligands can also suppress cancer immune surveillance through activation of Tregs. Thus, a parallel inhibition of the elevated TGF-βs and the elevated Activins can more effectively attenuate Tregs and thereby more effectively restore immune surveillance in cancer. Therefore, a multispecific polypeptide antagonist capable of neutralizing not only the elevated TGF-βs (i.e., TGF-β1, TGF-β2 and TGF-β3) but also the elevated Activins (i.e., Activin A, Activin B and Activin AB) in cancer may bring superior efficacy and better response rate for cancer treatment, including co-treatment in combination with immune check point inhibitor.

Disclosure of the Invention

[007] In one aspect, the present invention provides novel polypeptide-based multispecific antagonist molecules specifically designed to simultaneously neutralize Activin signaling and TGF-β signaling in a potent manner. In various embodiments, the multispecific antagonist molecule is designed as depicted in FIGS. 1-4.

[008] In various embodiments, the multispecific antagonist is a multispecific polypeptide molecule comprising a first antigen-binding molecule that specifically binds to Activin ligand or Activin-related ligand ("Activin-Binding Polypeptide") and a second antigen-binding molecule that specifically binds to TGF-β ligand ("TGF-β-Binding Polypeptide"). In various embodiments, the "Activin-Binding Polypeptide" is selected from any polypeptide that is capable binding Activin (i.e., Activin A, Activin B or Activin AB) and/or Activin-related ligand (i.e., GDF8 or GDF11), which includes, but is not limited to, an anti-Activin antibody (including anti-Activin A antibody and anti-Activin B antibody), a fragment of anti-Activin antibody, wild-type Activin Type 2A Receptor (ActRIIA) or Activin Type 2B Receptor (ActRIIB) extracellular domains (ECDs), modified ActRIIA and ActRIIB extracellular domains, wild-type and modified native Activin-binding proteins such as follistatin, follistatin-like protein and propeptide, and a phage display-derived polypeptide targeting Activin or Activin-related ligand, and the "TGF-β-Binding Polypeptide" is selected from the group consisting of an anti-TGF-β antibody, a fragment of anti-TGF-β antibody, wild-type TGF-β type-2 receptors (including TGFβRIIA and TGFβRIIB) extracellular domains (ECDs), modified TGFβRIIA and TGFβRIIB extracellular domains, and a phage display-derived antagonistic polypeptide targeting TGF-β ligand.

[009] In various embodiments, the multispecific antagonist molecule comprises an isolated antibody, or antigen-binding fragment thereof, that specifically binds to Activin or Activin-related ligand and an isolated antibody, or antigen-binding fragment thereof, that specifically binds to TGF-β ligand. In various embodiments, the isolated antibody or antigen-binding fragment thereof is selected from the group consisting of monoclonal Abs (mAbs), polyclonal Abs, Ab fragments (e.g., Fab, Fab', F(ab')2, Fv, Fc, etc.), chimeric Abs, mini-Abs or domain Abs (dAbs), dual specific Abs, bispecific Abs, heteroconjugate Abs, single chain Abs (SCA), single chain variable region fragments (ScFv), humanized Abs, fully human Abs, and any other modified configuration of the immunoglobulin (Ig) molecule that comprises an antigen recognition site of the required specificity. In various embodiments, the multispecific molecule comprises an isolated antibody or antigen-binding fragment thereof selected from the group consisting of a fully human, humanized and chimeric antibody.

[010] In various embodiments, the first antigen-binding molecule specifically binds an Activin or Activin-related ligand comprising an amino acid sequence set forth in SEQ ID NO: 1. In various embodiments, the first antigen-binding molecule specifically binds an Activin or Activin-related ligand comprising an amino acid sequence set forth in SEQ ID NO: 2. In various embodiments, the first antigen-binding molecule specifically binds an Activin or Activin-related ligand comprising an amino acid sequence set forth in SEQ ID NO: 3. In various embodiments, the first antigen-binding molecule specifically binds an Activin or Activin-related ligand comprising an amino acid sequence set forth in SEQ ID NO: 4. In various embodiments, the first antigen-binding molecule specifically binds an Activin or Activin-related ligand comprising an amino acid sequence set forth in SEQ ID NO: 5. In various embodiments, the first antigen-binding molecule specifically binds an Activin or Activin-related ligand comprising an amino acid sequence set forth in SEQ ID NO: 6. In various embodiments, the first antigen-binding molecule specifically binds an Activin or Activin-related ligand comprising an amino acid sequence set forth in SEQ ID NO: 7. In various embodiments, the first antigen-binding molecule specifically binds an Activin or Activin-related ligand comprising an amino acid sequence set forth in SEQ ID NO: 8. In various embodiments, the first antigen-binding molecule specifically binds an Activin or Activin-related ligand comprising an amino acid sequence set forth in SEQ ID NO: 9.

[011] In various embodiments, the first antigen-binding molecule that specifically binds to Activin or Activin-related ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 10; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 11; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 10 and the light chain amino acid sequence set forth in SEQ ID NO: 11; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 12; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 13; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 12 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 13.

[012] In various embodiments, the first antigen-binding molecule that specifically binds to Activin or Activin-related ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 14; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 15; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 14 and the light chain amino acid sequence set forth in SEQ ID NO: 15; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 16; an antibody comprising

the light chain variable region amino acid sequence set forth in SEQ ID NO: 17; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 16 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 17.

[013] In various embodiments, the second antigen-binding molecule specifically binds a TGF-β ligand comprising an amino acid sequence set forth in SEQ ID NO: 18. In various embodiments, the second antigen-binding molecule specifically binds a TGF-β ligand comprising an amino acid sequence set forth in SEQ ID NO: 19. In various embodiments, the second antigen-binding molecule specifically binds a TGF-β ligand comprising an amino acid sequence set forth in SEQ ID NO: 20. In various embodiments, the second antigen-binding molecule specifically binds a TGF-β ligand comprising an amino acid sequence set forth in SEQ ID NO: 21.

[014] In various embodiments, the second antigen-binding molecule that specifically binds to TGF-β ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 22; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 23; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 22 and the light chain amino acid sequence set forth in SEQ ID NO: 23; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 24; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 25; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 24 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 25.

[015] In various embodiments, the multispecific antagonist is a polypeptide molecule comprising a first antigen-binding molecule that specifically binds to Activin ligand and a second antigen-binding molecule that specifically binds to TGF-β ligand, wherein the Activin ligand binding molecule is selected from the group of polypeptides comprising the amino acid sequence set forth in SEQ ID NOs: 1-17, and the TGF-β ligand binding molecule is selected from the group of polypeptides comprising the amino acid sequence set forth in SEQ ID NOs: 18-25.

[016] In various embodiments, the multispecific antagonist is a polypeptide molecule comprising a first antigen-binding molecule that specifically binds to Activin ligand and a second antigen-binding molecule that specifically binds to TGF-β ligand, wherein the multispecific molecule is selected from the group consisting of: a multispecific molecule comprising a heavy chain selected from a heavy chain comprising the amino acid sequence set forth in SEQ ID

NOs: 72-84 and a light chain selected from a light chain comprising the amino acid sequence set forth in SEQ ID NOs: 11, 13, 15 , 17, 19, 21, 23 and 25.

[017] In various embodiments, the multispecific antagonist is a multispecific polypeptide molecule comprising a first antigen-binding molecule that specifically binds to Activin ligand and a second antigen-binding molecule that specifically binds to TGF-β ligand, wherein the multispecific molecule is selected from the group consisting of: a multispecific polypeptide molecule comprising the amino acid sequence set forth in SEQ ID NOs: 54-71.

[018] In another aspect, the present invention provides novel polypeptide-based bifunctional multispecific antagonist molecules specifically designed to simultaneously inhibit TGF-β, Activin, and T-cell immune checkpoint (including PD1, PDL1 or CTL4). In various embodiments, the bifunctional multispecific antagonist is a bifunctional multi-specific molecule comprising a first antigen-binding molecule that specifically binds to Activin ligand or Activin-related ligand ("Activin-Binding Polypeptide") and a second antigen-binding molecule that specifically binds to TGF-β ligand ("TGF-β-Binding Polypeptide") and a third antigen-binding molecule that specifically binds to either PD-1 ligand, PD-L1 ligand or CTLA-4 ligand ("PD-1/PD-L1/CTLA-4-Binding Polypeptide"). In various embodiments, the bifunctional multispecific antagonist molecule is designed as depicted in FIGS. 5-6.

[019] In various embodiments, the third antigen-binding molecule that specifically binds to PD-1 ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 26; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 27; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 26 and the light chain amino acid sequence set forth in SEQ ID NO: 27; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 28; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 29; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 28 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 29.

[020] In various embodiments, the third antigen-binding molecule that specifically binds to PD-1 ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 31; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30 and the light chain amino acid sequence set forth in SEQ ID NO: 31; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 32; an antibody comprising the

light chain variable region amino acid sequence set forth in SEQ ID NO: 33; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 32 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 33.

[021] In various embodiments, the third antigen-binding molecule that specifically binds to PD-1 ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 38; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 39; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 38 and the light chain amino acid sequence set forth in SEQ ID NO: 39; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 40; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 41; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 40 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 41.

[022] In various embodiments, the third antigen-binding molecule that specifically binds to PD-1 ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 42; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 43; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 42 and the light chain amino acid sequence set forth in SEQ ID NO: 43; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 44; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 45; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 44 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 45.

[023] In various embodiments, the third antigen-binding molecule that specifically binds to CTLA-4 ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 34; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 35; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 34 and the light chain amino acid sequence set forth in SEQ ID NO: 35; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 36; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 37; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 36 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 37.

[024] In various embodiments, the third antigen-binding molecule that specifically binds to PD-L1 ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 46; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 47; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 46 and the light chain amino acid sequence set forth in SEQ ID NO: 47; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 48; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 49; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 48 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 49.

[025] In various embodiments, the third antigen-binding molecule that specifically binds to PD-L1 ligand is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 50; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 51; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 50 and the light chain amino acid sequence set forth in SEQ ID NO: 51; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 52; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 53; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 52 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 53.

[026] In various embodiments, the bifunctional multispecific antagonist is a bifunctional multispecific molecule comprising a first antigen-binding polypeptide that specifically binds to Activin ligand and a second antigen-binding polypeptide that specifically binds to TGF-β ligand and a third antigen-binding polypeptide that specifically binds to either PD-1 ligand, PD-L1 ligand or CTLA-4 ligand, wherein the bifunctional multispecific molecule is selected from the group consisting of: a bifunctional multispecific molecule comprising a heavy chain selected from a heavy chain comprising the amino acid sequence set forth in SEQ ID NOs: 85-120 and a light chain selected from a light chain comprising the amino acid sequence set forth in SEQ ID NOs: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51 and 53. In various embodiments, the bifunctional multispecific antagonist molecule is a bifunctional multispecific antagonist molecule comprising a heavy chain selected from a heavy chain comprising the amino acid sequence set forth in SEQ ID NOs: 85-102 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 27. In various embodiments, the bifunctional multispecific antagonist molecule is a bifunctional multispecific antagonist molecule comprising a heavy chain selected from a heavy

chain comprising the amino acid sequence set forth in SEQ ID NOs: 103-120 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 35.

[027] In another aspect, the present disclosure provides a pharmaceutical composition comprising the isolated multispecific or bifunctional multispecific antagonist molecules in admixture with a pharmaceutically acceptable carrier.

[028] In another aspect, the present disclosure provides a method of treating or preventing various complex disease conditions whose pathogenesis involves the parallel activation of Activin signaling and TGF-β signaling.

[029] In various embodiments, the novel multispecific or bifunctional multispecific antagonist molecules of the present invention may have broad applications for the treatment of various disorders which include, but are not limited to, the following conditions: Blood disorders: ineffective erythropoiesis, anemia, pancytopenia, myelodysplastic syndromes; Fibrotic diseases: nonalcoholic steatohepatitis/NASH, liver fibrosis, pulmonary fibrosis, renal fibrosis, polycystic kidney disease, cardiac fibrosis, muscle fibrosis, myelo fibrosis, skin fibrosis, and fibrosis of the eye; Hematological malignancies: multiple myeloma, leukemia, and lymphoma; Solid cancers: melanoma, multiple myeloma, lung cancer, pancreatic cancer, colorectal cancer, liver cancer, gastric cancer, kidney cancer, bladder cancer, head and neck cancer, thyroid cancer, breast cancer, ovarian cancer, endometrial cancer, testicular cancer, prostate cancer, brain cancer, and sarcoma; Metastasis: bone metastasis, lung metastasis, liver metastasis, brain metastasis; Cancer treatment in combination with checkpoint inhibitors such as anti-PD1, anti-PDL1 and anti-CTL4 antibodies; Neuromuscular diseases: muscular dystrophy, spinal muscular atrophy, spinal cord injury, stroke; Pain: nociceptive pain, neuropathic pain; Wasting disorders: sarcopenia, cancer cachexia, cardiac cachexia, renal cachexia, rheumatoid cachexia, and anorexia nervosa; Bone disorders: bone metastasis, skeletal-related event in cancer, bone fragility, fracture, osteopenia, and osteoporosis; Cardiovascular diseases: pulmonary hypertension, myocardial infarction, heart failure; Metabolic disorders: insulin resistance, diabetic nephropathy, chronic kidney disease; Inflammatory diseases: rheumatoid arthritis, inflammatory bowel disease; Infections: SARS-CoV, cytokine storm syndrome, sepsis; and Trauma: burn injury.

[030] In another aspect, the disclosure provides uses of the bifunctional or bifunctional multispecific antagonist molecules for making a medicament for the treatment of any disorder or condition as described herein.

[031] In another aspect, the present disclosure provides isolated nucleic acid molecules comprising a polynucleotide encoding a multispecific or bifunctional multispecific

antagonist molecule of the present disclosure. In various embodiments, the isolated nucleic acid molecules comprise the polynucleotides described herein, and further comprise a polynucleotide encoding at least one heterologous protein described herein. In various embodiments, the nucleic acid molecules further comprise polynucleotides encoding the linkers or hinge linkers described herein.

[032] In another aspect, the present disclosure provides vectors comprising the nucleic acids described herein. In various embodiments, the vector is an expression vector. In another aspect, the present disclosure provides isolated cells comprising the nucleic acids of the disclosure. In various embodiments, the cell is a host cell comprising the expression vector of the disclosure. In another aspect, methods of making the multispecific or bifunctional multispecific antagonist molecules are provided by culturing the host cells under conditions promoting expression of the proteins or polypeptides.

[033] In another aspect, provided is a method for producing a multispecific antagonist molecule or bifunctional multispecific antagonist molecule comprising a first antigen-binding molecule that specifically binds to Activin, or Activin-related ligand, such as GDF8 or GDF11, and a second antigen-binding molecule that specifically binds to TGF-β as described herein, comprising the steps of a) transforming a host cell with vectors comprising polynucleotides encoding said multispecific or bifunctional multispecific antagonist molecule, b) culturing the host cell according under conditions suitable for the expression of the multispecific or bifunctional multispecific antagonist molecule and c) recovering the bifunctional antagonist molecule from the culture. The invention also encompasses a multispecific or bifunctional multispecific antagonist molecule produced by the method of the invention.

Brief Description of the Figures

[034] FIG. 1 depicts a representative mulrispecific antagonist molecule of the present invention. The “Activin-binding polypeptide”, as illustrated in this schematic, refers to any polypeptide that is capable binding Activin (i.e., Activin A, Activin B or Activin AB) and/or Activin-related ligand (i.e., GDF8 or GDF11), which includes, but not limited to, 1) anti-Activin antibody (including anti-Activin A antibody and anti-Activin B antibody), fragment of anti-Activin antibody, wild-type Activin Type 2A Receptor (ActRIIA) or Activin Type 2B Receptor (ActRIIB) extracellular domains (ECDs), modified ActRIIA and ActRIIB extracellular domains, wild-type and modified native Activin-binding proteins such as follistatin, follistatin-like protein and propeptide, and phage display-derived polypeptide capable of binding and sequestering Activin

and/or Activin-related ligand. The “TGF-β-binding polypeptide”, as illustrated in this schematic, refers to any polypeptide that is capable binding TGF-β (i.e., TGF-β1, TGF-β2 or TGF-β3), which includes, but is not limited to, anti-TGF-β antibody, fragment of anti-TGF-β antibody, extracellular domains (ECDs) of wild-type TGF-β type-2 receptors (including TGFβRIIA and TGFβRIIB), modified TGFβRIIA and TGFβRIIB extracellular domains, and phage display-derived antagonistic polypeptides that are capable of binding and neutralizing TGF-β. The “Linker”, as shown in this schematic, refers to various methods for fusing different polypeptide fusion partners to generate bispecific and multi-specific molecules, which includes, but not limited to, the use of any peptide linker or chemical linker.

[035] FIG. 2 depicts two bifunctional antagonist molecules of the present invention in different configurations (FIG. 2A and 2B) wherein the Activin-binding polypeptide is an Activin Receptor ECD and the TGF-β-binding polypeptide is an TGF-β Receptor ECD attached via an Fc domain.

[036] FIGS. 3A and 3B depict two representative bifunctional antagonist molecules of the present invention wherein: (A) the Activin-binding polypeptide is an anti-Activin antibody and the TGF-β-binding polypeptide is an TGF-β Receptor ECD attached via a linker to the heavy chain CH3 of the anti-Activin antibody; or (B) the TGF-β-binding polypeptide is an anti-TGF-β antibody and the Activin-binding polypeptide is a Activin Receptor ECD attached via a linker to the heavy chain CH3 of the anti-TGF-β antibody. In alternative embodiments, the TGF-β Receptor ECD (or TNF Receptor ECD) is attached to the anti-Activin antibody (or anti-TGF-β antibody) via a linker at the heavy chain variable region (VH) of the antibody. In alternative embodiments, the TGF-β Receptor ECD (or Activin Receptor ECD) is attached to the anti-Activin antibody (or anti-TGF-β antibody) via a linker at the light chain variable region (VL) of the antibody. In alternative embodiments, the TGF-β Receptor ECD (or TNF Receptor ECD) is attached to the anti-Activin antibody (or anti-TGF-β antibody) via a linker at an internal site rather than at the heavy chain CH3, VL, or VH sites of the antibody.

[037] FIG. 4 depicts a bifunctional antagonist molecule of the present invention in the form of a bispecific antibody wherein the Activin-binding polypeptide is represented by the variable regions (V_L and V_H) of an anti-activin A antibody and the TGF-β-binding polypeptide is represented by the variable regions (V_L and V_H) of an anti-TGF-β antibody. The bispecific antibody depicted in FIG. 4 is only an example, as bispecific antibodies containing variable regions from anti-TGF-β antibody and anti-activin antibody can be constructed in various configurations that are different from the example as depicted in FIG. 4.

[038] FIG. 5 depicts a representative novel bifunctional multispecific antagonist molecule of the present invention capable of inhibiting T-Cell immune checkpoint, Activin and TGF-β via fusion between immune checkpoint inhibitor polypeptide (e.g., anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody heavy chain) (fusion partner A), Activin-binding polypeptide (fusion partner B) and TGFβ-binding polypeptide (fusion partner C). The "immune checkpoint inhibitor polypeptide", as illustrated in this schematic, refers to any antagonist polypeptides capable of binding and inhibiting PD-1, PD-L1 or CTLA-4, which includes, but not limited to, anti-PD1, anti-PDL1 and anti-CTLA4 antibodies or antibody fragments and PD-1 decoy receptor polypeptide. The "Activin-binding polypeptide", as illustrated in this schematic, refers to any polypeptide that is capable binding Activin (i.e., Activin A, Activin B or Activin AB) and/or Activin-related ligand (i.e., GDF8 or GDF11), which includes, but not limited to, 1) anti-Activin antibody (including anti-Activin A antibody and anti-Activin B antibody), fragment of anti-Activin antibody, wild-type Activin Type 2A Receptor (ActRIIA) or Activin Type 2B Receptor (ActRIIB) extracellular domains (ECDs), modified ActRIIA and ActRIIB extracellular domains, wild-type and modified native Activin-binding proteins such as follistatin, follistatin-like protein and propeptide, and phage display-derived polypeptide capable of binding and sequestering Activin and/or Activin-related ligand. The "TGFβ-binding polypeptide", as illustrated in this schematic, refers to any polypeptide that is capable binding TGFβ (i.e., TGFβ1, TGFβ2 or TGFβ3), which includes, but not limited to, anti-Activin antibody, fragment of anti-TGFβ antibody, extracellular domains (ECDs) of wild-type TGFβ type-2 receptors (including TGFβRIIA and TGFβRIIB), modified TGFβRIIA and TGFβRIIB extracellular domains, and phage display-derived antagonistic polypeptides that are capable of binding and neutralizing TGFβ. The "Linker", as shown in this schematic, refers to various methods for fusing different polypeptide fusion partners to generate bispecific and multi-specific molecules, which includes, but not limited to, the use of any peptide linker or chemical linker.

[039] FIGS. 6A and 6B depict two representative bifunctional antagonist molecules of the present invention wherein: (A) the immune checkpoint inhibitor polypeptide is an anti-PD-1 antibody, the Activin-binding polypeptide is an Activin Receptor ECD attached via a linker to the heavy chain CH3 of the anti-PD-1 antibody and the TGF-β-binding polypeptide is an TGF-β Receptor ECD attached via a linker to Activin Receptor ECD; or (B) the immune checkpoint inhibitor polypeptide is an anti-CTLA-4 antibody, the Activin-binding polypeptide is an Activin Receptor ECD attached via a linker to the heavy chain CH3 of the anti-CTLA-4 antibody and the TGF-β-binding polypeptide is an TGF-β Receptor ECD attached via a linker to Activin Receptor ECD.

[040] FIG. 7 depicts line graphs showing that multispecific antagonist molecules A115, A116, A117 and A118 potently neutralize Activin A and Activin B in cell-based assays. The IC_{50} values were calculated and plotted using Prism software (GraphPad Software).

[041] FIG. 8 depicts line graphs showing that multispecific antagonist molecules A115, A116, A117 and A118 potently neutralize TGF-β1 and TGF-β3 in cell-based assays. The IC_{50} values were calculated and plotted using Prism software (GraphPad Software).

[042] FIG. 9 depicts line graphs showing that multispecific antagonist molecules A115, A116, A117 and A118 potently neutralize GDF-8 and GDF-11 in cell-based assays. The IC_{50} values were calculated and plotted using Prism software (GraphPad Software).

[043] FIGS. 10-12 depict the inhibitory effects of multispecific antagonist A116 on cell migration and colony formation in A549 human non-small cell lung cancer cell cultures.

[044] FIG. 13 shows the histological images of H&E stained lung sections and Ashcraft Scores of the lung sections in a mouse model of bleomycin-induced pulmonary fibrosis. The data indicate that dual inhibition of TGF-β and activin by A116 markedly reduced bleomycin-induced lung fibrosis while activin inhibitor ActRIIA-Fc or TGF-β blocker TGFRII-Fc moderately inhibited bleomycin-induced lung fibrosis. Analysis of Ashcraft scores revealed that A116 treatment resulted in greater reduction of lung fibrosis compared to ActRIIA-Fc treatment or TGFRII-Fc treatment.

[045] FIG. 14 depicts the histology images of Masson's trichrome stained lung sections and a bar graph on quantitative analysis of collagen deposition area in the lung sections from mice with bleomycin-induced pulmonary fibrosis. The data demonstrate that A116 attenuated collagen deposition more effectively than ActRIIA-Fc or TGFRII-Fc in the bleomycin-induced lung fibrosis model.

[046] FIG. 15 shows the histology images of immunochemical staining of α-SMA, a marker for fibrosis, in the lung sections from control and bleomycin-treated mice. The lung sections were immunochemically stained with a primary anti-αSMA antibody in conjunction with an HRP-labeled secondary antibody. The results indicate that A116 was more effective than ActRIIA-Fc or TGFRII-Fc in preventing the induction of α-SMA in the lungs of bleomycin mice.

Mode(s) for Carrying out the Disclosure

Definitions

[047] The terms "polypeptide", "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. In various embodiments, "peptides", "polypeptides", and "proteins" are chains of amino acids whose alpha carbons are linked through peptide bonds. The terminal amino acid at one end of the chain (amino terminal) therefore has a free amino group, while the terminal amino acid at the other end of the chain (carboxy terminal) has a free carboxyl group. As used herein, the term "amino terminus" (abbreviated N-terminus) refers to the free α-amino group on an amino acid at the amino terminal of a peptide or to the α-amino group (imino group when participating in a peptide bond) of an amino acid at any other location within the peptide. Similarly, the term "carboxy terminus" refers to the free carboxyl group on the carboxy terminus of a peptide or the carboxyl group of an amino acid at any other location within the peptide. Peptides also include essentially any polyamino acid including, but not limited to, peptide mimetics such as amino acids joined by an ether as opposed to an amide bond

[048] Polypeptides of the disclosure include polypeptides that have been modified in any way and for any reason, for example, to: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (5) confer or modify other physicochemical or functional properties.

[049] An amino acid “substitution” as used herein refers to the replacement in a polypeptide of one amino acid at a particular position in a parent polypeptide sequence with a different amino acid. Amino acid substitutions can be generated using genetic or chemical methods well known in the art. For example, single or multiple amino acid substitutions (e.g., conservative amino acid substitutions) may be made in the naturally occurring sequence (e.g., in the portion of the polypeptide outside the domain(s) forming intermolecular contacts). A "conservative amino acid substitution" refers to the substitution in a polypeptide of an amino acid with a functionally similar amino acid. The following six groups each contain amino acids that are conservative substitutions for one another:

1) Alanine (A), Serine (S), and Threonine (T)
2) Aspartic acid (D) and Glutamic acid (E)
3) Asparagine (N) and Glutamine (Q)
4) Arginine (R) and Lysine (K)
5) Isoleucine (I), Leucine (L), Methionine (M), and Valine (V)
6) Phenylalanine (F), Tyrosine (Y), and Tryptophan (W)

[050] A “non-conservative amino acid substitution” refers to the substitution of a member of one of these classes for a member from another class. In making such changes, according to various embodiments, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

[051] The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art (see, for example, Kyte et al., 1982, J. Mol. Biol. 157:105-131). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in various embodiments, the substitution of amino acids whose hydropathic indices are within $\pm$2 is included. In various embodiments, those that are within $\pm$1 are included, and in various embodiments, those within $\pm$0.5 are included.

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

[053] The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0.+-.1); glutamate (+3.0.+-.1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5.+-.1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5) and tryptophan (-3.4). In making changes based upon similar hydrophilicity values, in various embodiments, the substitution of amino acids whose hydrophilicity values are within $\pm$2 is included, in various embodiments, those that are within $\pm$1 are included, and in various embodiments, those within $\pm$0.5 are included.

[054] Exemplary amino acid substitutions are set forth in Table 1.

Table 1

Original Residues	Exemplary Substitutions	Preferred Substitutions

Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	
Asp	Glu	
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

[055] A skilled artisan will be able to determine suitable variants of polypeptides as set forth herein using well-known techniques. In various embodiments, one skilled in the art may identify suitable areas of the molecule that may be changed without destroying activity by targeting regions not believed to be important for activity. In other embodiments, the skilled artisan can identify residues and portions of the molecules that are conserved among similar polypeptides. In further embodiments, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

[056] Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, the skilled artisan can predict the importance of amino acid residues in a polypeptide that correspond to amino acid residues important for activity or structure in similar polypeptides. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

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

[058] The term "polypeptide fragment" and “truncated polypeptide” as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion as compared to a corresponding full-length protein. In various embodiments, fragments can be, *e.g.,* at least 5, at least 10, at least 25, at least 50, at least 100, at least 150, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 600, at least 700, at least 800, at least 900 or at least 1000 amino acids in length. In various embodiments, fragments can also be, *e.g.,* at most 1000, at most 900, at most 800, at most 700, at most 600, at most 500, at most 450, at most 400, at most 350, at most 300, at most 250, at most 200, at most 150, at most 100, at most 50, at most 25, at most 10, or at most 5 amino acids in length. A fragment can further comprise, at either or both of its ends, one or more additional amino acids, for example, a sequence of amino acids from a different naturally-occurring protein (*e.g.,* an Fc or leucine zipper domain) or an artificial amino acid sequence (*e.g.*, an artificial linker sequence).

[059] The terms "polypeptide variant", “hybrid polypeptide” and “polypeptide mutant” as used herein refers to a polypeptide that comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. In various embodiments, the number of amino acid residues to be inserted, deleted, or substituted can be, *e.g.,* at least 1, at least 2, at least 3, at least 4, at least 5, at least 10, at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 225, at least 250, at least 275, at least 300, at least 350, at least 400, at least 450 or at least 500 amino acids in length. Hybrids of the present disclosure include fusion proteins.

[060] A "derivative" of a polypeptide is a polypeptide that has been chemically modified, *e.g.,* conjugation to another chemical moiety such as, for example, polyethylene glycol, albumin (*e.g.,* human serum albumin), phosphorylation, and glycosylation.

[061] The term "% sequence identity" is used interchangeably herein with the term "% identity" and refers to the level of amino acid sequence identity between two or more peptide sequences or the level of nucleotide sequence identity between two or more nucleotide sequences, when aligned using a sequence alignment program. For example, as used herein, 80% identity means the same thing as 80% sequence identity determined by a defined algorithm and means that a given sequence is at least 80% identical to another length of another sequence. In various embodiments, the % identity is selected from, *e.g.,* at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% or more sequence identity to a given sequence. In various embodiments, the % identity is in the range of, e.g., about 60% to about 70%, about 70% to about 80%, about 80% to about 85%, about 85% to about 90%, about 90% to about 95%, or about 95% to about 99%.

[062] The term "% sequence homology" is used interchangeably herein with the term "% homology" and refers to the level of amino acid sequence homology between two or more peptide sequences or the level of nucleotide sequence homology between two or more nucleotide sequences, when aligned using a sequence alignment program. For example, as used herein, 80% homology means the same thing as 80% sequence homology determined by a defined algorithm, and accordingly a homologue of a given sequence has greater than 80% sequence homology over a length of the given sequence. In various embodiments, the % homology is selected from, *e.g.,* at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% or more sequence homology to a given sequence. In various embodiments, the % homology is in the range of, e.g., about 60% to

about 70%, about 70% to about 80%, about 80% to about 85%, about 85% to about 90%, about 90% to about 95%, or about 95% to about 99%.

[063] Exemplary computer programs which can be used to determine identity between two sequences include, but are not limited to, the suite of BLAST programs, e.g., BLASTN, BLASTX, and TBLASTX, BLASTP and TBLASTN, publicly available on the Internet at the NCBI website. See also Altschul et al., J. Mol. Biol. 215:403-10, 1990 (with special reference to the published default setting, i.e., parameters w=4, t=17) and Altschul et al., Nucleic Acids Res., 25:3389-3402, 1997. Sequence searches are typically carried out using the BLASTP program when evaluating a given amino acid sequence relative to amino acid sequences in the GenBank Protein Sequences and other public databases. The BLASTX program is preferred for searching nucleic acid sequences that have been translated in all reading frames against amino acid sequences in the GenBank Protein Sequences and other public databases. Both BLASTP and BLASTX are run using default parameters of an open gap penalty of 11.0, and an extended gap penalty of 1.0, and utilize the BLOSUM-62 matrix.

[064] In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin & Altschul, Proc. Nat'l. Acad. Sci. USA, 90:5873-5787, 1993). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is, *e.g.,* less than about 0.1, less than about 0.01, or less than about 0.001.

[065] The term “modification” as used herein refers to any manipulation of the peptide backbone (e.g., amino acid sequence) or the post-translational modifications (e.g., glycosylation) of a polypeptide.

[066] The term "antigen binding molecule" as used herein refers in its broadest sense to a molecule that specifically binds an antigenic determinant. Examples of antigen binding molecules are antibodies, antibody fragments and scaffold antigen binding proteins. An "antigen binding molecule that binds to the same epitope" as a reference molecule refers to an antigen binding molecule that blocks binding of the reference molecule to its antigen in a competition assay by 50% or more, and conversely, the reference molecule blocks binding of the antigen binding molecule to its antigen in a competition assay by 50% or more.

[067] As used herein, the term "antigen-binding site" refers to the part of the antigen binding molecule that specifically binds to an antigenic determinant. More particularly, the term

"antigen-binding site" refers the part of an antibody that comprises the area which specifically binds to and is complementary to part or all of an antigen. Where an antigen is large, an antigen binding molecule may only bind to a particular part of the antigen, which part is termed an epitope. An antigen-binding site may be provided by, for example, one or more variable domains (also called variable regions). Preferably, an antigen-binding site comprises an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH).

[068] As used herein, the term "antigenic determinant" is synonymous with "antigen" and "epitope," and refers to a site (e.g., a contiguous stretch of amino acids or a conformational configuration made up of different regions of non-contiguous amino acids) on a polypeptide macromolecule to which an antigen binding moiety binds, forming an antigen binding moiety-antigen complex. Useful antigenic determinants can be found, for example, on the surfaces of tumor cells, on the surfaces of virus-infected cells, on the surfaces of other diseased cells, on the surface of immune cells, free in blood serum, and/or in the extracellular matrix (ECM). The proteins useful as antigens herein can be any native form the proteins from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. In various embodiments, the antigen is a human protein.

[069] The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, monospecific and multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

[070] The term "chimeric" antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[071] A "humanized" antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (e.g., CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of an antibody, e.g., a non-human antibody, refers to an antibody that has undergone humanization. Other forms of "humanized antibodies" encompassed by the present invention are those in which the constant region has been additionally modified or changed from that of the original antibody to

generate the properties according to the invention, especially in regard to C1q binding and/or Fc receptor (FcR) binding.

[072] A "human" antibody is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues.

[073] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen.

[074] The term "monospecific" antibody as used herein denotes an antibody that has one or more binding sites each of which bind to the same epitope of the same antigen. The term "bispecific" means that the antibody is able to specifically bind to at least two distinct antigenic determinants, for example two binding sites each formed by a pair of an antibody heavy chain variable domain (VH) and an antibody light chain variable domain (VL) binding to different antigens or to different epitopes on the same antigen. Such a bispecific antibody is an 1+1 format. Other bispecific antibody formats are 2+1 formats (comprising two binding sites for a first antigen or epitope and one binding site for a second antigen or epitope) or 2+2 formats (comprising two binding sites for a first antigen or epitope and two binding sites for a second antigen or epitope). Typically, a bispecific antibody comprises two antigen binding sites, each of which is specific for a different antigenic determinant.

[075] The term "valent" as used within the current application denotes the presence of a specified number of binding sites in an antigen binding molecule. As such, the terms "bivalent", "tetravalent", and "hexavalent" denote the presence of two binding sites, four binding sites, and six binding sites, respectively, in an antigen binding molecule. The bispecific antibodies according to the invention are at least "bivalent" and may be "trivalent" or "multivalent" (e.g., "tetravalent" or "hexavalent"). In various embodiments, the antibodies of the present invention have two or more binding sites and are bispecific. That is, the antibodies may be bispecific even in cases where there are more than two binding sites (i.e. that the antibody is

trivalent or multivalent). In particular, the invention relates to bispecific bivalent antibodies, having one binding site for each antigen they specifically bind to.

[076] The terms "full-length antibody", "intact antibody", and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure. "Native antibodies" refer to naturally occurring immunoglobulin molecules with varying structures. For example, native IgG-class antibodies are heterotetrameric glycoproteins of about 150,000 daltons, composed of two light chains and two heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3), also called a heavy chain constant region. Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a variable light domain or a light chain variable domain, followed by a light chain constant domain (CL), also called a light chain constant region. The heavy chain of an antibody may be assigned to one of five types, called alpha (IgA), delta (IgD), epsilon (IgE), gamma (IgG), or mu (IgM), some of which may be further divided into subtypes, e.g., gamma 1 (IgG1), gamma 2 (IgG2), gamma 3 (IgG3), gamma 4 (IgG4), alpha 1 (IgA1) and alpha 2 (IgA2). The light chain of an antibody may be assigned to one of two types, called kappa and lambda, based on the amino acid sequence of its constant domain.

[077] An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, $F(ab')_2$; diabodies, triabodies, tetrabodies, cross-Fab fragments; linear antibodies; single-chain antibody molecules (e.g., scFv); multispecific antibodies formed from antibody fragments and single domain antibodies. For a review of certain antibody fragments, see Hudson et al., Nat Med 9, 129-134 (2003). For a review of scFv fragments, see e.g., Pluckthun, in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); see also WO 93/16185; and U.S. Pat. Nos. 5,571,894 and 5,587,458. For discussion of Fab and F(ab')2 fragments comprising salvage receptor binding epitope residues and having increased in vivo half-life, see U.S. Pat. No. 5,869,046. Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific, see, for example, EP 404,097; WO 1993/01161; Hudson et al., Nat Med 9, 129-134 (2003); and Hollinger et al., Proc Natl Acad Sci USA 90, 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al., Nat Med 9, 129-134 (2003). Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a

portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, Mass.; see e.g., U.S. Pat. No. 6,248,516 B1). In addition, antibody fragments comprise single chain polypeptides having the characteristics of a VH domain, namely being able to assemble together with a VL domain, or of a VL domain, namely being able to assemble together with a VH domain to a functional antigen binding site and thereby providing the antigen binding property of full-length antibodies. Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (e.g., E. coli or phage), as described herein.

[078] Papain digestion of intact antibodies produces two identical antigen-binding fragments, called "Fab" fragments containing each the heavy- and light-chain variable domains and also the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. As used herein, Thus, the term "Fab fragment" refers to an antibody fragment comprising a light chain fragment comprising a VL domain and a constant domain of a light chain (CL), and a VH domain and a first constant domain (CH1) of a heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH are Fab' fragments wherein the cysteine residue(s) of the constant domains bear a free thiol group. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-combining sites (two Fab fragments) and a part of the Fc region.

[079] A "single chain Fab fragment" or "scFab" is a polypeptide consisting of an antibody heavy chain variable domain (VH), an antibody constant domain 1 (CH1), an antibody light chain variable domain (VL), an antibody light chain constant domain (CL) and a linker, wherein said antibody domains and said linker have one of the following orders in N-terminal to C-terminal direction: a) VH-CH1-linker-VL-CL, b) VL-CL-linker-VH-CH1, c) VH-CL-linker-VL-CH1 or d) VL-CH1-linker-VH-CL; and wherein said linker is a polypeptide of at least 30 amino acids, preferably between 32 and 50 amino acids. Said single chain Fab fragments are stabilized via the natural disulfide bond between the CL domain and the CH1 domain. In addition, these single chain Fab molecules might be further stabilized by generation of interchain disulfide bonds via insertion of cysteine residues (e.g., position 44 in the variable heavy chain and position 100 in the variable light chain according to Kabat numbering).

[080] A "single-chain variable fragment (scFv)" is a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of an antibody, connected with a short linker peptide of ten to about 25 amino acids. The linker is usually rich in glycine for flexibility, as well

as serine or threonine for solubility, and can either connect the N-terminus of the VH with the C-terminus of the VL, or vice versa. This protein retains the specificity of the original antibody, despite removal of the constant regions and the introduction of the linker. scFv antibodies are, e.g., described in Houston, J. S., Methods in Enzymol. 203 (1991) 46-96). In addition, antibody fragments comprise single chain polypeptides having the characteristics of a VH domain, namely being able to assemble together with a VL domain, or of a VL domain, namely being able to assemble together with a VH domain to a functional antigen binding molecule and thereby providing the antigen binding property of full-length antibodies.

[081] The term "Fc domain" or "Fc region" herein is used to define a C-terminal region of an antibody heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. Particularly, a human IgG heavy chain Fc region extends from Cys226, or from Pro230, to the carboxyl-terminus of the heavy chain. However, the C-terminal lysine (Lys447) of the Fc region may or may not be present. The amino acid sequences of the heavy chains are always presented with the C-terminal lysine, however variants without the C-terminal lysine are included in the invention.

[082] An IgG Fc region comprises an IgG CH2 and an IgG CH3 domain. The "CH2 domain" of a human IgG Fc region usually extends from an amino acid residue at about position 231 to an amino acid residue at about position 340. In one embodiment, a carbohydrate chain is attached to the CH2 domain. The CH2 domain herein may be a native sequence CH2 domain or variant CH2 domain. The "CH3 domain" comprises the stretch of residues C-terminal to a CH2 domain in an Fc region (i.e. from an amino acid residue at about position 341 to an amino acid residue at about position 447 of an IgG). The CH3 region herein may be a native sequence CH3 domain or a variant CH3 domain (e.g., a CH3 domain with an introduced "protuberance" ("knob") in one chain thereof and a corresponding introduced "cavity" ("hole") in the other chain thereof; see U.S. Pat. No. 5,821,333, expressly incorporated herein by reference). Such variant CH3 domains may be used to promote heterodimerization of two non-identical antibody heavy chains as herein described. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991.

[083] The "knob-into-hole" technology is described e.g., in U.S. Pat. Nos. 5,731,168; 7,695,936; Ridgway et al., Prot Eng 9, 617-621 (1996) and Carter, J Immunol Meth 248, 7-15 (2001). Generally, the method involves introducing a protuberance ("knob") at the interface of a first polypeptide and a corresponding cavity ("hole") in the interface of a second polypeptide,

such that the protuberance can be positioned in the cavity so as to promote heterodimer formation and hinder homodimer formation. Protuberances are constructed by replacing small amino acid side chains from the interface of the first polypeptide with larger side chains (e.g., tyrosine or tryptophan). Compensatory cavities of identical or similar size to the protuberances are created in the interface of the second polypeptide by replacing large amino acid side chains with smaller ones (e.g., alanine or threonine). The protuberance and cavity can be made by altering the nucleic acid encoding the polypeptides, e.g., by site-specific mutagenesis, or by peptide synthesis. In a specific embodiment a knob modification comprises the amino acid substitution T366W in one of the two subunits of the Fc domain, and the hole modification comprises the amino acid substitutions T366S, L368A and Y407V in the other one of the two subunits of the Fc domain. In a further specific embodiment, the subunit of the Fc domain comprising the knob modification additionally comprises the amino acid substitution S354C, and the subunit of the Fc domain comprising the hole modification additionally comprises the amino acid substitution Y349C. Introduction of these two cysteine residues results in the formation of a disulfide bridge between the two subunits of the Fc region, thus further stabilizing the dimer (Carter, J Immunol Methods 248, 7-15 (2001)).

[084] A "region equivalent to the Fc region of an immunoglobulin" is intended to include naturally occurring allelic variants of the Fc region of an immunoglobulin as well as variants having alterations which produce substitutions, additions, or deletions but which do not decrease substantially the ability of the immunoglobulin to mediate effector functions (such as antibody-dependent cellular cytotoxicity). For example, one or more amino acids can be deleted from the N-terminus or C-terminus of the Fc region of an immunoglobulin without substantial loss of biological function. Such variants can be selected according to general rules known in the art so as to have minimal effect on activity (see, e.g., Bowie, J. U. et al., Science 247:1306-10 (1990)).

[085] The term "effector functions" refers to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC), Fc receptor binding, antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), cytokine secretion, immune complex-mediated antigen uptake by antigen presenting cells, down regulation of cell surface receptors (e.g., B cell receptor), and B cell activation.

[086] An "activating Fc receptor" is an Fc receptor that following engagement by an Fc region of an antibody elicits signaling events that stimulate the receptor-bearing cell to perform

effector functions. Activating Fc receptors include FcγRIIIa (CD16a), FcγRI (CD64), FcγRIIa (CD32), and FcαRI (CD89). A particular activating Fc receptor is human FcγRIIIa (see UniProt accession no. P08637, version 141).

[087] A "blocking" antibody or an "antagonist" antibody is one that inhibits or reduces a biological activity of the antigen it binds. In some embodiments, blocking antibodies or antagonist antibodies substantially or completely inhibit the biological activity of the antigen. For example, the bispecific antibodies of the invention block the signaling through TGF-β and Activin so as to inhibit TGF-β/Activin-Smad2/3 signaling pathway.

[088] As used herein, “specific binding” is meant that the binding is selective for the antigen and can be discriminated from unwanted or non-specific interactions. The ability of an antigen binding molecule to bind to a specific antigen can be measured either through an enzyme-linked immunosorbent assay (ELISA) or other techniques familiar to one of skill in the art, e.g., Surface Plasmon Resonance (SPR) technique (analyzed on a BIAcore instrument) (Liljeblad et al., Glyco J 17, 323-329 (2000)), and traditional binding assays (Heeley, Endocr Res 28, 217-229 (2002)).

[089] The terms “affinity” or “binding affinity” as used herein refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (KD), which is the ratio of dissociation and association rate constants (koff and kon, respectively). A particular method for measuring affinity is Surface Plasmon Resonance (SPR). As used herein, the term "high affinity" of an antibody refers to an antibody having a Kd of 10^{-9} M or less and even more particularly 10^{-10} M or less for a target antigen. The term "low affinity" of an antibody refers to an antibody having a Kd of 10^{-8} M or higher. The term “reduced binding”, as used herein refers to a decrease in affinity for the respective interaction, as measured for example by SPR. Conversely, “increased binding” refers to an increase in binding affinity for the respective interaction.

[090] The term "a bispecific antibody comprising a first antigen-binding molecule that specifically binds to Activin or Activin-related ligand and a second antigen-binding molecule that specifically binds to TGF-β", "a bispecific antibody that specifically binds Activin or Activin-related ligand and TGF-β", "bispecific antigen binding molecule specific for Activin or Activin-related ligand and TGF-β" are used interchangeably herein and refer to a bispecific antibody that is capable of binding Activin or Activin-related ligand and TGF-β with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting Activin or Activin-related ligand and TGF-β.

[091] The terms "anti-Activin antibody" and "an antibody comprising an antigen-binding site that binds to Activin" refer to an antibody that is capable of binding Activin, especially a Activin polypeptide expressed on a cell surface, with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting Activin. In one embodiment, the extent of binding of an anti-Activin antibody to an unrelated, non-Activin protein is less than about 10% of the binding of the antibody to Activin as measured, e.g., by radioimmunoassay (RIA) or flow cytometry (FACS) or by a Surface Plasmon Resonance assay using a biosensor system such as a Biacore® system. In certain embodiments, an antigen binding molecule that binds to human Activin has a KD value of the binding affinity for binding to human Activin of, e.g., from 10^{-8} M to 10^{-13} M. In one preferred embodiment the respective KD value of the binding affinities is determined in a Surface Plasmon Resonance assay using the Extracellular domain (ECD) of human Activin (Activin-ECD) for the Activin binding affinity. The term "anti-Activin antibody" also encompasses bispecific antibodies that are capable of binding Activin and a second antigen.

[092] The terms "anti-TGF-β antibody" and "an antibody comprising an antigen-binding site that binds to TGF-β" refer to an antibody that is capable of binding TGF-β, especially a TGF-β polypeptide expressed on a cell surface, with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting TGF-β. In one embodiment, the extent of binding of an anti-TGF-β antibody to an unrelated, non-TGF-β protein is less than about 10% of the binding of the antibody to TGF-β as measured, e.g., by radioimmunoassay (RIA) or flow cytometry (FACS) or by a Surface Plasmon Resonance assay using a biosensor system such as a Biacore® system. In certain embodiments, an antigen binding molecule that binds to human TGF-β has a KD value of the binding affinity for binding to human TGF-β of, e.g., from 10^{-8} M to 10^{-13} M. In one preferred embodiment the respective KD value of the binding affinities is determined in a Surface Plasmon Resonance assay using the Extracellular domain (ECD) of human TGF-β (TGF-β-ECD) for the TGF-β binding affinity. The term "anti-TGF-β antibody" also encompasses bispecific antibodies that are capable of binding TGF-β and a second antigen.

[093] The term “fusion protein” as used herein refers to a fusion polypeptide molecule comprising two or more genes that originally coded for separate proteins, wherein the components of the fusion protein are linked to each other by peptide-bonds, either directly or through peptide linkers. The term “fused” as used herein refers to components that are linked by peptide bonds, either directly or via one or more peptide linkers.

[094] "Linker" refers to a molecule that joins two other molecules, either covalently, or through ionic, van der Waals or hydrogen bonds, e.g., a nucleic acid molecule that hybridizes to one complementary sequence at the 5' end and to another complementary sequence at the 3' end, thus joining two non-complementary sequences. A "cleavable linker" refers to a linker that can be degraded or otherwise severed to separate the two components connected by the cleavable linker. Cleavable linkers are generally cleaved by enzymes, typically peptidases, proteases, nucleases, lipases, and the like. Cleavable linkers may also be cleaved by environmental cues, such as, for example, changes in temperature, pH, salt concentration, etc.

[095] The term “peptide linker” as used herein refers to a peptide comprising one or more amino acids, typically about 2-20 amino acids. Peptide linkers are known in the art or are described herein. Suitable, non-immunogenic linker peptides include, for example, $(G_4S)_n$, $(SG_4)_n$ or $G_4(SG_4)$n peptide linkers. “n” is generally a number between 1 and 10, typically between 2 and 4.

[096] "Pharmaceutical composition" refers to a composition suitable for pharmaceutical use in an animal. A pharmaceutical composition comprises a pharmacologically effective amount of an active agent and a pharmaceutically acceptable carrier. "Pharmacologically effective amount" refers to that amount of an agent effective to produce the intended pharmacological result. "Pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, vehicles, buffers, and excipients, such as a phosphate buffered saline solution, 5% aqueous solution of dextrose, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents and/or adjuvants. Suitable pharmaceutical carriers and formulations are described in Remington's Pharmaceutical Sciences, 21st Ed. 2005, Mack Publishing Co, Easton. A "pharmaceutically acceptable salt" is a salt that can be formulated into a compound for pharmaceutical use including, e.g., metal salts (sodium, potassium, magnesium, calcium, etc.) and salts of ammonia or organic amines.

[097] As used herein, “treatment” (and grammatical variations thereof such as “treat” or “treating”) refers to clinical intervention in an attempt to alter the natural course of a disease in the individual being treated and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. As used herein, to "alleviate" a disease, disorder or condition means reducing the severity and/or occurrence frequency of the symptoms of the disease, disorder, or

condition. Further, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

[098] The term "effective amount" or “therapeutically effective amount” as used herein refers to an amount of a compound or composition sufficient to treat a specified disorder, condition or disease such as ameliorate, palliate, lessen, and/or delay one or more of its symptoms. In reference to cancers or other unwanted cell proliferation, an effective amount comprises an amount sufficient to: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and preferably stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer. An effective amount can be administered in one or more administrations.

[099] The phrase “administering” or "cause to be administered" refers to the actions taken by a medical professional (*e.g.*, a physician), or a person controlling medical care of a patient, that control and/or permit the administration of the agent(s)/compound(s) at issue to the patient. Causing to be administered can involve diagnosis and/or determination of an appropriate therapeutic regimen, and/or prescribing particular agent(s)/compounds for a patient. Such prescribing can include, for example, drafting a prescription form, annotating a medical record, and the like. Where administration is described herein, "causing to be administered" is also contemplated.

[0100] The terms "patient," "individual," and "subject" may be used interchangeably and refer to a mammal, preferably a human or a non-human primate, but also domesticated mammals (*e.g.*, canine or feline), laboratory mammals (*e.g.*, mouse, rat, rabbit, hamster, guinea pig), and agricultural mammals (*e.g.*, equine, bovine, porcine, ovine). In various embodiments, the patient can be a human (*e.g.,* adult male, adult female, adolescent male, adolescent female, male child, female child) under the care of a physician or other health worker in a hospital, psychiatric care facility, as an outpatient, or other clinical context. In various embodiments, the patient may be an immunocompromised patient or a patient with a weakened immune system including, but not limited to patients having primary immune deficiency, AIDS; cancer and transplant patients who are taking certain immunosuppressive drugs; and those with inherited diseases that affect the immune system (e.g., congenital agammaglobulinemia, congenital IgA deficiency). In various embodiments, the patient has an immunogenic cancer, including, but not limited to bladder cancer, lung cancer, melanoma, and other cancers reported to have a high rate of mutations (Lawrence et al., Nature, 499(7457): 214–218, 2013).

[0101] The term “immunotherapy” refers to cancer treatments which include, but are not limited to, treatment using depleting antibodies to specific tumor antigens; treatment using antibody-drug conjugates; treatment using agonistic, antagonistic, or blocking antibodies to co-stimulatory or co-inhibitory molecules (immune checkpoints) such as CTLA-4, PD-1, OX-40, CD137, GITR, LAG3, TIM-3, SIRP, CD40, CD47, Siglec 8, Siglec 9, Siglec 15, TIGIT and VISTA; treatment using bispecific T cell engaging antibodies (BiTE®) such as blinatumomab: treatment involving administration of biological response modifiers such as IL-2, IL-12, IL-15, IL-21, GM-CSF, IFN-α, IFN-β and IFN-γ; treatment using therapeutic vaccines such as sipuleucel-T; treatment using Bacilli Calmette-Guerin (BCG); treatment using dendritic cell vaccines, or tumor antigen peptide vaccines; treatment using chimeric antigen receptor (CAR)-T cells; treatment using CAR-NK cells; treatment using tumor infiltrating lymphocytes (TILs); treatment using adoptively transferred anti-tumor T cells (ex vivo expanded and/or TCR transgenic); treatment using TALL-104 cells; and treatment using immunostimulatory agents such as Toll-like receptor (TLR) agonists CpG and imiquimod.

[0102] “Resistant or refractory cancer” refers to tumor cells or cancer that do not respond to previous anti-cancer therapy including, e.g., chemotherapy, surgery, radiation therapy, stem cell transplantation, and immunotherapy. Tumor cells can be resistant or refractory at the beginning of treatment, or they may become resistant or refractory during treatment. Refractory tumor cells include tumors that do not respond at the onset of treatment or respond initially for a short period but fail to respond to treatment. Refractory tumor cells also include tumors that respond to treatment with anticancer therapy but fail to respond to subsequent rounds of therapies. For purposes of this invention, refractory tumor cells also encompass tumors that appear to be inhibited by treatment with anticancer therapy but recur up to five years, sometimes up to ten years or longer after treatment is discontinued. The anticancer therapy can employ chemotherapeutic agents alone, radiation alone, targeted therapy alone, immunotherapy alone, surgery alone, or combinations thereof. For ease of description and not limitation, it will be understood that the refractory tumor cells are interchangeable with resistant tumor.

[0103] The term "polymer" as used herein generally includes, but is not limited to, homopolymers; copolymers, such as, for example, block, graft, random and alternating copolymers; and terpolymers; and blends and modifications thereof. Furthermore, unless otherwise specifically limited, the term "polymer" shall include all possible geometrical configurations of the material. These configurations include, but are not limited to isotactic, syndiotactic, and random symmetries.

[0104] "Polynucleotide" refers to a polymer composed of nucleotide units. Polynucleotides include naturally occurring nucleic acids, such as deoxyribonucleic acid ("DNA") and ribonucleic acid ("RNA") as well as nucleic acid analogs. Nucleic acid analogs include those which include non-naturally occurring bases, nucleotides that engage in linkages with other nucleotides other than the naturally occurring phosphodiester bond or which include bases attached through linkages other than phosphodiester bonds. Thus, nucleotide analogs include, for example and without limitation, phosphorothioates, phosphorodithioates, phosphorotriesters, phosphoramidates, boranophosphates, methylphosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs), and the like. Such polynucleotides can be synthesized, for example, using an automated DNA synthesizer. The term "nucleic acid" typically refers to large polynucleotides. The term "oligonucleotide" typically refers to short polynucleotides, generally no greater than about 50 nucleotides. It will be understood that when a nucleotide sequence is represented by a DNA sequence (i.e., A, T, G, C), this also includes an RNA sequence (i.e., A, U, G, C) in which "U" replaces "T."

[0105] Conventional notation is used herein to describe polynucleotide sequences: the left-hand end of a single-stranded polynucleotide sequence is the 5'-end; the left-hand direction of a double-stranded polynucleotide sequence is referred to as the 5'-direction. The direction of 5' to 3' addition of nucleotides to nascent RNA transcripts is referred to as the transcription direction. The DNA strand having the same sequence as an mRNA is referred to as the "coding strand"; sequences on the DNA strand having the same sequence as an mRNA transcribed from that DNA and which are located 5' to the 5'-end of the RNA transcript are referred to as "upstream sequences"; sequences on the DNA strand having the same sequence as the RNA and which are 3' to the 3' end of the coding RNA transcript are referred to as "downstream sequences."

[0106] "Complementary" refers to the topological compatibility or matching together of interacting surfaces of two polynucleotides. Thus, the two molecules can be described as complementary, and furthermore, the contact surface characteristics are complementary to each other. A first polynucleotide is complementary to a second polynucleotide if the nucleotide sequence of the first polynucleotide is substantially identical to the nucleotide sequence of the polynucleotide binding partner of the second polynucleotide, or if the first polynucleotide can hybridize to the second polynucleotide under stringent hybridization conditions.

[0107] "Hybridizing specifically to" or "specific hybridization" or "selectively hybridize to", refers to the binding, duplexing, or hybridizing of a nucleic acid molecule preferentially to a particular nucleotide sequence under stringent conditions when that sequence is present in a

complex mixture (e.g., total cellular) DNA or RNA. The term "stringent conditions" refers to conditions under which a probe will hybridize preferentially to its target subsequence, and to a lesser extent to, or not at all to, other sequences. "Stringent hybridization" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization experiments such as Southern and northern hybridizations are sequence-dependent and are different under different environmental parameters. An extensive guide to the hybridization of nucleic acids can be found in Tijssen, 1993, Laboratory Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Acid Probes, part I, chapter 2, "Overview of principles of hybridization and the strategy of nucleic acid probe assays", Elsevier, N.Y.; Sambrook et al., 2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, 3.sup.rd ed., NY; and Ausubel et al., eds., Current Edition, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY.

[0108] Generally, highly stringent hybridization and wash conditions are selected to be about 5°C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Very stringent conditions are selected to be equal to the Tm for a particular probe. An example of stringent hybridization conditions for hybridization of complementary nucleic acids which have more than about 100 complementary residues on a filter in a Southern or northern blot is 50% formalin with 1 mg of heparin at 42°C, with the hybridization being carried out overnight. An example of highly stringent wash conditions is 0.15 M NaCl at 72°C for about 15 minutes. An example of stringent wash conditions is a 0.2 x SSC wash at 65°C for 15 minutes. See Sambrook et al. for a description of SSC buffer. A high stringency wash can be preceded by a low stringency wash to remove background probe signal. An exemplary medium stringency wash for a duplex of, e.g., more than about 100 nucleotides, is 1 x SSC at 45°C for 15 minutes. An exemplary low stringency wash for a duplex of, e.g., more than about 100 nucleotides, is 4-6 x SSC at 40°C for 15 minutes. In general, a signal to noise ratio of 2 x (or higher) than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization.

[0109] "Primer" refers to a polynucleotide that is capable of specifically hybridizing to a designated polynucleotide template and providing a point of initiation for synthesis of a complementary polynucleotide. Such synthesis occurs when the polynucleotide primer is placed under conditions in which synthesis is induced, i.e., in the presence of nucleotides, a complementary polynucleotide template, and an agent for polymerization such as DNA

polymerase. A primer is typically single-stranded but may be double-stranded. Primers are typically deoxyribonucleic acids, but a wide variety of synthetic and naturally occurring primers are useful for many applications. A primer is complementary to the template to which it is designed to hybridize to serve as a site for the initiation of synthesis but need not reflect the exact sequence of the template. In such a case, specific hybridization of the primer to the template depends on the stringency of the hybridization conditions. Primers can be labeled with, e.g., chromogenic, radioactive, or fluorescent moieties and used as detectable moieties.

[0110] "Probe," when used in reference to a polynucleotide, refers to a polynucleotide that is capable of specifically hybridizing to a designated sequence of another polynucleotide. A probe specifically hybridizes to a target complementary polynucleotide but need not reflect the exact complementary sequence of the template. In such a case, specific hybridization of the probe to the target depends on the stringency of the hybridization conditions. Probes can be labeled with, e.g., chromogenic, radioactive, or fluorescent moieties and used as detectable moieties. In instances where a probe provides a point of initiation for synthesis of a complementary polynucleotide, a probe can also be a primer.

[0111] A "vector" is a polynucleotide that can be used to introduce another nucleic acid linked to it into a cell. One type of vector is a "plasmid," which refers to a linear or circular double stranded DNA molecule into which additional nucleic acid segments can be ligated. Another type of vector is a viral vector (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), wherein additional DNA segments can be introduced into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors comprising a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. An "expression vector" is a type of vector that can direct the expression of a chosen polynucleotide.

[0112] A "regulatory sequence" is a nucleic acid that affects the expression (e.g., the level, timing, or location of expression) of a nucleic acid to which it is operably linked. The regulatory sequence can, for example, exert its effects directly on the regulated nucleic acid, or through the action of one or more other molecules (e.g., polypeptides that bind to the regulatory sequence and/or the nucleic acid). Examples of regulatory sequences include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Further examples of regulatory sequences are described in, for example, Goeddel, 1990, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, Calif. and

Baron et al., 1995, Nucleic Acids Res. 23:3605-06. A nucleotide sequence is "operably linked" to a regulatory sequence if the regulatory sequence affects the expression (e.g., the level, timing, or location of expression) of the nucleotide sequence.

[0113] A "host cell" is a cell that can be used to express a polynucleotide of the disclosure. A host cell can be a prokaryote, for example, *E. coli*, or it can be a eukaryote, for example, a single-celled eukaryote (e.g., a yeast or other fungus), a plant cell (e.g., a tobacco or tomato plant cell), an animal cell (e.g., a human cell, a monkey cell, a hamster cell, a rat cell, a mouse cell, or an insect cell) or a hybridoma. Typically, a host cell is a cultured cell that can be transformed or transfected with a polypeptide-encoding nucleic acid, which can then be expressed in the host cell. The phrase "recombinant host cell" can be used to denote a host cell that has been transformed or transfected with a nucleic acid to be expressed. A host cell also can be a cell that comprises the nucleic acid but does not express it at a desired level unless a regulatory sequence is introduced into the host cell such that it becomes operably linked with the nucleic acid. It is understood that the term host cell refers not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to, e.g., mutation or environmental influence, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0114] The term "isolated molecule" (where the molecule is, for example, a polypeptide or a polynucleotide) is a molecule that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other molecules from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a molecule that is chemically synthesized, or expressed in a cellular system different from the cell from which it naturally originates, will be "isolated" from its naturally associated components. A molecule also may be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art. Molecule purity or homogeneity may be assayed by a number of means well known in the art. For example, the purity of a polypeptide sample may be assayed using polyacrylamide gel electrophoresis and staining of the gel to visualize the polypeptide using techniques well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

[0115] A protein or polypeptide is "substantially pure," "substantially homogeneous," or "substantially purified" when at least about 60% to 75% of a sample exhibits a single species of polypeptide. The polypeptide or protein may be monomeric or multimeric. A substantially pure

polypeptide or protein will typically comprise about 50%, 60%, 70%, 80% or 90% W/W of a protein sample, more usually about 95%, and preferably will be over 99% pure. Protein purity or homogeneity may be indicated by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel with a stain well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

[0116] The terms "label" or "labeled" as used herein refers to incorporation of another molecule in the antibody. In one embodiment, the label is a detectable marker, e.g., incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or calorimetric methods). In another embodiment, the label or marker can be therapeutic, e.g., a drug conjugate or toxin. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic labels (e.g., horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent markers, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags), magnetic agents, such as gadolinium chelates, toxins such as pertussis toxin, taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. In various embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

[0117] The term "heterologous" as used herein refers to a composition or state that is not native or naturally found, for example, that may be achieved by replacing an existing natural composition or state with one that is derived from another source. Similarly, the expression of a protein in an organism other than the organism in which that protein is naturally expressed constitutes a heterologous expression system and a heterologous protein.

[0118] It is understood that aspect and embodiments of the disclosure described herein include “consisting” and/or “consisting essentially of” aspects and embodiments.

[0119] 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".

[0120] As used herein and in the appended claims, the singular forms "a," "or," and "the" include plural referents unless the context clearly dictates otherwise. It is understood that aspects and variations of the disclosure described herein include "consisting" and/or "consisting essentially of" aspects and variations.

Activin and Activin-related Ligands

[0121] Activins, including Activin A, Activin B and Activin AB, and Activin-related proteins, including Myostatin (GDF-8) and GDF-11, mediate Smad2/3 signaling through binding and activation of their high-affinity receptors ActRIIA and ActRIIB on the cell surface. The Activins and related proteins play a critical role in the regulation of a wide range of biology activities, including mesoderm induction, cell differentiation, myogenesis, bone remodeling, hematopoiesis, fibrogenesis, and reproductive physiology. Follistatin (FST), a secreted glycoprotein, binds to the Activins and Activin-related ligands to negatively control their signaling activities.

[0122] In various embodiments, the bifunctional molecule of the present invention is capable of binding an Activin or Activin-related ligand having an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NOs: 1-9:

Human ActRIIA-ECD
ETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYD
RTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVTPKPP (SEQ ID NO: 1)

Human ActRIIB-ECD
ETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWLDDFNCYD
RQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEV TYEPPPTAPT (SEQ ID NO: 2)

Human Follistatin 315
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNSISEDTEEEEEDEDQDYSFPISSI
LEW (SEQ ID NO: 3)

Human Follistatin ΔHBS (modified Follistatin)

GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNSISEDTEEEEEDEDQDYSFPISSI
LEW (SEQ ID NO: 4)

Human Follistatin 288
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCN (SEQ ID NO: 5)

Modified human ActRIIB ECD
ETRECIYYNANWELERTNQSGLERCEGDQDKRLHCYASWRNSSGTIELVKKGCWLDDINCYD
RQECVATKENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPT (SEQ ID NO: 6)

Modified human ActRIIB ECD
ETRECIYYNANWELERTNQSGLERCYGDKDKRRHCYASWRNSSGTIELVKKGCWLDDFNCYD
RQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPT (SEQ ID NO: 7)

Modified human ActRIIB ECD
ETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWDDDFNCY
DRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPT (SEQ ID NO: 8)

Modified human ActRIIA ECD
GAILGRSETQECLFYNANWELERTNQTGVEPCEGEKDKRLHCYATWRNISGSIEIVKKGCWLD
DFNCYDRTDCVETEENPQVYFCCCEGNMCNEKFSYFPEMEVTQPTS (SEQ ID NO: 9)

[0123] In various embodiments, the multispecific polypeptide molecule is capable of binding an Activin or Activin-related ligand having an amino acid sequence selected from the group consisting of the amino acid sequences set forth in Table 2:

Table 2

Polypeptides containing Activin and Activin-related ligands

LIGAND	DATABASE	ACCESSION NO
Activin A	UniProtKB	A4D1W7-1
Activin B	UniProtKB	P09529-1
GDF8	UniProtKB	A1C2F0-1

GDF11	UniProtKB	O95390-1

TGF-β Ligands

[0124] Transforming Growth Factor-Beta (TGF-β), including TGF-β1, TGF-β2 and TGF-β3, mediates Smad2/3 signaling through its binding and activation of the high-affinity receptors TGFβRII and TGFβRIIB on the cell surface. TGF-β plays a critical role in the regulation of a wide range of biology activities, including immune function, cell proliferation and differentiation, epithelial-mesenchymal transition, fibrogenesis, hematopoiesis, myogenesis, bone remodeling, cancer progression and metastasis. Elevated TGF-β levels and consequently increased Smad2/3 signaling have been implicated in pathogenesis and progression of many disease conditions including cancer, anemia, bone metastasis, bone loss, fibrosis, pain, muscle loss, insulin resistance, chronic kidney disease, liver disease, and cardiovascular diseases.

[0125] In various embodiments, the multispecific polypeptide molecule of the present invention is capable of binding an TGF-β ligand having an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NOs: 18-21:

Human TGF-β Receptor II isoform 1
MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDN
QKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKK
KPGETFFMCSCSSDECNDNIIFSEEYNTSNPDLLLVIFQVTGISLLPPLGVAISVIIIFYCYRVNRQ
QKLSSTWETGKTRKLMEFSEHCAIILEDDRSDISSTCANNINHNTELLPIELDTLVGKGRFAEVY
KAKLKQNTSEQFETVAVKIFPYEEYASWKTEKDIFSDINLKHENILQFLTAEERKTELGKQYWLIT
AFHAKGNLQEYLTRHVISWEDLRKLGSSLARGIAHLHSDHTPCGRPKMPIVHRDLKSSNILVKN
DLTCCLCDFGLSLRLDPTLSVDDLANSGQVGTARYMAPEVLESRMNLENVESFKQTDVYSMAL
VLWEMTSRCNAVGEVKDYEPPFGSKVREHPCVESMKDNVLRDRGRPEIPSFWLNHQGIQMV
CETLTECWDHDPEARLTAQCVAERFSELEHLDRLSGRSCSEEKIPEDGSLNTTK
(SEQ ID NO: 18)

Human TGF-β Receptor II-ECD isoform 1 (TGF-β RIIB-ECD)
TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCV
AVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFS
EEYNTSNPD (SEQ ID NO: 19)

Human TGF-β Receptor II isoform 2
MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTD
NNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHD
PKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDLLLVIFQVTG
ISLLPPLGVAISVIIIFYCYRVNRQQKLSSTWETGKTRKLMEFSEHCAIILEDDRSDISSTCANNIN
HNTELLPIELDTLVGKGRFAEVYKAKLKQNTSEQFETVAVKIFPYEEYASWKTEKDIFSDINLKHE
NILQFLTAEERKTELGKQYWLITAFHAKGNLQEYLTRHVISWEDLRKLGSSLARGIAHLHSDHTP
CGRPKMPIVHRDLKSSNILVKNDLTCCLCDFGLSLRLDPTLSVDDLANSGQVGTARYMAPEVLE

SRMNLENVESFKQTDVYSMALVLWEMTSRCNAVGEVKDYEPPFGSKVREHPCVESMKDNVL
RDRGRPEIPSFWLNHQGIQMVCETLTECWDHDPEARLTAQCVAERFSELEHLDRLSGRSCSE
EKIPEDGSLNTTK (SEQ ID NO: 20)

Human TGF-β Receptor II-ECD isoform 2 (TGF-β RIIA-ECD)
TIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTC
DNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKE
KKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 21)

[0126] In various embodiments, the multispecific polypeptide molecule is capable of binding a TGF-β ligand having an amino acid sequence selected from the group consisting of the amino acid sequences set forth in Table 3:

Table 3

Polypeptides containing TGF-β ligands

LIGAND	DATABASE	ACCESSION NO
TGF-β1	UniProtKB	P01137-1
TGF-β2	UniProtKB	P61812-1
TGF-β3	UniProtKB	P10600-1

Activin and/or TGF-β Antibodies and Antibody Fragments

[0127] Methods of generating novel antibodies that bind to Activin or Activin-related ligand and/or TGF-β ligands and/or receptors are known to those skilled in the art. For example, a method for generating a monoclonal antibody that binds specifically to an Activin or Activin-related ligand and/or TGF-β ligand may comprise administering to a mouse an amount of an immunogenic composition comprising the Activin or Activin-related ligand and/or TGF-β ligand effective to stimulate a detectable immune response, obtaining antibody-producing cells (e.g., cells from the spleen) from the mouse and fusing the antibody-producing cells with myeloma cells to obtain antibody-producing hybridomas, and testing the antibody-producing hybridomas to identify a hybridoma that produces a monoclonal antibody that binds specifically to the Activin or Activin-related ligand and/or TGF-β ligand. Once obtained, a hybridoma can be propagated in a cell culture, optionally in culture conditions where the hybridoma-derived cells produce the monoclonal antibody that binds specifically to Activin or Activin-related ligand and/or TGF-β ligand. The monoclonal antibody may be purified from the cell culture. A variety

of different techniques are then available for testing an antigen/antibody interaction to identify particularly desirable antibodies.

[0128] Other suitable methods of producing or isolating antibodies of the requisite specificity can used, including, for example, methods which select recombinant antibody from a library, or which rely upon immunization of transgenic animals (e.g., mice) capable of producing a full repertoire of human antibodies. See e.g., Jakobovits et al., Proc. Natl. Acad. Sci. (U.S.A.), 90: 2551-2555, 1993; Jakobovits et al., Nature, 362: 255-258, 1993; Lonberg et al., U.S. Pat. No. 5,545,806; and Surani et al., U.S. Pat. No. 5,545,807.

[0129] Antibodies can be engineered in numerous ways. They can be made as single-chain antibodies (including small modular immunopharmaceuticals or SMIPs™), Fab and $F(ab')_2$ fragments, etc. Antibodies can be humanized, chimerized, deimmunized, or fully human. Numerous publications set forth the many types of antibodies and the methods of engineering such antibodies. For example, see U.S. Pat. Nos. 6,355,245; 6,180,370; 5,693,762; 6,407,213; 6,548,640; 5,565,332; 5,225,539; 6,103,889; and 5,260,203.

[0130] Chimeric antibodies can be produced by recombinant DNA techniques known in the art. For example, a gene encoding the Fc constant region of a murine (or other species) monoclonal antibody molecule is digested with restriction enzymes to remove the region encoding the murine Fc, and the equivalent portion of a gene encoding a human Fc constant region is substituted (see Robinson et al., International Patent Publication PCT/US86/02269; Akira, et al., European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison et al., European Patent Application 173,494; Neuberger et al., International Application WO 86/01533; Cabilly et al. U.S. Pat. No. 4,816,567; Cabilly et al., European Patent Application 125,023; Better et al., Science, 240:1041-1043, 1988; Liu et al., Proc. Natl. Acad. Sci. (U.S.A.), 84:3439-3443, 1987; Liu et al., J. Immunol., 139:3521-3526, 1987; Sun et al., Proc. Natl. Acad. Sci. (U.S.A.), 84:214-218, 1987; Nishimura et al., Canc. Res., 47:999-1005, 1987; Wood et al., Nature, 314:446-449, 1985; and Shaw et al., J. Natl Cancer Inst., 80:1553-1559, 1988).

[0131] Methods for humanizing antibodies have been described in the art. In some embodiments, a humanized antibody has one or more amino acid residues introduced from a source that is nonhuman, in addition to the nonhuman CDRs. Humanization can be essentially performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525, 1986; Riechmann et al., Nature, 332:323-327, 1988; Verhoeyen et al., Science, 239:1534-1536, 1988), by substituting hypervariable region sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S.

Patent No. 4,816,567) wherein substantially less than an intact human variable region has been substituted by the corresponding sequence from a nonhuman species. In practice, humanized antibodies are typically human antibodies in which some hypervariable region residues and possibly some framework region residues are substituted by residues from analogous sites in rodent antibodies.

[0132] U.S. Patent No. 5,693,761 to Queen et al, discloses a refinement on Winter et al. for humanizing antibodies, and is based on the premise that ascribes avidity loss to problems in the structural motifs in the humanized framework which, because of steric or other chemical incompatibility, interfere with the folding of the CDRs into the binding-capable conformation found in the mouse antibody. To address this problem, Queen teaches using human framework sequences closely homologous in linear peptide sequence to framework sequences of the mouse antibody to be humanized. Accordingly, the methods of Queen focus on comparing framework sequences between species. Typically, all available human variable region sequences are compared to a particular mouse sequence and the percentage identity between correspondent framework residues is calculated. The human variable region with the highest percentage is selected to provide the framework sequences for the humanizing project. Queen also teaches that it is important to retain in the humanized framework, certain amino acid residues from the mouse framework critical for supporting the CDRs in a binding-capable conformation. Potential criticality is assessed from molecular models. Candidate residues for retention are typically those adjacent in linear sequence to a CDR or physically within 6Å of any CDR residue.

[0133] Another method of humanizing antibodies, referred to as "framework shuffling", relies on generating a combinatorial library with nonhuman CDR variable regions fused in frame into a pool of individual human germline frameworks (Dall'Acqua et al., Methods, 36:43, 2005). The libraries are then screened to identify clones that encode humanized antibodies which retain good binding.

[0134] Methods for making fully human antibodies have been described in the art. By way of example, a method for producing an anti-Activin antibody or antigen-binding fragment thereof comprises the steps of synthesizing a library of human antibodies on phage, screening the library with Activin polypeptide or an antibody-binding portion thereof, isolating phage that bind Activin polypeptide, and obtaining the antibody from the phage. By way of another example, one method for preparing the library of antibodies for use in phage display techniques comprises the steps of immunizing a non-human animal comprising human immunoglobulin loci with Activin polypeptide or an antigenic portion thereof to create an immune response,

extracting antibody-producing cells from the immunized animal; isolating RNA encoding heavy and light chains of antibodies of the invention from the extracted cells, reverse transcribing the RNA to produce cDNA, amplifying the cDNA using primers, and inserting the cDNA into a phage display vector such that antibodies are expressed on the phage. Recombinant anti- Activin antibodies of the invention may be obtained in this way.

[0135] Recombinant human anti-Activin and/or TGF-β antibodies of the invention can also be isolated by screening a recombinant combinatorial antibody library. Preferably the library is a scFv phage display library, generated using human V_L and V_H cDNAs prepared from mRNA isolated from B cells. Methods for preparing and screening such libraries are known in the art. Kits for generating phage display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, catalog no. 27-9400-01; and the Stratagene SurfZAP™ phage display kit, catalog no. 240612). There also are other methods and reagents that can be used in generating and screening antibody display libraries (see, e.g., U.S. Pat. No. 5,223,409; PCT Publication Nos. WO 92/18619, WO 91/17271, WO 92/20791, WO 92/15679, WO 93/01288, WO 92/01047, WO 92/09690; Fuchs et al., Bio/Technology, 9:1370-1372 (1991); Hay et al., Hum. Antibod. Hybridomas, 3:81-85, 1992; Huse et al., Science, 246:1275-1281, 1989; McCafferty et al., Nature, 348:552-554, 1990; Griffiths et al., EMBO J., 12:725-734, 1993; Hawkins et al., J. Mol. Biol., 226:889-896, 1992; Clackson et al., Nature, 352:624-628, 1991; Gram et al., Proc. Natl. Acad. Sci. (U.S.A.), 89:3576-3580, 1992; Garrad et al., Bio/Technology, 9:1373-1377, 1991; Hoogenboom et al., Nuc. Acid Res., 19:4133-4137, 1991; and Barbas et al., Proc. Natl. Acad. Sci. (U.S.A.), 88:7978-7982, 1991), all incorporated herein by reference.

[0136] Human antibodies are also produced by immunizing a non-human, transgenic animal comprising within its genome some or all of human immunoglobulin heavy chain and light chain loci with a human IgE antigen, e.g., a XenoMouse™ animal (Abgenix, Inc./Amgen, Inc.--Fremont, Calif.). XenoMouse™ mice are engineered mouse strains that comprise large fragments of human immunoglobulin heavy chain and light chain loci and are deficient in mouse antibody production. See, e.g., Green et al., Nature Genetics, 7:13-21, 1994 and U.S. Pat. Nos. 5,916,771, 5,939,598, 5,985,615, 5,998,209, 6,075,181, 6,091,001, 6,114,598, 6,130,364, 6,162,963 and 6,150,584. XenoMouse™ mice produce an adult-like human repertoire of fully human antibodies and generate antigen-specific human antibodies. In some embodiments, the XenoMouse™ mice contain approximately 80% of the human antibody V gene repertoire through introduction of megabase sized, germline configuration fragments of the human heavy chain loci and kappa light chain loci in yeast artificial chromosome (YAC). In other embodiments, XenoMouse™ mice further contain approximately all of the human lambda light

chain locus. See Mendez et al., Nature Genetics, 15:146-156, 1997; Green and Jakobovits, J. Exp. Med., 188:483-495, 1998; and WO 98/24893. In one aspect, the present invention provides a method for making anti-Activin and/or TGF-β antibodies from non-human, non-mouse animals by immunizing non-human transgenic animals that comprise human immunoglobulin loci with an Activin and/or TGF-β polypeptide. One can produce such animals using the methods described in the above-cited documents.

Anti-Activin Antibodies

[0137] In various embodiments of the present invention, the anti-Activin antibody is an anti-Activin A antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 10:

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGLSWVRQAPGQGLEWMGWIIPYNGNTNSA
QKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYFCARDRDYGVNYDAFDIWGQGTMVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNVYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK (SEQ ID NO: 10)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 11:

SYEVTQAPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSG
SNSGNTATLTISGTQAMDEADYYCQAWDSSTAVFGGGTKLTVLRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 11)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 10 and the light chain amino acid sequence set forth in SEQ ID NO: 11;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 12:

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGLSWVRQAPGQGLEWMGWIIPYNGNTNSA
QKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYFCARDRDYGVNYDAFDIWGQGTMVTVSS
(SEQ ID NO: 12)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 13:

SYEVTQAPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSG
SNSGNTATLTISGTQAMDEADYYCQAWDSSTAVFGGGTKLTVL (SEQ ID NO: 13)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 12 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 13.

[0138] In various embodiments, the invention provides antibodies, comprising a heavy chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 10, 11, 12 or 13; wherein the antibody binds specifically to human Activin A.

[0139] In various embodiments of the present invention, the anti-Activin antibody is an anti-Activin A antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 14:

QVQLQESGPGLVKPSETLSLTCTVSGGSFSSHFWSWIRQPPGKGLEWIGYILYTGGTSFNPSL
KSRVSMSVGTSKNQFSLKLSSVTAADTAVYYCARARSGITFTGIIVPGSFDIWGQGTMVTVSSA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGK (SEQ ID NO: 14)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 15:

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 15)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 14 and the light chain amino acid sequence set forth in SEQ ID NO: 15;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 16:

QVQLQESGPGLVKPSETLSLTCTVSGGSFSSHFWSWIRQPPGKGLEWIGYILYTGGTSFNPSL
KSRVSMSVGTSKNQFSLKLSSVTAADTAVYYCARARSGITFTGIIVPGSFDIWGQGTMVTVSS
(SEQ ID NO: 16)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 17:

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK (SEQ ID NO: 17)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 16 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 17.

[0140] In various embodiments, the invention provides antibodies, comprising a heavy chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 14, 15, 16 or 17; wherein the antibody binds specifically to human Activin A.

Anti- TGF-β Antibodies

[0141] In various embodiments of the present invention, the anti-TGF-β antibody is an anti-TGF-β antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 22:

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG

PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 22)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 23:

ETVLTQSPGTLSLSPGERATLSCRASQSLGSSYLAWYQQKPGQAPRLLIYGASSRAPGIPDRF
SGSGSGTDFTLTISRLEPEDFAVYYCQQYADSPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 23)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 22 and the light chain amino acid sequence set forth in SEQ ID NO: 23;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 24:

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSS
(SEQ ID NO: 24)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 25:

ETVLTQSPGTLSLSPGERATLSCRASQSLGSSYLAWYQQKPGQAPRLLIYGASSRAPGIPDRF
SGSGSGTDFTLTISRLEPEDFAVYYCQQYADSPITFGQGTRLEIK (SEQ ID NO: 25)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 24 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 25.

[0142] In various embodiments, the invention provides antibodies, comprising a heavy chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at

least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 22, 23, 24 or 25; wherein the antibody binds specifically to human TGF-β.

PD-1 and PD-L1 and CTLA-4 Ligands

[0143] A number of immune-checkpoint protein antigens have been reported to be expressed on various immune cells, including, e.g., SIRP (expressed on macrophage, monocytes, dendritic cells), CD47 (highly expressed on tumor cells and other cell types), VISTA (expressed on monocytes, dendritic cells, B cells, T cells), CD152 (expressed by activated CD8+ T cells, CD4+ T cells and regulatory T cells), CD279 (expressed on tumor infiltrating lymphocytes, expressed by activated T cells (both CD4 and CD8), regulatory T cells, activated B cells, activated NK cells, anergic T cells, monocytes, dendritic cells), CD274 (expressed on T cells, B cells, dendritic cells, macrophages, vascular endothelial cells, pancreatic islet cells), and CD223 (expressed by activated T cells, regulatory T cells, anergic T cells, NK cells, NKT cells, and plasmacytoid dendritic cells)(see, e.g., Pardoll, D., Nature Reviews Cancer, 12:252-264, 2012). Antibodies that bind to an antigen which is determined to be an immune-checkpoint protein are known to those skilled in the art. For example, various anti-CD276 antibodies have been described in the art (see, e.g., U.S. Pat. Public. No. 20120294796 (Johnson et al) and references cited therein); various anti-CD272 antibodies have been described in the art (see, e.g., U.S. Pat. Public. No. 20140017255 (Mataraza et al) and references cited therein); various anti-CD152/CTLA-4 antibodies have been described in the art (see, e.g., U.S. Pat. Public. No. 20130136749 (Korman et al) and references cited therein); various anti-LAG-3/CD223 antibodies have been described in the art (see, e.g., U.S. Pat. Public. No. 20110150892 (Thudium et al) and references cited therein); various anti-CD279 (PD-1) antibodies have been described in the art (see, e.g., U.S. Patent No. 7,488,802 (Collins et al) and references cited therein); various anti-CD274 (PD-L1) antibodies have been described in the art (see, e.g., U.S. Pat. Public. No. 20130122014 (Korman et al) and references cited therein); various anti-TIM-3 antibodies have been described in the art (see, e.g., U.S. Pat. Public. No. 20140044728 (Takayanagi et al) and references cited therein); and various anti-B7-H4 antibodies have been described in the art (see, e.g., U.S. Pat. Public. No. 20110085970 (Terrett et al) and references cited therein); and various anti-TIGIT antibodies have been described in the art (see, e.g., U.S. Pat. Public. No. 20180169239A1 (Grogan) and references cited therein). Each of these references is hereby incorporated by reference in its entirety for the specific antibodies and

sequences taught therein. In various embodiments, the bifunctional multispecific antagonist molecule is capable of binding an immune-checkpoint protein ligand selected from the group consisting of, but not limited to, CD279 (PD-1), CD274 (PDL-1), CD276, CD272, CD152, CD223 (LAG-3), CD40, SIRPα, CD47, OX-40, GITR, ICOS, CD27, 4-1BB, TIM-3, B7-H3, B7-H4, TIGIT, and VISTA.

[0144] In various embodiments, the bifunctional multispecific antagonist molecule is capable of binding a PD-1 ligand, a PD-L1 ligand, or CTLA-4 ligand having an amino acid sequence selected from the group consisting of the amino acid sequences set forth in Table 4:

Table 4

Polypeptides containing PD-1, PD-L1 CTLA-4 ligands

LIGAND	DATABASE	ACCESSION NO
PD-1	UniProtKB	Q15116-1
PD-L1	UniProtKB	Q9NZQ7-1
CTLA-4	UniProtKB	P16410-1

Anti-PD-1 and anti-PD-L1 and anti-CTLA-4 Antibodies

[0145] In various embodiments of the present invention, the anti-PD-1 antibody is an anti-PD-1 antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 26:

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGK (SEQ ID NO: 26)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 27:

EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPA
RFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
HKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 27)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 26 and the light chain amino acid sequence set forth in SEQ ID NO: 27;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 28:

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSS
(SEQ ID NO: 28)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 29:

EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPA
RFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIK (SEQ ID NO: 29)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 28 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 29.

[0146] In various embodiments, the invention provides antibodies, comprising a heavy chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 26, 27, 28 or 29; wherein the antibody binds specifically to human PD-1.

[0147] In various embodiments of the present invention, the anti-PD-1 antibody is an anti-PD-1 antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30:

QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYA
DSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPL
APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS
SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLS
LGK (SEQ ID NO: 30)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 31:

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSG
SGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 31)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30 and the light chain amino acid sequence set forth in SEQ ID NO: 31;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 32:

QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYA
DSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS
(SEQ ID NO: 32)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 33:

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSG
SGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIK (SEQ ID NO: 33)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 32 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 33.

[0148] In various embodiments, the invention provides antibodies, comprising a heavy chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 30, 31, 32 or 33; wherein the antibody binds specifically to human PD-1.

[0149] In various embodiments of the present invention, the anti-PD-1 antibody is an anti-PD-1 antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 38:

EVQLLESGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYFA
DSVKGRFTISRDNSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGTLVTVSSASTKGP
SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH
NHYTQKSLSLSLGK (SEQ ID NO: 38)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 39:

DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPSRFSGS
GSGTDFTLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFRRTVAAPSVFIFPPSDEQLKSGT
ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 39)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 38 and the light chain amino acid sequence set forth in SEQ ID NO: 39;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 40:

EVQLLESGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYFA
DSVKGRFTISRDNSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGTLVTVSS

(SEQ ID NO: 40)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 41:

DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPSRFSGS
GSGTDFTLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFR (SEQ ID NO: 41)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 40 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 41.

[0150] In various embodiments, the invention provides antibodies, comprising a heavy chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 38, 39, 40 or 41; wherein the antibody binds specifically to human PD-1.

[0151] In various embodiments of the present invention, the anti-PD-1 antibody is an anti-PD-1 antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 42:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSIYPSGGITFYADT
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVTTVDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 42)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 43:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSN
RFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGTKVTVLGQPKANPTVTLFPPSS

EELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQW
KSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 43)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 42 and the light chain amino acid sequence set forth in SEQ ID NO: 43;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 44:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSIYPSGGITFYADT
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVTTVDYWGQGTLVTVSS
(SEQ ID NO: 44)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 45:

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSN
RFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGTKVTVL (SEQ ID NO: 45)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 44 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 45.

[0152] In various embodiments, the invention provides antibodies, comprising a heavy chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 42, 43, 44 or 45; wherein the antibody binds specifically to human PD-1.

[0153] In various embodiments of the present invention, the anti-CTLA-4 antibody is an anti-CTLA-4 antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 34:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 34)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 35:

EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 35)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 34 and the light chain amino acid sequence set forth in SEQ ID NO: 35;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 36:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSS
(SEQ ID NO: 36)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 37:

EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK (SEQ ID NO: 37)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 36 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 37.

[0154] In various embodiments, the invention provides antibodies, comprising a heavy

chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 34, 35, 36 or 37; wherein the antibody binds specifically to human CTLA-4.

[0155] In various embodiments of the present invention, the anti-PD-L1 antibody is an anti-PD-L1 antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 46:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 46)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 47:

DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 47)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 46 and the light chain amino acid sequence set forth in SEQ ID NO: 47;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 48:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS
(SEQ ID NO: 48)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 49:

DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIK (SEQ ID NO: 49)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 48 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 49.

[0156] In various embodiments, the invention provides antibodies, comprising a heavy chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 46, 47, 48 or 49; wherein the antibody binds specifically to human PD-L1.

[0157] In various embodiments of the present invention, the anti-PD-L1 antibody is an anti-PD-L1 antibody that is a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 50:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYYV
DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQGTLVTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEFEGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO: 50)

a human antibody or antigen-binding fragment comprising the light chain amino acid sequence set forth in SEQ ID NO: 51:

EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS

GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 51)

or a human antibody or antigen-binding fragment comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 50 and the light chain amino acid sequence set forth in SEQ ID NO: 51;

a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 52:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYYV
DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQGTLVTVSS
(SEQ ID NO: 52)

a human antibody or antigen-binding fragment comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 53:

EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGTKVEIK (SEQ ID NO: 53)

or a human antibody or antigen-binding fragment comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 52 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 53.

[0158] In various embodiments, the invention provides antibodies, comprising a heavy chain, a light chain, or both a heavy chain and light chain; a heavy chain variable region, a light chain variable region, or both a heavy chain variable region and light chain variable region; wherein the heavy chain, light chain, heavy chain variable region, or light chain variable region comprises a sequence that has at least about 75%, at least about 80%, at least about 85%, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% identity to the amino acid sequences as set forth in SEQ ID NOs: 50, 51, 52 or 53; wherein the antibody binds specifically to human PD-L1.

Multispecific Antagonist Molecules

[0159] In one aspect, the present invention provides novel polypeptide-based

bifunctional antagonist molecules specifically designed to simultaneously neutralize Activin signaling and TGF-β signaling in a potent manner and comprising a first antigen-binding molecule that specifically binds to Activin ligand and a second antigen-binding molecule that specifically binds to TGF-β ligand. In various embodiments, the multispecific antagonist molecule comprises an isolated antibody, or antigen-binding fragment thereof, that specifically binds to Activin and an isolated antibody, or antigen-binding fragment thereof, that specifically binds to TGF-β ligand. Importantly, these multispecific antagonists also provide advantageous properties such as producibility, stability, binding affinity, biological activity, specific targeting of certain cells, targeting efficiency and reduced toxicity.

Exemplary Multispecific Antagonist Molecules

[0160] In various embodiments, the bifunctional antagonist molecules of the present invention are selected from the group of molecules designed and comprising the fusion partners as described in Table 5:

Table 5

ID	Fusion Partner A (Activin-Binding Polypeptide)	Linker	Fusion Partner B (TGF-β-Binding Polypeptide)
	SEQ ID NO:	SEQ ID NOs:	SEQ ID NO:
A115	SEQ ID NO: 1	124-143	SEQ ID NO: 19
A116	SEQ ID NO: 1	124-143	SEQ ID NO: 21
A140	SEQ ID NO: 2	124-143	SEQ ID NO: 19
A141	SEQ ID NO: 2	124-143	SEQ ID NO: 21
A142	SEQ ID NO: 3	124-143	SEQ ID NO: 19
A143	SEQ ID NO: 3	124-143	SEQ ID NO: 21
A117	SEQ ID NO: 4	124-143	SEQ ID NO: 19
A118	SEQ ID NO: 4	124-143	SEQ ID NO: 21
A144	SEQ ID NO: 5	124-143	SEQ ID NO: 19
A145	SEQ ID NO: 5	124-143	SEQ ID NO: 21
A146	SEQ ID NO: 6	124-143	SEQ ID NO: 19
A147	SEQ ID NO: 6	124-143	SEQ ID NO: 21
A148	SEQ ID NO: 7	124-143	SEQ ID NO: 19
A149	SEQ ID NO: 7	124-143	SEQ ID NO: 21
A150	SEQ ID NO: 8	124-143	SEQ ID NO: 19
A151	SEQ ID NO: 8	124-143	SEQ ID NO: 21
A152	SEQ ID NO: 9	124-143	SEQ ID NO: 19
A153	SEQ ID NO: 9	124-143	SEQ ID NO: 21
A154	SEQ ID NO: 12 and SEQ ID NO: 13	124-143	SEQ ID NO: 19
A155	SEQ ID NO: 12 and SEQ ID NO: 13	124-143	SEQ ID NO: 21
A156	SEQ ID NO: 16 and SEQ ID NO: 17	124-143	SEQ ID NO: 19
A157	SEQ ID NO: 16 and SEQ ID NO: 17	124-143	SEQ ID NO: 21
A158	SEQ ID NO: 1	124-143	SEQ ID NO: 24 and SEQ ID NO: 25
A159	SEQ ID NO: 2	124-143	SEQ ID NO: 24 and SEQ ID NO: 25
A160	SEQ ID NO: 3	124-143	SEQ ID NO: 24 and SEQ ID NO: 25

A161	SEQ ID NO: 4	124-143	SEQ ID NO: 24 and SEQ ID NO: 25
A162	SEQ ID NO: 5	124-143	SEQ ID NO: 24 and SEQ ID NO: 25
A163	SEQ ID NO: 6	124-143	SEQ ID NO: 24 and SEQ ID NO: 25
A164	SEQ ID NO: 7	124-143	SEQ ID NO: 24 and SEQ ID NO: 25
A165	SEQ ID NO: 8	124-143	SEQ ID NO: 24 and SEQ ID NO: 25
A166	SEQ ID NO: 9	124-143	SEQ ID NO: 24 and SEQ ID NO: 25
A167	SEQ ID NO: 12 and SEQ ID NO: 13	124-143	SEQ ID NO: 24 and SEQ ID NO: 25
A168	SEQ ID NO: 16 and SEQ ID NO: 17	124-143	SEQ ID NO: 24 and SEQ ID NO: 25

[0161] In various embodiments, the multispecific antagonist molecule of the present invention specifically designed to simultaneously neutralize Activin signaling and TGF-β signaling in a potent manner and comprising a first antigen-binding molecule that specifically binds to Activin ligand and a second antigen-binding molecule that specifically binds to TGF-β ligand is selected from the group of molecules as described in Table 6:

Table 6

Multispecific Antagonist Molecule	**SEQ ID NO:**
A115	SEQ ID NO: 54
A116	SEQ ID NO: 55
A140	SEQ ID NO: 56
A141	SEQ ID NO: 57
A142	SEQ ID NO: 58
A117	SEQ ID NO: 60
A118	SEQ ID NO: 61
A143	SEQ ID NO: 59
A144	SEQ ID NO: 62
A145	SEQ ID NO: 63
A146	SEQ ID NO: 64
A147	SEQ ID NO: 65
A148	SEQ ID NO: 66
A149	SEQ ID NO: 67
A150	SEQ ID NO: 68
A151	SEQ ID NO: 69
A152	SEQ ID NO: 70
A153	SEQ ID NO: 71
A216	SEQ ID NO: 121

Bifunctional Multispecific Antagonist Molecules

[0162] In another aspect, the present invention provides novel polypeptide-based bifunctional multispecific antagonist molecules specifically designed to simultaneously inhibiting TGF-β, Activin and T-cell immune checkpoint (including PD1, PDL1 or CTL4). In various embodiments, the bifunctional multispecific antagonist molecule is a bifunctional multispecific molecule comprising a first antigen-binding molecule that specifically binds to Activin ligand or Activin-related ligand ("Activin-Binding Polypeptide") and a second antigen-binding molecule

that specifically binds to TGF-β ligand ("TGF-β-Binding Polypeptide") and a third antigen-binding molecule that specifically binds to either PD-1 ligand, PD-L1 ligand or CTLA-4 ligand ("PD-1/PD-L1/CTLA-4-Binding Polypeptide"). Importantly, these bifunctional multispecific antagonists also provide advantageous properties such as producibility, stability, binding affinity, biological activity, specific targeting of certain cells, targeting efficiency and reduced toxicity.

Exemplary Bifunctional Multispecific Antagonist Molecules

[0163] In various embodiments, the bifunctional multispecific antagonist molecules of the present invention are selected from the group of molecules designed and comprising the fusion partners as described in Tables 7 and 8:

Table 7

Fusion Partner A (PD-1/CTLA-4-Binding Polypeptide)		**Fusion Partner B (Activin-Binding Polypeptide)**		**Fusion Partner C (TGF-β-Binding Polypeptide)**
SEQ ID NO:		**SEQ ID NO:**		**SEQ ID NO:**
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 19
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 21
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 19
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 21
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 19
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 21
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 19
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 21
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 19
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 21
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 19
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 21
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 19
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 21
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 19
SEQ ID NO: 28 and	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 21

SEQ ID NO: 29				
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 19
SEQ ID NO: 28 and SEQ ID NO: 29	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 21
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 19
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 21
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 19
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 21
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 19
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 21
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 19
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 21
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 19
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 21
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 19
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 21
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 19
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 21
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 19
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 21
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 19
SEQ ID NO: 36 and SEQ ID NO: 37	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 21
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 19
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 21
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 19
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 21
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 19
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 21
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 19
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 21
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 19
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 21

SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 19
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 21
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 19
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 21
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 19
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 21
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 19
SEQ ID NO: 32 and SEQ ID NO: 33	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 21
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 19
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 21
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 19
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 21
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 19
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 21
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 19
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 21
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 19
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 21
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 19
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 21
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 19
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 21
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 19
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 21
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 19
SEQ ID NO: 40 and SEQ ID NO: 41	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 21
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 19
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 21
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 19
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 21
SEQ ID NO: 44 and	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 19

SEQ ID NO: 45				
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 21
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 19
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 21
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 19
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 21
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 19
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 21
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 19
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 21
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 19
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 21
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 19
SEQ ID NO: 44 and SEQ ID NO: 45	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 21
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 19
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 21
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 19
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 21
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 19
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 21
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 19
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 21
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 19
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 21
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 19
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 21
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 19
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 21
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 19
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 21
SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 19

SEQ ID NO: 48 and SEQ ID NO: 49	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 21
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 19
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 1	Linker	SEQ ID NO: 21
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 19
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 2	Linker	SEQ ID NO: 21
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 19
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 3	Linker	SEQ ID NO: 21
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 19
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 4	Linker	SEQ ID NO: 21
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 19
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 5	Linker	SEQ ID NO: 21
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 19
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 6	Linker	SEQ ID NO: 21
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 19
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 7	Linker	SEQ ID NO: 21
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 19
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 8	Linker	SEQ ID NO: 21
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 19
SEQ ID NO: 52 and SEQ ID NO: 53	Linker	SEQ ID NO: 9	Linker	SEQ ID NO: 21

Table 8

Bifunctional Multispecific Antagonist Molecule	**SEQ ID NOs:**
A169	SEQ ID NO: 85 and SEQ ID NO: 27
A170	SEQ ID NO: 86 and SEQ ID NO: 27
A171	SEQ ID NO: 87 and SEQ ID NO: 27
A172	SEQ ID NO: 88 and SEQ ID NO: 27
A173	SEQ ID NO: 89 and SEQ ID NO: 27
A174	SEQ ID NO: 90 and SEQ ID NO: 27
A175	SEQ ID NO: 91 and SEQ ID NO: 27
A176	SEQ ID NO: 92 and SEQ ID NO: 27
A177	SEQ ID NO: 93 and SEQ ID NO: 27
A178	SEQ ID NO: 94 and SEQ ID NO: 27
A179	SEQ ID NO: 95 and SEQ ID NO: 27
A180	SEQ ID NO: 96 and SEQ ID NO: 27
A181	SEQ ID NO: 97 and SEQ ID NO: 27

A182	SEQ ID NO: 98 and SEQ ID NO: 27
A183	SEQ ID NO: 99 and SEQ ID NO: 27
A184	SEQ ID NO: 100 and SEQ ID NO: 27
A185	SEQ ID NO: 101 and SEQ ID NO: 27
A186	SEQ ID NO: 102 and SEQ ID NO: 27
A187	SEQ ID NO: 103 and SEQ ID NO: 35
A188	SEQ ID NO: 104and SEQ ID NO: 35
A189	SEQ ID NO: 105 and SEQ ID NO: 35
A190	SEQ ID NO: 106 and SEQ ID NO: 35
A191	SEQ ID NO: 107 and SEQ ID NO: 35
A192	SEQ ID NO: 108 and SEQ ID NO: 35
A193	SEQ ID NO: 109 and SEQ ID NO: 35
A194	SEQ ID NO: 110 and SEQ ID NO: 35
A195	SEQ ID NO: 111 and SEQ ID NO: 35
A196	SEQ ID NO: 112 and SEQ ID NO: 35
A197	SEQ ID NO: 113 and SEQ ID NO: 35
A198	SEQ ID NO: 114 and SEQ ID NO: 35
A199	SEQ ID NO: 115 and SEQ ID NO: 35
A200	SEQ ID NO: 116 and SEQ ID NO: 35
A201	SEQ ID NO: 117 and SEQ ID NO: 35
A202	SEQ ID NO: 118 and SEQ ID NO: 35
A203	SEQ ID NO: 119 and SEQ ID NO: 35
A204	SEQ ID NO: 120 and SEQ ID NO: 35

Linkers

[0164] In various embodiments, the first antigen-binding molecule that specifically binds to Activin or Activin-related ligand is attached to the second antigen-binding molecule that specifically binds to TGF-β ligand by a linker and/or a hinge linker peptide. The linker or hinge linker may be an artificial sequence of between 5, 10, 15, 20, 30, 40 or more amino acids that are relatively free of secondary structure or display α-helical conformation.

[0165] Peptide linker provides covalent linkage and additional structural and/or spatial flexibility between protein domains. As known in the art, peptide linkers contain flexible amino acid residues, such as glycine and serine. In various embodiments, peptide linker may include 1-100 amino acids. In various embodiments, a spacer can contain motif of GGGSGGGS (SEQ ID NO: 131). In other embodiments, a linker can contain motif of GGGGS (SEQ ID NO: 134)n, wherein n is an integer from 1 to 10. In other embodiments, a linker can also contain amino acids other than glycine and serine. In another embodiment, a linker can contain other protein motifs, including but not limited to, sequences of α-helical conformation such as AEAAAKEAAAKEAAAKA (SEQ ID NO: 129). In various embodiments, linker length and composition can be tuned to optimize activity or developability, including but not limited to, expression level and aggregation propensity. In another embodiment, the peptide linker can be a simple chemical bond, e.g., an amide bond (e.g., by chemical conjugation of PEG).

[0166] Exemplary peptide linkers are provided in Table 9:

Table 9

Linker Sequence	SEQ ID NO:
GGGSGGGSGGGS	124
GGGS	125
GSSGGSGGSGGSG	126
GSSGT	127
GGGGSGGGGSGGGS	128
AEAAAKEAAAKEAAAKA	129
GGGGSGGGGSGGGGSGGGGS	130
GGGSGGGS	131
GSGST	132
GGSS	133
GGGGS	134
GGSG	135
SGGG	136
GSGS	137
GSGSGS	138
GSGSGSGS	139
GSGSGSGSGS	140
GSGSGSGSGSGS	141
GGGGSGGGGS	142
GGGGSGGGGSGGGGS	143

Polynucleotides

[0167] In another aspect, the present disclosure provides isolated nucleic acid molecules comprising a polynucleotide encoding a multispecific or bifunctional multispecific antagonist molecule of the present disclosure. The subject nucleic acids may be single-stranded or double stranded. Such nucleic acids may be DNA or RNA molecules. DNA includes, for example, cDNA, genomic DNA, synthetic DNA, DNA amplified by PCR, and combinations thereof. Genomic DNA encoding multispecific or bifunctional multispecific antagonist molecules is obtained from genomic libraries which are available for a number of species. Synthetic DNA is available from chemical synthesis of overlapping oligonucleotide fragments followed by assembly of the fragments to reconstitute part or all of the coding regions and flanking sequences. RNA may be obtained from prokaryotic expression vectors which direct high-level synthesis of mRNA, such as vectors using T7 promoters and RNA polymerase. cDNA is obtained from libraries prepared from mRNA isolated from various tissues that express a multispecific or bifunctional multispecific antagonist molecule. The DNA molecules of the

disclosure include full-length genes as well as polynucleotides and fragments thereof. The full-length gene may also include sequences encoding the N-terminal signal sequence.

[0168] In various embodiments, the isolated nucleic acid molecules comprise the polynucleotides described herein, and further comprise a polynucleotide encoding at least one heterologous protein described herein. In various embodiments, the nucleic acid molecules further comprise polynucleotides encoding the linkers or hinge linkers described herein.

[0169] In various embodiments, the recombinant nucleic acids of the present disclosure may be operably linked to one or more regulatory nucleotide sequences in an expression multispecific or bifunctional multispecific antagonist molecule. Accordingly, the term regulatory sequence includes promoters, enhancers, and other expression control elements. Exemplary regulatory sequences are described in Goeddel; Gene Expression Technology: Methods in Enzymology, Academic Press, San Diego, Calif. (1990). Typically, said one or more regulatory nucleotide sequences may include, but are not limited to, promoter sequences, leader or signal sequences, ribosomal binding sites, transcriptional start and termination sequences, translational start and termination sequences, and enhancer or activator sequences. Constitutive or inducible promoters as known in the art are contemplated by the present disclosure. The promoters may be either naturally occurring promoters, or hybrid promoters that combine elements of more than one promoter. An expression construct may be present in a cell on an episome, such as a plasmid, or the expression construct may be inserted in a chromosome. In various embodiments, the expression vector contains a selectable marker gene to allow the selection of transformed host cells. Selectable marker genes are well known in the art and will vary with the host cell used.

[0170] In another aspect of the present disclosure, the subject nucleic acid is provided in an expression vector comprising a nucleotide sequence encoding a multispecific or bifunctional multispecific antagonist molecule and operably linked to at least one regulatory sequence. The term "expression vector" refers to a plasmid, phage, virus or vector for expressing a polypeptide from a polynucleotide sequence. Vectors suitable for expression in host cells are readily available and the nucleic acid molecules are inserted into the vectors using standard recombinant DNA techniques. Such vectors can include a wide variety of expression control sequences that control the expression of a DNA sequence when operatively linked to it may be used in these vectors to express DNA sequences encoding a multispecific or bifunctional multispecific antagonist molecule. Such useful expression control sequences, include, for example, the early and late promoters of SV40, tet promoter, adenovirus or cytomegalovirus immediate early promoter, RSV promoters, the lac system, the trp system, the TAC or TRC

system, T7 promoter whose expression is directed by T7 RNA polymerase, the major operator and promoter regions of phage lambda , the control regions for fd coat protein, the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase, e.g., PhoS, the promoters of the yeast a-mating factors, the polyhedron promoter of the baculovirus system and other sequences known to control the expression of genes of prokaryotic or eukaryotic cells or their viruses, and various combinations thereof. It should be understood that the design of the expression vector may depend on such factors as the choice of the host cell to be transformed and/or the type of protein desired to be expressed. Moreover, the vector's copy number, the ability to control that copy number and the expression of any other protein encoded by the vector, such as antibiotic markers, should also be considered.

[0171] A recombinant nucleic acid of the present disclosure can be produced by ligating the cloned gene, or a portion thereof, into a vector suitable for expression in either prokaryotic cells, eukaryotic cells (yeast, avian, insect or mammalian), or both. Expression vehicles for production of a recombinant multispecific or bifunctional multispecific antagonist molecule include plasmids and other vectors. For instance, suitable vectors include plasmids of the types: pBR322-derived plasmids, pEMBL-derived plasmids, pEX-derived plasmids, pBTac-derived plasmids and pUC-derived plasmids for expression in prokaryotic cells, such as *E. coli*.

[0172] Some mammalian expression vectors contain both prokaryotic sequences to facilitate the propagation of the vector in bacteria, and one or more eukaryotic transcription units that are expressed in eukaryotic cells. The pcDNAI/amp, pcDNAI/neo, pRc/CMV, pSV2gpt, pSV2neo, pSV2-dhfr, pTk2, pRSVneo, pMSG, pSVT7, pko-neo and pHyg derived vectors are examples of mammalian expression vectors suitable for transfection of eukaryotic cells. Some of these vectors are modified with sequences from bacterial plasmids, such as pBR322, to facilitate replication and drug resistance selection in both prokaryotic and eukaryotic cells. Alternatively, derivatives of viruses such as the bovine papilloma virus (BPV-1), or Epstein-Barr virus (pHEBo, pREP-derived and p205) can be used for transient expression of proteins in eukaryotic cells. Examples of other viral (including retroviral) expression systems can be found below in the description of gene therapy delivery systems. The various methods employed in the preparation of the plasmids and in transformation of host organisms are well known in the art. For other suitable expression systems for both prokaryotic and eukaryotic cells, as well as general recombinant procedures, see Molecular Cloning A Laboratory Manual, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press, 1989) Chapters 16 and 17. In some instances, it may be desirable to express the recombinant polypeptides by the use of a baculovirus expression system. Examples of such baculovirus expression systems include

pVL-derived vectors (such as pVL1392, pVL1393 and pVL941), pAcUW-derived vectors (such as pAcUW1), and pBlueBac-derived vectors (such as the B-gal containing pBlueBac III).

[0173] In various embodiments, a vector will be designed for production of the subject multispecific or bifunctional multispecific antagonist molecule in CHO cells, such as a Pcmv-Script vector (Stratagene, La Jolla, Calif.), pcDNA4 vectors (Invitrogen, Carlsbad, Calif.) and pCI-neo vectors (Promega, Madison, Wis.). As will be apparent, the subject gene constructs can be used to cause expression of the subject multispecific or bifunctional multispecific antagonist molecule in cells propagated in culture, e.g., to produce proteins, including fusion proteins or variant proteins, for purification.

[0174] Accordingly, the present disclosure further pertains to methods of producing the subject multispecific or bifunctional multispecific antagonist molecules. For example, a host cell transfected with an expression vector encoding a multispecific or bifunctional multispecific antagonist molecule can be cultured under appropriate conditions to allow expression of the bifunctional antagonist molecule to occur. The multispecific or bifunctional multispecific antagonist molecule may be secreted and isolated from a mixture of cells and medium containing the multispecific or bifunctional multispecific antagonist molecule. Alternatively, the multispecific or bifunctional multispecific antagonist molecule may be retained cytoplasmically or in a membrane fraction and the cells harvested, lysed and the protein isolated. A cell culture includes host cells, media and other byproducts. Suitable media for cell culture are well known in the art.

[0175] The polypeptides and proteins of the present disclosure can be purified according to protein purification techniques are well known to those of skill in the art. These techniques involve, at one level, the crude fractionation of the proteinaceous and non-proteinaceous fractions. Having separated the peptide polypeptides from other proteins, the peptide or polypeptide of interest can be further purified using chromatographic and electrophoretic techniques to achieve partial or complete purification (or purification to homogeneity). The term "isolated polypeptide" or "purified polypeptide" as used herein, is intended to refer to a composition, isolatable from other components, wherein the polypeptide is purified to any degree relative to its naturally obtainable state. A purified polypeptide therefore also refers to a polypeptide that is free from the environment in which it may naturally occur. Generally, "purified" will refer to a polypeptide composition that has been subjected to fractionation to remove various other components, and which composition substantially retains its expressed biological activity. Where the term "substantially purified" is used, this designation will refer to a peptide or polypeptide composition in which the polypeptide or peptide forms the

major component of the composition, such as constituting about 50%, about 60%, about 70%, about 80%, about 85%, or about 90% or more of the proteins in the composition.

[0176] Various techniques suitable for use in purification will be well known to those of skill in the art. These include, for example, precipitation with ammonium sulphate, PEG, antibodies (immunoprecipitation) and the like or by heat denaturation, followed by centrifugation; chromatography such as affinity chromatography (Protein-A columns), ion exchange, gel filtration, reverse phase, hydroxylapatite, hydrophobic interaction chromatography; isoelectric focusing; gel electrophoresis; and combinations of these techniques. As is generally known in the art, it is believed that the order of conducting the various purification steps may be changed, or that certain steps may be omitted, and still result in a suitable method for the preparation of a substantially purified polypeptide.

Pharmaceutical Compositions

[0177] In another aspect, the present disclosure provides a pharmaceutical composition comprising the isolated multispecific or bifunctional multispecific antagonist molecules in admixture with a pharmaceutically acceptable carrier. Such pharmaceutically acceptable carriers are well known and understood by those of ordinary skill and have been extensively described (see, e.g., Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company, 1990). The pharmaceutically acceptable carriers may be included for purposes of modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. Such pharmaceutical compositions may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the polypeptide. Suitable pharmaceutically acceptable carriers include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates, other organic acids); bulking agents (such as mannitol or glycine), chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides and other carbohydrates (such as glucose, mannose, or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring; flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counter ions (such as

sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides (preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants.

[0178] The primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Other exemplary pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which may further include sorbitol or a suitable substitute thereof. In one embodiment of the present disclosure, compositions may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (Remington's Pharmaceutical Sciences, supra) in the form of a lyophilized cake or an aqueous solution. Further, the therapeutic composition may be formulated as a lyophilizate using appropriate excipients such as sucrose. The optimal pharmaceutical composition will be determined by one of ordinary skill in the art depending upon, for example, the intended route of administration, delivery format, and desired dosage.

[0179] When parenteral administration is contemplated, the therapeutic pharmaceutical compositions may be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired multispecific or bifunctional multispecific antagonist molecule in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which a polypeptide is formulated as a sterile, isotonic solution, properly preserved. In various embodiments, pharmaceutical formulations suitable for injectable administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Optionally, the

suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

[0180] In various embodiments, the therapeutic pharmaceutical compositions may be formulated for targeted delivery using a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Examples of lipids useful in liposome production include phosphatidyl compounds, such as phosphatidylglycerol, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, sphingolipids, cerebrosides, and gangliosides. Illustrative phospholipids include egg phosphatidylcholine, dipalmitoylphosphatidylcholine, and distearoylphosphatidylcholine. The targeting of liposomes is also possible based on, for example, organ-specificity, cell-specificity, and organelle-specificity and is known in the art.

[0181] In various embodiments, oral administration of the pharmaceutical compositions is contemplated. Pharmaceutical compositions that are administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), one or more therapeutic compounds of the present disclosure may be mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as

water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

[0182] In various embodiments, topical administration of the pharmaceutical compositions, either to skin or to mucosal membranes, is contemplated. The topical formulations may further include one or more of the wide variety of agents known to be effective as skin or stratum corneum penetration enhancers. Examples of these are 2-pyrrolidone, N-methyl-2-pyrrolidone, dimethylacetamide, dimethylformamide, propylene glycol, methyl or isopropyl alcohol, dimethyl sulfoxide, and azone. Additional agents may further be included to make the formulation cosmetically acceptable. Examples of these are fats, waxes, oils, dyes, fragrances, preservatives, stabilizers, and surface-active agents. Keratolytic agents such as those known in the art may also be included. Examples are salicylic acid and sulfur. Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required. The ointments, pastes, creams and gels may contain, in addition to a subject compound of the disclosure (e.g., a multispecific or bifunctional multispecific antagonist molecule), excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0183] Additional pharmaceutical compositions contemplated for use herein include formulations involving polypeptides in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art.

[0184] An effective amount of a pharmaceutical composition to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the molecule delivered, the indication for which the polypeptide is

being used, the route of administration, and the size (body weight, body surface or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1 mg/kg to up to about 100 mg/kg or more, depending on the factors mentioned above. Polypeptide compositions may be preferably injected or administered intravenously. Long-acting pharmaceutical compositions may be administered every three to four days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation. The frequency of dosing will depend upon the pharmacokinetic parameters of the polypeptide in the formulation used. Typically, a composition is administered until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as multiple doses (at the same or different concentrations/dosages) over time, or as a continuous infusion. Further refinement of the appropriate dosage is routinely made. Appropriate dosages may be ascertained through use of appropriate dose-response data.

[0185] The route of administration of the pharmaceutical composition is in accord with known methods, e.g., orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, intra-ocular, intraarterial, intraportal, intralesional routes, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, or intraperitoneal; as well as intranasal, enteral, topical, sublingual, urethral, vaginal, or rectal means, by sustained release systems or by implantation devices. Where desired, the compositions may be administered by bolus injection or continuously by infusion, or by implantation device. Alternatively, or additionally, the composition may be administered locally via implantation of a membrane, sponge, or another appropriate material on to which the desired molecule has been absorbed or encapsulated. Where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of the desired molecule may be via diffusion, timed-release bolus, or continuous administration.

Therapeutic Uses

[0186] In another aspect, the present disclosure provides a method of treating or preventing various complex disease conditions whose pathogenesis involve the activation of TGF-β/Activin-mediated Smad2/3 signaling pathway.

[0187] In various embodiments, the novel multispecific or bifunctional multispecific antagonist molecules of the present invention may have broad applications for the treatment of various disorders which include, but are not limited to, the following conditions: Blood disorders:

ineffective erythropoiesis, anemia, pancytopenia, myelodysplastic syndromes; Fibrotic diseases: nonalcoholic steatohepatitis/NASH, liver fibrosis, pulmonary fibrosis, renal fibrosis, polycystic kidney disease, cardiac fibrosis, muscle fibrosis, myelo fibrosis, skin fibrosis, and fibrosis of the eye; Hematological malignancies: multiple myeloma, leukemia, and lymphoma; Solid cancers: melanoma, multiple myeloma, lung cancer, pancreatic cancer, colorectal cancer, liver cancer, gastric cancer, kidney cancer, bladder cancer, head and neck cancer, thyroid cancer, breast cancer, ovarian cancer, endometrial cancer, testicular cancer, prostate cancer and brain cancer; Metastasis: bone metastasis, lung metastasis, liver metastasis, brain metastasis and sarcoma; Cancer treatment in combination with checkpoint inhibitors such as anti-PD1, anti-PDL1 and anti-CTL4 antibodies; Neuromuscular diseases: muscular dystrophy, spinal muscular atrophy, spinal cord injury, stroke; Pain: nociceptive pain, neuropathic pain; Wasting disorders: sarcopenia, cancer cachexia, cardiac cachexia, renal cachexia, rheumatoid cachexia, and anorexia nervosa; Bone disorders: bone metastasis, skeletal-related event in cancer, bone fragility, fracture, osteopenia, and osteoporosis; Cardiovascular diseases: pulmonary hypertension, myocardial infarction, heart failure; Metabolic disorders: insulin resistance, diabetic nephropathy, chronic kidney disease; Inflammatory diseases: rheumatoid arthritis, inflammatory bowel disease; Infections: SARS-CoV, cytokine storm syndrome, sepsis; and Trauma: burn injury.

[0188] The present disclosure provides for a method of treating cardiovascular disease in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier, wherein such administration attenuates the inflammation and fibrosis of vasculatures and muscles, including smooth muscle, cardiac muscle and skeletal muscle. Specifically, a multispecific antagonist molecule of the present disclosure is useful in treating heart failure, pulmonary hypertension, myocarditis, coronary artery disease, myocardial infarction, cardiac arrhythmias, heart valve disease, cardiomyopathy, pericardial disease, aorta disease, Marfan syndrome and cardiac atrophy.

[0189] The present disclosure provides for a method of treating cardiac dysfunction or heart failure in a subject comprising administering an effective amount of a multispecific antagonist molecule into the subject. The modulation may improve cardiac function of said subject by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%. The improvement of cardiac function can be evaluated by echocardiography to measure 1) cardiac

pump functions focusing on the ejected blood volume and the efficiency of ejection and 2) myocardial functions focusing on the strength of myocardial contraction.

[0190] The present disclosure provides for methods for treating metabolic disorders in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier. Specifically, a multispecific antagonist molecule of the present disclosure is useful in treating a metabolic disease selected from obesity, dyslipidemia, diabetes, insulin resistance, sarcopenic obesity, steatosis, and metabolic syndrome, as well as diabetic myopathy, nephropathy, neuropathy, retinopathy, bone loss, impaired glucose tolerance, hyperglycemia, and androgen deprivation.

[0191] The present disclosure provides for a method of treating cancer cells as well as cancer cell metastasis in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific or bifunctional multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier, wherein such administration inhibits the growth and/or proliferation of a cancer cell. Specifically, a multispecific or bifunctional multispecific antagonist molecule of the present disclosure is useful in treating disorders characterized as cancer. Such disorders include, but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases, lymphomas, sarcomas, multiple myeloma and leukemia. Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ. Examples of cancers of the respiratory tract include, but are not limited to, small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma. Examples of brain cancers include, but are not limited to, brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor. Tumors of the male reproductive organs include, but are not limited to, prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus. Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers. Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers. Eye cancers include, but are not limited to, intraocular melanoma and retinoblastoma. Examples of liver cancers include, but are not limited to, hepatocellular

carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma. Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer. Head-and-neck cancers include, but are not limited to nasopharyngeal cancer, and lip and oral cavity cancer. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system. Sarcomas include, but are not limited to, sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma. Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia. In certain embodiments, the cancer will be a cancer with high expression of TNF-α and TGF-β, e.g., pancreatic cancer, gastric cancer, ovarian cancer, colorectal cancer, melanoma, leukemia, lung cancer, prostate cancer, brain cancer, bladder cancer, and head-neck cancer.

[0192] The present disclosure provides for a method of treating chronic kidney disease (CKD) in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier, wherein such administration attenuates the loss of kidney function and prevents muscle loss or inhibits kidney fibrosis. Specifically, a multispecific antagonist molecule of the present disclosure is useful in treating CKD including interstitial fibrosis, renal failure, and kidney dialysis as well as protein energy wasting (PEW) associated with CKD. The modulation may improve CKD or PEW of said subject by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%. The improvement of renal function can be evaluated by measuring protein/creatinine ratio (PCR) in the urine and glomerular filtration rate (GFR). Improvement of PEW can be evaluated by measuring serum levels of albumin and inflammatory cytokines, rate of protein synthesis and degradation, body mass, muscle mass, physical activity and nutritional outcomes.

[0193] The present disclosure provides for methods for treating autoimmune disease in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier. Specifically, a bifunctional antagonist molecule of the present disclosure is useful in treating an autoimmune disorder selected from

multiple sclerosis, diabetes (type-1), glomerulonephritis, myasthenia gravis, psoriasis, systemic sclerosis and systemic lupus erythematosus, polymyositis and primary biliary cirrhosis.

[0194] The present disclosure provides for methods for treating arthritis in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier. Specifically, a bifunctional antagonist molecule of the present disclosure is useful in treating an arthritis selected from rheumatoid arthritis and osteoarthritis.

[0195] The present disclosure provides for methods for treating anorexia in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier. Specifically, a bifunctional antagonist molecule of the present disclosure is useful in treating an anorexia selected from anorexia nervosa and anorexia-cachexia syndrome.

[0196] The present disclosure provides for methods for treating liver disease in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier. Specifically, a multispecific antagonist molecule of the present disclosure is useful in treating a liver disease selected from non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, alcoholic fatty liver disease, liver cirrhosis, liver failure, autoimmune hepatitis and hepatocellular carcinoma.

[0197] The present disclosure provides for methods for organ or tissue transplantation in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier. Specifically, a multispecific antagonist molecule of the present disclosure is useful in treating a transplantation selected from organ transplantations of the heart, kidneys, liver, lungs, pancreas, intestine and thymus or from tissues transplantations of the bones, tendons, cornea, skin, heart valves, nerves and veins.

[0198] The present disclosure provides for methods for treating anemia in a subject, comprising administering to said subject a therapeutically effective amount (either as monotherapy or in a combination therapy regimen) of a multispecific antagonist molecule of the present disclosure in pharmaceutically acceptable carrier. In various embodiments, the anemia is selected from various anemia disorders including cancer-associated anemia, chemotherapy-induced anemia, chronic kidney disease-associated anemia, iron-deficiency anemia, iron and

hemochromatosis, thalassemia, sickle cell disease, aplastic anemia, myelodysplastic syndromes, pancytopenia and bone marrow failure.

[0199] The present disclosure provides methods for treating fibrosis in a subject, comprising administering a therapeutically effective amount of the pharmaceutical compositions of the invention to a subject in need thereof. In one embodiment, the subject is a human subject. In various embodiments, the fibrosis is selected from pulmonary fibrosis (such as idiopathic pulmonary fibrosis and cystic fibrosis), liver fibrosis (such as non-alcoholic steatohepatitis and liver cirrhosis), airway fibrosis (such as asthma), cardiac fibrosis (such as myocardial infarction, diastolic dysfunction or cardiac valve disease), renal fibrosis (such as interstitial fibrosis), myelofibrosis, idiopathic retroperitoneal fibrosis, nephrogenic fibrosing dermopathy, intestinal fibrosis in inflammatory bowel diseases (inducing Crohn's disease), keloid, scleroderma, systemic sclerosis, and arthrofibrosis.

[0200] The present disclosure provides methods of treating pain in a subject, comprising administering a therapeutically effective amount of the pharmaceutical compositions of the invention to a subject in need thereof. In one embodiment, the subject is a human subject. In various embodiments, the pain is selected from neuropathic pain, inflammatory pain, or cancer pain.

[0201] The present disclosure provides methods of treating bone disease in a subject, comprising administering a therapeutically effective amount of the pharmaceutical compositions of the invention to a subject in need thereof. In one embodiment, the subject is a human subject. In various embodiments, the bone disease is selected from osteomalacia, osteoporosis, osteogenesis imperfecta, fibrodysplasia ossificans progressive, corticosteroid-induced bone loss, bone fracture, and bone metastasis.

[0202] The present disclosure provides for a method of inhibiting loss of muscle mass and/or muscle function in a subject comprising administering an effective amount of a multispecific antagonist molecule into the subject. The modulation may attenuate the loss of the muscle mass and/or function of said subject by at least 5%, 10%, at least 25%, at least 50%, at least 75%, or at least 90%. The inhibition of loss of muscle mass and function can be evaluated by using imaging techniques and physical strength tests. Examples of imaging techniques for muscle mass evaluation include Dual-Energy X-Ray Absorptiometry (DEXA), Magnetic Resonance Imaging (MRI), and Computed Tomography (CT). Examples of muscle function tests include grip strength test, stair climbing test, short physical performance battery (SPPB) and 6-minute walk, as well as maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) that are used to measure respiratory muscle strength.

[0203] "Therapeutically effective amount" or “therapeutically effective dose” refers to that amount of the therapeutic agent being administered which will relieve to some extent one or more of the symptoms of the disorder being treated.

[0204] A therapeutically effective dose can be estimated initially from cell culture assays by determining an IC_{50}. A dose can then be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by HPLC. The exact composition, route of administration and dosage can be chosen by the individual physician in view of the subject's condition.

[0205] Dosage regimens can be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response). For example, a single bolus can be administered, several divided doses (multiple or repeat or maintenance) can be administered over time and the dose can be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the present disclosure will be dictated primarily by the unique characteristics of the antibody and the particular therapeutic or prophylactic effect to be achieved.

[0206] Thus, the skilled artisan would appreciate, based upon the disclosure provided herein, that the dose and dosing regimen is adjusted in accordance with methods well-known in the therapeutic arts. That is, the maximum tolerable dose can be readily established, and the effective amount providing a detectable therapeutic benefit to a subject may also be determined, as can the temporal requirements for administering each agent to provide a detectable therapeutic benefit to the subject. Accordingly, while certain dose and administration regimens are exemplified herein, these examples in no way limit the dose and administration regimen that may be provided to a subject in practicing the present disclosure.

[0207] It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated and may include single or multiple doses. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering

or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. Further, the dosage regimen with the compositions of this disclosure may be based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the subject, the severity of the condition, the route of administration, and the particular antibody employed. Thus, the dosage regimen can vary widely, but can be determined routinely using standard methods. For example, doses may be adjusted based on pharmacokinetic or pharmacodynamic parameters, which may include clinical effects such as toxic effects and/or laboratory values. Thus, the present disclosure encompasses intra-subject dose-escalation as determined by the skilled artisan. Determining appropriate dosages and regimens are well-known in the relevant art and would be understood to be encompassed by the skilled artisan once provided the teachings disclosed herein.

[0208] An exemplary, non-limiting daily dosing range for a therapeutically or prophylactically effective amount of a multispecific or bifunctional multispecific antagonist molecule of the disclosure can be 0.001 to 100 mg/kg, 0.001 to 90 mg/kg, 0.001 to 80 mg/kg, 0.001 to 70 mg/kg, 0.001 to 60 mg/kg, 0.001 to 50 mg/kg, 0.001 to 40 mg/kg, 0.001 to 30 mg/kg, 0.001 to 20 mg/kg, 0.001 to 10 mg/kg, 0.001 to 5 mg/kg, 0.001 to 4 mg/kg, 0.001 to 3 mg/kg, 0.001 to 2 mg/kg, 0.001 to 1 mg/kg, 0.010 to 50 mg/kg, 0.010 to 40 mg/kg, 0.010 to 30 mg/kg, 0.010 to 20 mg/kg, 0.010 to 10 mg/kg, 0.010 to 5 mg/kg, 0.010 to 4 mg/kg, 0.010 to 3 mg/kg, 0.010 to 2 mg/kg, 0.010 to 1 mg/kg, 0.1 to 50 mg/kg, 0.1 to 40 mg/kg, 0.1 to 30 mg/kg, 0.1 to 20 mg/kg, 0.1 to 10 mg/kg, 0.1 to 5 mg/kg, 0.1 to 4 mg/kg, 0.1 to 3 mg/kg, 0.1 to 2 mg/kg, 0.1 to 1 mg/kg, 1 to 50 mg/kg, 1 to 40 mg/kg, 1 to 30 mg/kg, 1 to 20 mg/kg, 1 to 10 mg/kg, 1 to 5 mg/kg, 1 to 4 mg/kg, 1 to 3 mg/kg, 1 to 2 mg/kg, or 1 to 1 mg/kg body weight. It is to be noted that dosage values may vary with the type and severity of the conditions to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

[0209] In various embodiments, the total dose administered will achieve a plasma antibody concentration in the range of, e.g., about 1 to 1000 µg/ml, about 1 to 750 µg/ml, about 1 to 500 µg/ml, about 1 to 250 µg/ml, about 10 to 1000 µg/ml, about 10 to 750 µg/ml, about 10 to 500 µg/ml, about 10 to 250 µg/ml, about 20 to 1000 µg/ml, about 20 to 750 µg/ml, about 20 to 500 µg/ml, about 20 to 250 µg/ml, about 30 to 1000 µg/ml, about 30 to 750 µg/ml, about 30 to

500 µg/ml, about 30 to 250 µg/ml.

[0210] Toxicity and therapeutic index of the pharmaceutical compositions of the disclosure can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effective dose is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compositions that exhibit large therapeutic indices are generally preferred.

[0211] The dosing frequency of the administration of the multispecific or bifunctional multispecific antagonist molecule pharmaceutical composition depends on the nature of the therapy and the particular disease being treated. The subject can be treated at regular intervals, such as weekly or monthly, until a desired therapeutic result is achieved. Exemplary dosing frequencies include, but are not limited to: once weekly without break; once weekly, every other week; once every 2 weeks; once every 3 weeks; weakly without break for 2 weeks, then monthly; weakly without break for 3 weeks, then monthly; monthly; once every other month; once every three months; once every four months; once every five months; or once every six months, or yearly.

Combination Therapy

[0212] As used herein, the terms "co-administration", "co-administered" and "in combination with", referring to the a multispecific or bifunctional multispecific antagonist molecule of the disclosure and one or more other therapeutic agents, is intended to mean, and does refer to and include the following: simultaneous administration of such combination of a multispecific or bifunctional multispecific antagonist molecule of the disclosure and therapeutic agent(s) to a subject in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said subject; substantially simultaneous administration of such combination of a multispecific or bifunctional multispecific antagonist molecule of the disclosure and therapeutic agent(s) to a subject in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said subject, whereupon said components are released at substantially the same time to said subject; sequential administration of such combination of a multispecific or bifunctional multispecific antagonist molecule of the disclosure and therapeutic agent(s) to a subject in need of treatment, when such components are formulated apart from each other into separate dosage forms which

are taken at consecutive times by said subject with a significant time interval between each administration, whereupon said components are released at substantially different times to said subject; and sequential administration of such combination of a multispecific or bifunctional multispecific antagonist molecule of the disclosure and therapeutic agent(s) to a subject in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner whereupon they are concurrently, consecutively, and/or overlappingly released at the same and/or different times to said subject, where each part may be administered by either the same or a different route.

[0213] In another aspect, the present disclosure provides a method for treating cancer or cancer metastasis in a subject, comprising administering a therapeutically effective amount of the pharmaceutical compositions of the invention in combination with a second therapy selected from the group consisting of: cytotoxic chemotherapy, immunotherapy, small molecule kinase inhibitor targeted therapy, surgery, radiation therapy, and stem cell transplantation. In various embodiments, the combination therapy may comprise administering to the subject a therapeutically effective amount of immunotherapy, including, but are not limited to, treatment using depleting antibodies to specific tumor antigens; treatment using antibody-drug conjugates; treatment using agonistic, antagonistic, or blocking antibodies to co-stimulatory or co-inhibitory molecules (immune checkpoints) such as CTLA-4, PD-1, PD-L1, OX-40, CD137, TIGIT, GITR, LAG3, TIM-3, CD47, SIRPα, ICOS, and VISTA; treatment using bispecific T cell engaging antibodies (BiTE®) such as blinatumomab: treatment involving administration of biological response modifiers such as TNF family, IL-1, IL-4, IL-7, IL-12, IL-15, IL-17, IL-21, IL-22, GM-CSF, IFN-α, IFN-β and IFN-γ; treatment using therapeutic vaccines such as sipuleucel-T; treatment using dendritic cell vaccines, or tumor antigen peptide vaccines; treatment using chimeric antigen receptor (CAR)-T cells; treatment using CAR-NK cells; treatment using tumor infiltrating lymphocytes (TILs); treatment using adoptively transferred anti-tumor T cells (ex vivo expanded and/or TCR transgenic); treatment using TALL-104 cells; and treatment using immunostimulatory agents such as Toll-like receptor (TLR: TLR7, TLR8, and TLR 9) agonists CpG and imiquimod; wherein the combination therapy provides increased effector cell killing of tumor cells, i.e., a synergy exists between the multispecific antagonists molecule or bifunctional multispecific antagonist molecule and the immunotherapy when co-administered.

[0214] In various embodiments, the combination therapy comprises administering a multispecific or bifunctional multispecific antagonist molecule and the second agent composition simultaneously, either in the same pharmaceutical composition or in separate pharmaceutical composition. In various embodiments, a multispecific or bifunctional multispecific antagonist

molecule composition and the second agent composition are administered sequentially, i.e., a multispecific or bifunctional multispecific antagonist molecule composition is administered either prior to or after the administration of the second agent composition.

[0215] In various embodiments, the administrations of a multispecific or bifunctional multispecific antagonist molecule composition and the second agent composition are concurrent, i.e., the administration period of a multispecific or bifunctional multispecific antagonist molecule composition and the second agent composition overlap with each other.

[0216] In various embodiments, the administrations of a multispecific or bifunctional multispecific antagonist molecule composition and the second agent composition are non-concurrent. For example, in various embodiments, the administration of a multispecific or bifunctional multispecific antagonist molecule composition is terminated before the second agent composition is administered. In various embodiments, the administration second agent composition is terminated before a bifunctional antagonist molecule composition is administered.

[0217] The following examples are offered to more fully illustrate the disclosure but are not construed as limiting the scope thereof.

Example 1

[0218] The multispecific and/or bifunctional multispecific antagonist molecules of the present disclosure can be prepared according to recombinant DNA techniques that are well known to those of skill in the art. In this example, the preparation of the bifunctional antagonist molecules is generally described.

[0219] cDNAs encoding various novel multispecific or bifunctional multispecific antagonistic polypeptides were generated via gene synthesis and subcloned into mammalian expression plasmids. CHO cells were transiently or stably transfected with the mammalian expression plasmids encoding the individual multispecific or bifunctional multispecific polypeptide antagonists. Transiently transfected CHO cells or stably transfected CHO pools were grown in high-density suspension cultures in a CO_2 shaking incubator at 32°C for 6 to 8 days. The culture media were collected after passing through a 0.22μm filter unit (Millipore Corporation, MA). The recombinantly expressed multispecific or bifunctional multispecific polypeptides were purified from the culture media via Protein A affinity chromatography using an AKTA PFLC system (GE Healthcare).

Example 2

[0220] Binding activities of individual multispecific or bifunctional multispecific antagonists to human ligands or target proteins were measured by biolayer interferometry (BLI) using Octet RED96 (FortéBIO, Pall Corporation, USA). Binding analysis was performed by first capturing the polypeptide multispecific or bifunctional multispecific antagonists to biosensors. To measure the rate of association and dissociation, the polypeptide antagonists-captured biosensors were dipped in wells containing different concentrations of specific ligands or target proteins (such as Activin A, Activin B, Activin AB, myostatin, GDF-8, GDF-11, TGF-β1, TGF-β3, PD1 and CTLA4) diluted in 1x kinetic buffer for 10 min followed by 10-20 min in 1x kinetic buffer. The polypeptide antagonists-captured sensors were also submerged in wells containing 1x kinetic buffer to allow single reference subtraction in order to compensate for natural dissociation of the captured polypeptide antagonists. The binding sensorgrams were collected using the 8-channel detection mode on the biosensor. Data were acquired and analyzed using the FortéBIO Data acquisition software v11.1 (FortéBIO, Pall Corporation, USA).

[0221] The binding affinities of multispecific antagonist molecules A115, A116, A117 and A118 were examined using BLI analysis. As depicted in Table 10, multispecific polypeptide antagonists A115, A116, A117 and A118 were able to selectively bind to a subset of the TGF-β superfamily, including Activin A, Activin B, Activin AB, GDF-8, GDF-11, TGF-β1 and TGF-β3 with high affinity. A216, a multispecific polypeptide antagonist engineered in a configuration different from A116 was examined for its ligand binding, and the data demonstrated that A216 had high binding affinities similar to A116. Therefore, multispecific polypeptide antagonists engineered in different configurations can achieve high-affinity ligand binding.

Table 10

Binding Affinity KD (M)							
	Activin A	**Activin B**	**Activin AB**	**GDF-8**	**GDF-11**	**TGF-β1**	**TGF-β3**
A115	~ 1.18E-11	~ 1.0E-12	~ 1.0E-12	~ 1.0E-12	~ 6.06E-09	~ 4.43E-10	~ 1.0E-12
A116	~ 1.0E-12	~ 1.0E-12	~ 1.0E-12	~ 1.0E-12	~ 8.35E-09	~ 4.07E-10	~ 1.0E-12
A117	~ 1.95E-10	~ 1.26E-10	~ 5.17E-12	~ 5.17E-12	~ 6.12E-09	~ 5.34E-10	~ 1.0E-12
A118	~ 1.0E-12	~ 1.0E-12	~ 1.0E-12	~ 1.0E-12	~ 9.15E-09	~ 6.12E-10	~ 1.0E-12
A216	~1.12E-10	~ 1..0E-12	~ 1.0E-12	~ 1.95E-12	~5.0E-12	~1.0E-12	~2.1E-12

[0222] Moreover, the ligand binding affinities of antibody-based multispecific antagonists A155 and A167 were examined using BLI analysis. As shown in Table 11, A155 and A167 were able to bind activin A, TGF-β1 and TGF-β3 with high affinities.

Table 11

	Activin A Binding Affinity (KD M)	**TGF-β1 Binding Affinity (KD M)**	**TGF-β3 Binding Affinity (KD M)**
A155	~3.0E-10	~1.0E-12	~2.0E-08
A167	~2.0E-10	~1.0E-12	~6.0-08

Example 3

[0223] Smad2/3 signaling assay. An engineered luciferase reporter cell line C2C12-CAGA-luc capable of sensing Smad2/3 signaling was used to measure ligand signaling activities in cell cultures. To measure neutralizing activity of multispecific antagonist, 2 nM of human activin A, activin B, Activin AB, myostatin, GDF-11, TGF-β1, or TGF-β3 was preincubated with increasing concentrations of each individual antagonist at 0.00004 nM,

0.0004 nM, 0.004 nM, 0.04 nM, 0.4 nM, 4 nM, 40 nM and 400 nM for 1 hour at room temperature and the preincubated reaction mixtures were then added to the C2C12-CAGA-luc reporter cell cultures. After incubation for 5 hours in CO2 incubator at 37°C, the luciferase activities of the reporter cultures were measured by using LuminoSkan Ascent (Thermo Scientific). The IC_{50} values were analyzed and plotted using Prism software (GraphPad Software).

[0224] As depicted in FIGS. 6-8, bifunctional multi-specific antagonists A115, A116, A117 and A118 A-119 and A-120 strongly neutralize Activin A and Activin B (FIG. 6), TGF-β1 and TGF-β3 (FIG. 7), and GDF-8 and GDF-11 (FIG. 8) in cell-based assays.

Example 4

[0225] Elevated activin and TGF-β have been implicated in cancer cell migration and metastasis. Both activin and TGF-β are highly up-regulated in the tumor microenvironment and a parallel upregulation of activin and TGF-β in the tumor microenvironment has been widely documented. To mimic the parallel upregulation of activin A and TGF-β1 in the tumor microenvironment, activin A and TGF-β1 were added together to A549 lung cancer cell cultures. Under this condition, the effect of A116, a multispecific antagonist of activin and TGF-β, A116, on cancer cell migration was examined in comparison with ActRIIA-Fc (activin inhibitor) and TGFRII-Fc (TGF-β inhibitor), respectively, in a cell migration assay.

[0226] Cancer cell migration assay. To examine the effect of multispecific antagonist of activin and TGF-β on cancer cell migration, a cell monolayer scratch assay was performed using A549 human non-small cell lung cancer cells. A549 cancer cells were plated in multi-well plates and grown as monolayer cultures in DMEM supplemented with 10% fetal bovine serum (FBS) in a CO2 incubator at 37°C. When the cells reached 90% confluence, the cultures were scratched with a 200µl pipette tip to generate a wound gap on the cell monolayer across each well. The cultures were then switched to DMEM supplemented with 0.2% FBS with or without addition of the following agents: 1) None (control), 2) Activin A (50 ng/mL) + TGF- β1 (5 ng/mL), 3) Activin A (50 ng/mL) + TGF-β1 (5 ng/mL) + ActRIIA-Fc (2.5 µg/mL), 4) Activin A (50 ng/mL) + TGF-β1 (5 ng/mL) + TGFRII-Fc (2.5 µg/mL), and 5) Activin A (50 ng/mL) + TGF-β1 (5 ng/mL) + A116 (2.5 µg/mL). At 48 hours after treatment, the cell cultures were photographed using an inverted microscope quipped with a digital camera.

[0227] FIG. 10 depicts the effect of multifunctional peptide antagonist A116 on migration of A549 lung cancer cells. As shown in panel A, the scratch gap remained large in untreated A549 control cultures at 48 hours of incubation. In contrast, with combined activin A and TGF-β1 treatment, the scratch gap was completely closed at 48 hours of incubation, indicating that activin A and TGF-β1 dramatically accelerated the migration of A549 lung cancer cells. Under the same condition, inhibition of activin A by ActRIIA-Fc or inhibition of TGF-β1 by TGFRII-Fc failed to prevent the closure of the scratch gaps at 48 hours of incubation (panels C and D), suggesting that inhibiting activin A or TGF-β1 alone was not sufficient to prevent the accelerated cancer cell migration when both activin A and TGF-β1 were elevated. However, in the presence of high activin and TGF-β1, addition of multispecific antagonist A116 highly effectively prevented the narrowing of the scratch gap in the A549 cancer cell cultures, as the size of the scratch gap of A216-treated culture remained approximately the same as that of the untreated control culture (panel E). These results demonstrate that multispecific antagonist A116 is able to inhibit the accelerated cancer cell migration mediated by activin A and TGF-β in parallel. The results suggest that the novel multispecific antagonists of activin and TGF-β disclosed in the present invention may represent a promising new approach to treating cancer metastasis as these novel antagonists may more effectively prevent cancer cell migration and metastasis by simultaneously blocking elevated activin and TGF-β in the tumor microenvironment.

Example 5

[0228] It has been documented in the literature that the expression levels of activin A and TGF-β are elevated in parallel in various types of malignancies including lung cancer. To evaluate the influence of multispecific antagonist of activin and TGF-β on tumorigenic potential of cancer cells, a colony formation assay was performed in human A549 non-small cell lung cancer cells. To mimic the elevated activin and TGF-β in the cancer microenvironment, exogenous activin A and TGF-β1 were added together to the cell culture medium in A549 lung cancer cell cultures, the effect of multispecific polypeptide antagonist A116 was examined in comparison with ActRIIA-Fc and TGFRII-Fc, respectively, in colony formation assay.

[0229] Cancer cell colony formation assay. To examine the effect of multispecific antagonist of activin and TGF-β on the tumorigenic potential of cancer cells, colony formation assay was performed in A549 human lung cancer cell cultures. A549 lung cancer cells were plated in 6-well plates at the density of ~500 cells per well in DMEM supplemented with 0.2% FBS and incubated for 14 days in the presence of the following agents: 1) Activin A (50 ng/mL)

+ TGF-β1 (5 ng/mL), 2) Activin A (50 ng/mL) + TGF-β1 (5 ng/mL) + ActRIIA-Fc (2.5 μg/mL), 3) Activin A (50 ng/mL) and TGF-β1 (5 ng/mL) + TGFRII-Fc (2.5 μg/mL), and 4) Activin A (50 ng/mL) and TGF-β1 (5 ng/mL) + A116 (2.5 μg/mL). The culture media were replaced twice per week, and colony densities were counted on day 14 with colony formation being defined as >50 cells per colony. Representative microscopic images were taken with a digital camera.

[0230] FIG. 11 depicts the effect of A116 on A549 colony formation in the presence of exogenously added activin A and TGF-β1. As shown in panels A-D, the densities of A549 colony were lower in cultures treated with ActRIIA-Fc, TGFRII-Fc or A116, suggesting that inhibiting activin or TGF-β had an inhibitory effect on colony formation. However, the inhibitory effect of A116 on A549 colony formation was significantly greater compared to that of ActRIIA-Fc or TGFRII-Fc, indicating that parallel inhibition of activin A and TGF-β1 by A116 was more effective in suppressing the colony formation by A549 cancer cells (FIG. 12). The enhanced anti-tumorigenic effect of A116 suggests that the novel multispecific antagonists of activin and TGF-β disclosed in the present invention represent a promising new approach for cancer treatment.

Example 6

[0231] TGF-β is a major driver of tissue fibrosis and TGF-β-mediated Smad2/3 signaling plays a central role in the pathogenesis of fibrosis. Like TGF-β, activin A as well as activin B also mediates Smad2/3 signaling and plays a critical part in the pathogenesis of fibrosis. It has been shown that TGF-β and activin A are upregulated in parallel in fibrotic disease tissues and elevated TGF-β and activin A act in concert to promote disease progression by stimulating collagen overproduction and extracellular matrix deposition. Due to the parallel involvement TGF-β and activin in fibrosis, dual targeting of elevated TGF-β and activin may improve treatment efficacy. Therefore, in order to more effectively combat fibrotic diseases, it is important to explore novel antagonists capable of inhibiting TGF-β and activin simultaneously.

[0232] In this example, A116, a novel polypeptide-based multispecific antagonist capable of simultaneously neutralizing TGF-β and activin, was evaluated in comparison with ActRIIA-Fc, an activin-neutralizing protein, and TGFRII-Fc, a TGF-β-neutralizing protein, respectively, for its ability to attenuate bleomycin-induced lung fibrosis in mice.

[0233] Bleomycin-induce pulmonary fibrosis mouse model study. All procedures involving animals were approved by the Institutional Committee of Animal Care. Eight-week-old male C57BL/6 mice were purchased from the Jackson Laboratories. Mice were maintained in a

12-h light/dark cycle and with access to water and rodent laboratory chow ad libitum. Mice were acclimated for 1 week before receiving treatment. Bleomycin (Sigma) was dissolved in sterile 0.9% saline and administered as a single dose of 0.5mg/kg per animal. Control animals received saline alone. All animals received intratracheal injection (IT) instillations of either bleomycin or saline on day 0. Mice were randomly assigned to the following groups: (1) IT saline (Control); (2) IT bleomycin (Bleomycin), (3) IT bleomycin with ActRIIA-Fc treatment (Bleomycin + ActRIIA-Fc-Fc); (4) IT bleomycin with TGFRII-Fc (Bleomycin + TGFRII-Fc); (4) IT bleomycin with A1116 treatment (Bleomycin + A116). Starting on Day -2, ActRIIA-Fc, TGFRII-Fc, and A-120 were given to the individual mouse groups, respectively, once per week via SC administration at the dose between 5 and 10 mg/kg as normalized with the molecular weight of each agent. After two weeks of treatment, the animals were sacrificed, and the right lung tissues were collected in cassettes and fixed in neutral buffered formalin. For histological assessment, the samples were dehydrated in a graded ethanol series, clarified in xylene and embedded in paraffin. Sections of 4-6 μm thickness were cut and stained with Hematoxylin and Eosin (H&E), Masson's trichrome (TM) and anti-alpha-SMA antibody coupled with HRP. Fibrotic lung injury was assessed histologically through Ashcroft scoring system (Hübner et al. 2008. PMID: 18476815; DOI: 10.2144/000112729). Ashcroft scores were analyzed at the magnification of 10X.

[0234] FIG. 13 shows the histological images of H&E-stained lung sections and Ashcraft Scores of the lung sections in a mouse model of bleomycin-induced pulmonary fibrosis. The data indicate that dual inhibition of TGF-β and activin by A116 markedly reduced bleomycin-induced lung fibrosis while activin inhibitor ActRIIA-Fc or TGF-β blocker TGFRII-Fc moderately inhibited bleomycin-induced lung fibrosis. Analysis of Ashcraft scores revealed that A116 treatment resulted in greater reduction of lung fibrosis compared to ActRIIA-Fc treatment or TGFRII-Fc treatment.

[0235] FIG. 14 depicts the histology images of Masson's trichrome stained lung sections and a bar graph on quantitative analysis of collagen deposition area in the lung sections from mice with bleomycin-induced pulmonary fibrosis. The data demonstrate that A116 attenuated collagen deposition more effectively than ActRIIA-Fc or TGFRII-Fc in the bleomycin-induced lung fibrosis model.

[0236] FIG. 15 shows the histology images of immunochemical staining of α-SMA, a marker for fibrosis, in the lung sections from control and bleomycin-treated mice. The lung sections were immunochemically stained with a primary anti-αSMA antibody in conjunction with

an HRP-labeled secondary antibody. The results indicate that A116 was more effective than ActRIIA-Fc or TGFRII-Fc in preventing the induction of α-SMA in the lungs of bleomycin mice.

[0237] Taken together, the experimental data from mice with bleomycin-induced lung fibrosis demonstrated A116 to be more effective than ActRIIA-Fc or TGFRII-Fc in preventing fibrosis. The enhanced anti-fibrosis effect seen upon dual inhibition of activin and TGF-β by A116 in the bleomycin mouse model suggests that A116 and other novel multispecific antagonists of activin and TGF-β of the present invention may represent a more efficacious therapeutic approach to combatting fibrotic diseases.

[0238] All of the articles and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present invention. While the articles and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the articles and methods without departing from the spirit and scope of the invention. All such variations and equivalents apparent to those skilled in the art, whether now existing or later developed, are deemed to be within the spirit and scope of the invention as defined by the appended claims. All patents, patent applications, and publications mentioned in the specification are indicative of the levels of those of ordinary skill in the art to which the invention pertains. All patents, patent applications, and publications are herein incorporated by reference in their entirety for all purposes and to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety for any and all purposes. The invention illustratively described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

Sequence Listings

[0239] The nucleic and amino acid sequences listed in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases and three letter code for amino acids, as defined in 37 C.F.R. 1.822.

SEQ ID NOs: 1-9 are amino acid sequences of various Activin or Activin-related ligands.

SEQ ID NOs: 10 and 14 are amino acid sequences of a heavy chain of various antibodies which specifically binds to Activin or Activin-related ligand.

SEQ ID NOs: 11 and 15 are amino acid sequences of a light chain of various antibodies which specifically binds to Activin or Activin-related ligand.

SEQ ID NOs: 12 and 16 are amino acid sequences of a heavy chain variable region of various antibodies which specifically binds to Activin or Activin-related ligand.

SEQ ID NOs: 13 and 17 are amino acid sequences of a light chain variable region of various antibodies which specifically binds to Activin or Activin-related ligand.

SEQ ID NOs: 18-21 are amino acid sequences of various TGF-β ligands.

SEQ ID NO: 22 is an amino acid sequence of a heavy chain of an antibody which specifically binds to TGF-β ligand.

SEQ ID NO: 23 is an amino acid sequences of a light chain of an antibody which specifically binds to TGF-β ligand.

SEQ ID NO: 24 is an amino acid sequence of a heavy chain variable region of an antibody which specifically binds to TGF-β ligand.

SEQ ID NO: 25 is an amino acid sequences of a light chain variable region of an antibody which specifically binds to TGF-β ligand.

SEQ ID NOs: 26, 30, 38 and 42 are amino acid sequences of a heavy chain of various antibodies which specifically binds to PD-1 ligand.

SEQ ID NOs: 27, 31, 39 and 43 are amino acid sequences of a light chain of various antibodies which specifically binds to PD-1 ligand.

SEQ ID NOs: 28, 32, 40 and 44 are amino acid sequences of a heavy chain variable region of various antibodies which specifically binds to PD-1 ligand.

SEQ ID NOs: 29, 33, 41 and 45 are amino acid sequences of a light chain variable region of various antibodies which specifically binds to PD-1 ligand.

SEQ ID NO: 34 is an amino acid sequence of a heavy chain of an antibody which specifically binds to CTLA-4 ligand.

SEQ ID NO: 35 is an amino acid sequences of a light chain of an antibody which specifically binds to CTLA-4 ligand.

SEQ ID NO: 36 is an amino acid sequence of a heavy chain variable region of an antibody which specifically binds to CTLA-4 ligand.

SEQ ID NO: 37 is an amino acid sequences of a light chain variable region of an antibody which specifically binds to CTLA-4 ligand.

SEQ ID NOs: 46 and 50 are amino acid sequences of a heavy chain of various antibodies which specifically binds to PD-L1 ligand.

SEQ ID NOs: 47 and 51 are amino acid sequences of a light chain of various antibodies which specifically binds to PD-L1 ligand.

SEQ ID NOs: 48 and 52 are amino acid sequences of a heavy chain variable region of various antibodies which specifically binds to PD-L1 ligand.

SEQ ID NOs: 49 and 53 are amino acid sequences of a light chain variable region of various antibodies which specifically binds to PD-L1 ligand.

SEQ ID NOs: 54-71 are the amino acid sequences of various multispecific antagonist molecules that specifically binds to Activin or Activin-related ligand and that specifically binds to TGF-β ligand.

SEQ ID NOs: 72-84 are the amino acid sequences of a heavy chain of a multispecific antagonist molecule that specifically binds to Activin or Activin-related ligand or TGF-β ligand.

SEQ ID NOs: 85-120 are the amino acid sequences of a heavy chain of a bifunctional multispecific antagonist molecule that specifically binds to Activin or Activin-related ligand, TGF-β ligand, and to either PD-1 ligand or CTLA-4 ligand or PD-L1 ligand.

SEQ ID NO: 121 is the amino acid sequence of a multispecific antagonist molecule that specifically binds to Activin or Activin-related ligand and that specifically binds to TGF-β ligand.

SEQ ID NO: 122 is the amino acid sequences of a heavy chain of a multispecific antagonist molecule that specifically binds to Activin or Activin-related ligand or TGF-β ligand.

SEQ ID NO: 123 is the amino acid sequences of a light chain of a multispecific antagonist molecule that specifically binds to Activin or Activin-related ligand or TGF-β ligand.

SEQ ID NOs: 124-143 are the amino acid sequences of various peptide linker sequences.

SEQUENCE LISTINGS

Human ActRIIA-ECD
ETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYD
RTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVTPKPP (SEQ ID NO: 1)

Human ActRIIB-ECD
ETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWLDDFNCYD
RQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPT (SEQ ID NO: 2)

Human Follistatin 315
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE

QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNSISEDTEEEEEDEDQDYSFPISSI
LEW (SEQ ID NO: 3)

Human Follistatin ΔHBS (modified Follistatin)
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNSISEDTEEEEEDEDQDYSFPISSI
LEW (SEQ ID NO: 4)

Human Follistatin 288
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCN (SEQ ID NO: 5)

Modified human ActRIIB ECD
ETRECIYYNANWELERTNQSGLERCEGDQDKRLHCYASWRNSSGTIELVKKGCWLDDINCYD
RQECVATKENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPT (SEQ ID NO: 6)

Modified human ActRIIB ECD
ETRECIYYNANWELERTNQSGLERCYGDKDKRRHCYASWRNSSGTIELVKKGCWLDDFNCYD
RQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPT (SEQ ID NO: 7)

Modified human ActRIIB ECD
ETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWDDDFNCY
DRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPT (SEQ ID NO: 8)

Modified human ActRIIA ECD
GAILGRSETQECLFYNANWELERTNQTGVEPCEGEKDKRLHCYATWRNISGSIEIVKKGCWLD
DFNCYDRTDCVETEENPQVYFCCCEGNMCNEKFSYFPEMEVTQPTS (SEQ ID NO: 9)

Anti-Activin antibody heavy chain amino acid sequence
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGLSWVRQAPGQGLEWMGWIIPYNGNTNSA
QKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYFCARDRDYGVNYDAFDIWGQGTMVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNVYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK (SEQ ID NO: 10)

Anti-Activin A antibody light chain amino acid sequence
SYEVTQAPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSG
SNSGNTATLTISGTQAMDEADYYCQAWDSSTAVFGGGTKLTVLRTVAAPSVFIFPPSDEQLKS

GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 11)

Anti-Activin A antibody heavy chain variable region amino acid sequence
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGLSWVRQAPGQGLEWMGWIIPYNGNTNSA
QKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYFCARDRDYGVNYDAFDIWGQGTMVTVSS
(SEQ ID NO: 12)

Anti-Activin A antibody light chain variable region amino acid sequence
SYEVTQAPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSG
SNSGNTATLTISGTQAMDEADYYCQAWDSSTAVFGGGTKLTVL (SEQ ID NO: 13)

Anti-Activin A antibody heavy chain amino acid sequence
QVQLQESGPGLVKPSETLSLTCTVSGGSFSSHFWSWIRQPPGKGLEWIGYILYTGGTSFNPSL
KSRVSMSVGTSKNQFSLKLSSVTAADTAVYYCARARSGITFTGIIVPGSFDIWGQGTMVTVSSA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGK (SEQ ID NO: 14)

Anti-Activin A antibody light chain amino acid sequence
EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 15)

Anti-Activin A antibody heavy chain variable region amino acid sequence
QVQLQESGPGLVKPSETLSLTCTVSGGSFSSHFWSWIRQPPGKGLEWIGYILYTGGTSFNPSL
KSRVSMSVGTSKNQFSLKLSSVTAADTAVYYCARARSGITFTGIIVPGSFDIWGQGTMVTVSS
(SEQ ID NO: 16)

Anti-Activin A antibody light chain variable region amino acid sequence
EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK (SEQ ID NO: 17)

Human TGF-β Receptor II isoform 1
MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDN
QKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKK
KPGETFFMCSCSSDECNDNIIFSEEYNTSNPDLLLVIFQVTGISLLPPLGVAISVIIIFYCYRVNRQ
QKLSSTWETGKTRKLMEFSEHCAIILEDDRSDISSTCANNINHNTELLPIELDTLVGKGRFAEVY
KAKLKQNTSEQFETVAVKIFPYEEYASWKTEKDIFSDINLKHENILQFLTAEERKTELGKQYWLIT
AFHAKGNLQEYLTRHVISWEDLRKLGSSLARGIAHLHSDHTPCGRPKMPIVHRDLKSSNILVKN
DLTCCLCDFGLSLRLDPTLSVDDLANSGQVGTARYMAPEVLESRMNLENVESFKQTDVYSMAL
VLWEMTSRCNAVGEVKDYEPPFGSKVREHPCVESMKDNVLRDRGRPEIPSFWLNHQGIQMV
CETLTECWDHDPEARLTAQCVAERFSELEHLDRLSGRSCSEEKIPEDGSLNTTK
(SEQ ID NO: 18)

Human TGF-β Receptor II-ECD isoform 1 (TGF-β RIIB-ECD)
TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCV
AVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFS
EEYNTSNPD (SEQ ID NO: 19)

Human TGF-β Receptor II isoform 2
MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTD
NNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHD
PKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDLLLVIFQVTG
ISLLPPLGVAISVIIIFYCYRVNRQQKLSSTWETGKTRKLMEFSEHCAIILEDDRSDISSTCANNIN
HNTELLPIELDTLVGKGRFAEVYKAKLKQNTSEQFETVAVKIFPYEEYASWKTEKDIFSDINLKHE
NILQFLTAEERKTELGKQYWLITAFHAKGNLQEYLTRHVISWEDLRKLGSSLARGIAHLHSDHTP
CGRPKMPIVHRDLKSSNILVKNDLTCCLCDFGLSLRLDPTLSVDDLANSGQVGTARYMAPEVLE
SRMNLENVESFKQTDVYSMALVLWEMTSRCNAVGEVKDYEPPFGSKVREHPCVESMKDNVL
RDRGRPEIPSFWLNHQGIQMVCETLTECWDHDPEARLTAQCVAERFSELEHLDRLSGRSCSE
EKIPEDGSLNTTK (SEQ ID NO: 20)

Human TGF-β Receptor II-ECD isoform 2 (TGF-β RIIA-ECD)
TIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTC
DNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKE
KKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 21)

Anti-TGF-β antibody heavy chain amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 22)

Anti-TGF-β antibody light chain amino acid sequence
ETVLTQSPGTLSLSPGERATLSCRASQSLGSSYLAWYQQKPGQAPRLLIYGASSRAPGIPDRF
SGSGSGTDFTLTISRLEPEDFAVYYCQQYADSPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 23)

Anti-TGF-β antibody heavy chain variable region amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSS
(SEQ ID NO: 24)

Anti-TGF-β antibody light chain variable region amino acid sequence
ETVLTQSPGTLSLSPGERATLSCRASQSLGSSYLAWYQQKPGQAPRLLIYGASSRAPGIPDRF
SGSGSGTDFTLTISRLEPEDFAVYYCQQYADSPITFGQGTRLEIK (SEQ ID NO: 25)

Anti-PD1 antibody heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGK (SEQ ID NO: 26)

Anti-PD1 antibody light chain amino acid sequence
EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPA
RFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
HKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 27)

Anti-PD1 antibody heavy chain variable region amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSS
(SEQ ID NO: 28)

Anti-PD1 antibody light chain variable region amino acid sequence
EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPA
RFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIK (SEQ ID NO: 29)

Anti-PD1 antibody heavy chain amino acid sequence
QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYA
DSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPL
APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS
SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLS
LGK (SEQ ID NO: 30)

Anti-PD1 antibody light chain amino acid sequence
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSG
SGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 31)

Anti-PD1 antibody heavy chain variable region amino acid sequence
QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYA
DSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS
(SEQ ID NO: 32)

Anti-PD1 antibody light chain variable region amino acid sequence

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSG
SGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIK (SEQ ID NO: 33)

Anti-CTLA-4 antibody heavy chain amino acid sequence
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 34)

Anti-CTLA-4 antibody light chain amino acid sequence
EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 35)

Anti-CTLA-4 antibody heavy chain variable region amino acid sequence
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSS
(SEQ ID NO: 36)

Anti-CTLA-4 antibody light chain variable region amino acid sequence
EIVLTQSPGTLSLSPGERATLSCRASQSVGSSYLAWYQQKPGQAPRLLIYGAFSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK (SEQ ID NO: 37)

Anti-PD1 antibody heavy chain amino acid sequence
EVQLLESGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYFA
DSVKGRFTISRDNSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGTLVTVSSASTKGP
SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH
NHYTQKSLSLSLGK (SEQ ID NO: 38)

Anti-PD1 antibody light chain amino acid sequence
DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPSRFSGS
GSGTDFTLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFRRTVAAPSVFIFPPSDEQLKSGT
ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 39)

Anti-PD1 antibody heavy chain variable region amino acid sequence
EVQLLESGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYFA
DSVKGRFTISRDNSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGTLVTVSS

(SEQ ID NO: 40)

Anti-PD1 antibody light chain variable region amino acid sequence
DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPSRFSGS
GSGTDFTLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFR (SEQ ID NO: 41)

Anti-PD1 antibody heavy chain amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSIYPSGGITFYADT
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVTTVDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 42)

Anti-PD1 antibody light chain amino acid sequence
QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSN
RFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGTKVTVLGQPKANPTVTLFPPSS
EELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQW
KSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 43)

Anti-PD1 antibody heavy chain variable region amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSIYPSGGITFYADT
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVTTVDYWGQGTLVTVSS
(SEQ ID NO: 44)

Anti-PD1 antibody light chain variable region amino acid sequence
QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSN
RFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGTKVTVL (SEQ ID NO: 45)

Anti-PD-L1 antibody heavy chain amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 46)

Anti-PD-L1 antibody light chain amino acid sequence
DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 47)

Anti-PD-L1 antibody heavy chain variable region amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA
DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSS
(SEQ ID NO: 48)

Anti-PD1 antibody light chain variable region amino acid sequence
DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIK (SEQ ID NO: 49)

Anti-PD-L1 antibody heavy chain amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYYV
DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQGTLVTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEFEGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG
FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO: 50)

Anti-PD-L1 antibody light chain amino acid sequence
EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 51)

Anti-PD-L1 antibody heavy chain variable region amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYYV
DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQGTLVTVSS
(SEQ ID NO: 52)

Anti-PD1 antibody light chain variable region amino acid sequence
EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIPDRFS
GSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGTKVEIK (SEQ ID NO: 53)

A115 amino acid sequence
ETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYD
RTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVTPKPPGGGGSGGGGSGG
GGSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGG
GSTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEV
CVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNII
FSEEYNTSNPD (SEQ ID NO: 54)

A116 amino acid sequence
ETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYD
RTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVTPKPPGGGGSGGGGSGG

GGSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGG
GSTIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFS
TCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIM
KEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 55)

A140 amino acid sequence
ETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWLDDFNCYD
RQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPTGGGGSGGGGSGGG
GSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGG
STIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVC
VAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIF
SEEYNTSNPD (SEQ ID NO: 56)

A141 amino acid sequence
ETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWLDDFNCYD
RQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPTGGGGSGGGGSGGG
GSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGG
STIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMK
EKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 57)

A142 amino acid sequence
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNSISEDTEEEEEDEDQDYSFPISSI
LEWGGGGSGGGGSGGGGSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
KGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSC
MSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 58)

A143 amino acid sequence
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNSISEDTEEEEEDEDQDYSFPISSI
LEWGGGGSGGGGSGGGGSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV

TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
KGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNG
AVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKL
PYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 59)

A117 amino acid sequence
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNSISEDTEEEEEDEDQDYSFPISSI
LEWGGGGSGGGGSGGGGSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
KGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSC
MSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 60)

A118 amino acid sequence
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNSISEDTEEEEEDEDQDYSFPISSI
LEWGGGGSGGGGSGGGGSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
KGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNG
AVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKL
PYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 61)

A144 amino acid sequence
GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNGGGGSGGGGSGGGGSEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP
QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSTIPPHVQ
KSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKN
DENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTS
NPD (SEQ ID NO: 62)

A145 amino acid sequence

GNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPC
KETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKE
QPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTY
SSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPDS
KSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCNGGGGSGGGGSGGGGSEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP
QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSTIPPHVQ
KSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSC
MSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 63)

A146 amino acid sequence
ETRECIYYNANWELERTNQSGLERCEGDQDKRLHCYASWRNSSGTIELVKKGCWLDDINCYD
RQECVATKENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPTGGGGSGGGGSGGG
GSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGG
STIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVC
VAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIF
SEEYNTSNPD (SEQ ID NO: 64)

A147 amino acid sequence
ETRECIYYNANWELERTNQSGLERCEGDQDKRLHCYASWRNSSGTIELVKKGCWLDDINCYD
RQECVATKENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPTGGGGSGGGGSGGG
GSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGG
STIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMK
EKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 65)

A148 amino acid sequence
ETRECIYYNANWELERTNQSGLERCYGDKDKRRHCYASWRNSSGTIELVKKGCWLDDFNCYD
RQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPTGGGGSGGGGSGGG
GSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGG
STIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVC
VAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIF
SEEYNTSNPD (SEQ ID NO: 66)

A149 amino acid sequence
ETRECIYYNANWELERTNQSGLERCYGDKDKRRHCYASWRNSSGTIELVKKGCWLDDFNCYD
RQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPTGGGGSGGGGSGGG
GSEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA

KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGG
STIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMK
EKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 67)

A150 amino acid sequence
ETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWDDDFNCY
DRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTGGGGSGGGGSGGGG
SEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGS
TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCV
AVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFS
EEYNTSNPD (SEQ ID NO: 68)

A151 amino acid sequence
ETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWDDDFNCY
DRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTGGGGSGGGGSGGGG
SEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGS
TIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTC
DNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKE
KKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 69)

A152 amino acid sequence
GAILGRSETQECLFYNANWELERTNQTGVEPCEGEKDKRLHCYATWRNISGSIEIVKKGCWLD
DFNCYDRTDCVETEENPQVYFCCCEGNMCNEKFSYFPEMEVTQPTSGGGGSGGGGSGGGG
SEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGS
TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCV
AVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFS
EEYNTSNPD (SEQ ID NO: 70)

A153 amino acid sequence
GAILGRSETQECLFYNANWELERTNQTGVEPCEGEKDKRLHCYATWRNISGSIEIVKKGCWLD
DFNCYDRTDCVETEENPQVYFCCCEGNMCNEKFSYFPEMEVTQPTSGGGGSGGGGSGGGG
SEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGS
TIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTC
DNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKE
KKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 71)

A154 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGLSWVRQAPGQGLEWMGWIIPYNGNTNSA
QKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYFCARDRDYGVNYDAFDIWGQGTMVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNVYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGKGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCD
VRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASP
KCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 72)

A155 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGLSWVRQAPGQGLEWMGWIIPYNGNTNSA
QKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYFCARDRDYGVNYDAFDIWGQGTMVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNVYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGKGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHI
NNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENI
TLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD
(SEQ ID NO: 73)

A156 Heavy chain amino acid sequence
QVQLQESGPGLVKPSETLSLTCTVSGGSFSSHFWSWIRQPPGKGLEWIGYILYTGGTSFNPSL
KSRVSMSVGTSKNQFSLKLSSVTAADTAVYYCARARSGITFTGIIVPGSFDIWGQGTMVTVSSA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVR
FSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCI
MKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 74)

A157 Heavy chain amino acid sequence
QVQLQESGPGLVKPSETLSLTCTVSGGSFSSHFWSWIRQPPGKGLEWIGYILYTGGTSFNPSL
KSRVSMSVGTSKNQFSLKLSSVTAADTAVYYCARARSGITFTGIIVPGSFDIWGQGTMVTVSSA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHIN
NDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENIT
LETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD
(SEQ ID NO: 75)

A158 Heavy chain amino acid sequence

QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGKGGGGSGGGGSGGGGSETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCF
ATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEVTQ
PTSNPVTPKPP (SEQ ID NO: 76)

A159 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGKGGGGSGGGGSGGGGSETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYA
SWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGP
EVTYEPPPTAPT (SEQ ID NO: 77)

A160 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGKGGGGSGGGGSGGGGSGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSW
TEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITW
KGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAY
CVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTG
GKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKHS
GSCNSISEDTEEEEEDEDQDYSFPISSILEW (SEQ ID NO: 78)

A161 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGKGGGGSGGGGSGGGGSGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSW
TEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNITW
KGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAY
CVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTG

GKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKHS
GSCNSISEDTEEEEEDEDQDYSFPISSILEW (SEQ ID NO: 79)

A162 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGKGGGGSGGGGSGGGGSGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSW
TEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNITW
KGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAY
CVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTG
GKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKHS
GSCNSISEDTEEEEEDEDQDYSFPISSILEW (SEQ ID NO: 80)

A163 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGKGGGGSGGGGSGGGGSETRECIYYNANWELERTNQSGLERCEGDQDKRLHCYA
SWRNSSGTIELVKKGCWLDDINCYDRQECVATKENPQVYFCCCEGNFCNERFTHLPEAGGPE
VTYEPPPTAPT (SEQ ID NO: 81)

A164 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGKGGGGSGGGGSGGGGSETRECIYYNANWELERTNQSGLERCYGDKDKRRHCYA
SWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGP
EVTYEPPPTAPT (SEQ ID NO: 82)

A165 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGKGGGGSGGGGSGGGGSETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYA

SWRNSSGTIELVKKGCWDDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGP
EVTYEPPPT (SEQ ID NO: 83)

A166 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLEWMGGVIPIVDIANYAQ
RFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGKGGGGSGGGGSGGGGSGAILGRSETQECLFYNANWELERTNQTGVEPCEGEKD
KRLHCYATWRNISGSIEIVKKGCWLDDFNCYDRTDCVETEENPQVYFCCCEGNMCNEKFSYF
PEMEVTQPTS (SEQ ID NO: 84)

A169 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRH
CFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEV
TQPTSNPVTPKPPGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGA
VKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLP
YHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 85)

A170 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRH
CFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEV
TQPTSNPVTPKPPGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICP
SCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEV
CVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNII
FSEEYNTSNPD (SEQ ID NO: 86)

A171 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS

TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGEQDKRLHC
YASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAG
GPEVTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNG
AVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKL
PYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 87)

A172 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGEQDKRLHC
YASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAG
GPEVTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIIC
PSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQE
VCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPD (SEQ ID NO: 88)

A173 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLST
SWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNI
TWKGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNN
AYCVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQC
TGGKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKH
SGSCNSISEDTEEEEEDEDQDYSFPISSILEWGGGGSGGGGSGGGGSGGGGSGGGGSTIPP
HVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVW
RKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEY
NTSNPD (SEQ ID NO: 89)

A174 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS

TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLST
SWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNI
TWKGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNN
AYCVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQC
TGGKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKH
SGSCNSISEDTEEEEEDEDQDYSFPISSILEWGGGGSGGGGSGGGGSGGGGSGGGGSTIPP
HVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQ
KSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKP
GETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 90)

A175 Heavy chain amino acid sequence

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLST
SWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNI
TWKGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNN
AYCVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQC
TGGKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKH
SGSCNSISEDTEEEEEDEDQDYSFPISSILEWGGGGSGGGGSGGGGSGGGGSGGGGSTIPP
HVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVW
RKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEY
NTSNPD (SEQ ID NO: 91)

A176 Heavy chain amino acid sequence

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLST
SWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNI
TWKGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNN
AYCVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQC
TGGKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKH
SGSCNSISEDTEEEEEDEDQDYSFPISSILEWGGGGSGGGGSGGGGSGGGGSGGGGSTIPP

HVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQ
KSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKP
GETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 92)

A177 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLST
SWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNI
TWKGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNN
AYCVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQC
TGGKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKH
SGSCNGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKFPQLCK
FCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDA
ASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 93)

A178 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLST
SWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNI
TWKGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNN
AYCVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQC
TGGKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKH
SGSCNGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPSCNRTAH
PLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNT
SNPD (SEQ ID NO: 94)

A179 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH

YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGDQDKRLHC
YASWRNSSGTIELVKKGCWLDDINCYDRQECVATKENPQVYFCCCEGNFCNERFTHLPEAGG
PEVTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGA
VKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLP
YHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 95)

A180 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGDQDKRLHC
YASWRNSSGTIELVKKGCWLDDINCYDRQECVATKENPQVYFCCCEGNFCNERFTHLPEAGG
PEVTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICP
SCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEV
CVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNII
FSEEYNTSNPD (SEQ ID NO: 96)

A181 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCYGDKDKRRHC
YASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAG
GPEVTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNG
AVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKL
PYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 97)

A182 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCYGDKDKRRHC
YASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAG
GPEVTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIIC
PSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQE

VCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPD (SEQ ID NO: 98)

A183 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGEQDKRLHC
YASWRNSSGTIELVKKGCWDDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAG
GPEVTYEPPPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVK
FPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYH
DFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 99)

A184 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGEQDKRLHC
YASWRNSSGTIELVKKGCWDDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAG
GPEVTYEPPPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPSC
NRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCV
AVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFS
EEYNTSNPD (SEQ ID NO: 100)

A185 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGAILGRSETQECLFYNANWELERTNQTGVEPCEGE
KDKRLHCYATWRNISGSIEIVKKGCWLDDFNCYDRTDCVETEENPQVYFCCCEGNMCNEKFS
YFPEMEVTQPTSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAV
KFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPY
HDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 101)

A186 Heavy chain amino acid sequence

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGSGGGGAILGRSETQECLFYNANWELERTNQTGVEPCEGE
KDKRLHCYATWRNISGSIEIVKKGCWLDDFNCYDRTDCVETEENPQVYFCCCEGNMCNEKFS
YFPEMEVTQPTSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPS
CNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVC
VAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIF
SEEYNTSNPD (SEQ ID NO: 102)

A187 Heavy chain amino acid sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGKGGGGSGGGGSGGGGETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFA
TWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEVTQP
TSNPVTPKPPGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKF
PQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHD
FILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 103)

A188 Heavy chain amino acid sequence

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRH
CFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEV
TQPTSNPVTPKPPGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICP
SCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEV
CVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNII
FSEEYNTSNPD (SEQ ID NO: 104)

A189 Heavy chain amino acid sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV

TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYAS
WRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPE
VTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVK
FPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYH
DFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 105)

A190 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGEQDKRLHC
YASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAG
GPEVTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIIC
PSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQE
VCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPD (SEQ ID NO: 106)

A191 Heavy chain amino acid sequence
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTE
EDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKG
PVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVT
CNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKK
CLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSC
NSISEDTEEEEEDEDQDYSFPISSILEWGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQK
SVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKND
ENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSN
PD (SEQ ID NO: 107)

A192 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLST
SWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNI
TWKGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNN
AYCVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQC
TGGKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKH
SGSCNSISEDTEEEEEDEDQDYSFPISSILEWGGGGSGGGGSGGGGSGGGGSGGGGSTIPP
HVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQ
KSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKP
GETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 108)

A193 Heavy chain amino acid sequence
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTE
EDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNITWKG
PVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVT
CNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKK
CLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSC
NSISEDTEEEEEDEDQDYSFPISSILEWGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQK
SVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKND
ENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSN
PD (SEQ ID NO: 109)

A194 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLST
SWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGQSCVVDQTGSPRCVCAPDCSNI
TWKGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNN
AYCVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQC
TGGKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKH
SGSCNSISEDTEEEEEDEDQDYSFPISSILEWGGGGSGGGGSGGGGSGGGGSGGGGSTIPP
HVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQ
KSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKP
GETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 110)

A195 Heavy chain amino acid sequence
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLSTSWTE
EDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNITWKG
PVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNNAYCVT
CNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKK
CLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSC
NGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDV
RFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPK
CIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 111)

A196 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGNCWLRQAKNGRCQVLYKTELSKEECCSTGRLST
SWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGPGKKCRMNKKNKPRCVCAPDCSNI
TWKGPVCGLDGKTYRNECALLKARCKEQPELEVQYQGRCKKTCRDVFCPGSSTCVVDQTNN
AYCVTCNRICPEPASSEQYLCGNDGVTYSSACHLRKATCLLGRSIGLAYEGKCIKAKSCEDIQC
TGGKKCLWDFKVGRGRCSLCDELCPDSKSDEPVCASDNATYASECAMKEAACSSGVLLEVKH
SGSCNGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPSCNRTAH
PLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNT
SNPD (SEQ ID NO: 112)

A197 Heavy chain amino acid sequence
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGDQDKRLHCYAS
WRNSSGTIELVKKGCWLDDINCYDRQECVATKENPQVYFCCCEGNFCNERFTHLPEAGGPEV
TYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKF

PQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHD
FILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 113)

A198 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGDQDKRLHC
YASWRNSSGTIELVKKGCWLDDINCYDRQECVATKENPQVYFCCCEGNFCNERFTHLPEAGG
PEVTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICP
SCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEV
CVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNII
FSEEYNTSNPD (SEQ ID NO: 114)

A199 Heavy chain amino acid sequence
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCYGDKDKRRHCYAS
WRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPE
VTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVK
FPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYH
DFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 115)

A200 Heavy chain amino acid sequence
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCYGDKDKRRHC
YASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAG
GPEVTYEPPPTAPTGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIIC
PSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQE
VCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPD (SEQ ID NO: 116)

A201 Heavy chain amino acid sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPKGGGGSGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYAS
WRNSSGTIELVKKGCWDDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPE
VTYEPPPTGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKFPQ
LCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFIL
EDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 117)

A202 Heavy chain amino acid sequence

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGSGGGGETRECIYYNANWELERTNQSGLERCEGEQDKRLHC
YASWRNSSGTIELVKKGCWDDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAG
GPEVTYEPPPTGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPSC
NRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCV
AVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFS
EEYNTSNPD (SEQ ID NO: 118)

A203 Heavy chain amino acid sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVTFISYDGNNKYYA
DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAIYYCARTGWLGPFDYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPKGGGGSGGGGSGGGGAILGRSETQECLFYNANWELERTNQTGVEPCEGEKDKR
LHCYATWRNISGSIEIVKKGCWLDDFNCYDRTDCVETEENPQVYFCCCEGNMCNEKFSYFPE
MEVTQPTSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSVNNDMIVTDNNGAVKFPQ
LCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFIL
EDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 119)

A204 Heavy chain amino acid sequence

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNF
NEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK

DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGKGGGGSGGGGSGGGGGAILGRSETQECLFYNANWELERTNQTGVEPCEGE
KDKRLHCYATWRNISGSIEIVKKGCWLDDFNCYDRTDCVETEENPQVYFCCCEGNMCNEKFS
YFPEMEVTQPTSGGGGSGGGGSGGGGSGGGGSGGGGSTIPPHVQKSDVEMEAQKDEIICPS
CNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVC
VAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIF
SEEYNTSNPD (SEQ ID NO: 120)

A216 amino acid sequence
EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSE
TQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYDR
TDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVTPKPPGGGGSGGGGSGGG
GSTIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFS
TCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIM
KEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 121)

A167 Heavy chain amino acid sequence
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGLSWVRQAPGQGLEWMGWIIPYNGNTNSA
QKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYFCARDRDYGVNYDAFDIWGQGTMVTVSSG
GGGSGGGGSGGGGSQVQLVQSGAEVKKPGSSVKVSCKASGYTFSSNVISWVRQAPGQGLE
WMGGVIPIVDIANYAQRFKGRVTITADESTSTTYMELSSLRSEDTAVYYCASTLGLVLDAMDYW
GQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC
SVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 122)

A167 Light chain amino acid sequence
SYEVTQAPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSG
SNSGNTATLTISGTQAMDEADYYCQAWDSSTAVFGGGTKLTVLGGGGSGGGGSGGGGSETV
LTQSPGTLSLSPGERATLSCRASQSLGSSYLAWYQQKPGQAPRLLIYGASSRAPGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYADSPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGECA (SEQ ID NO: 123)

Peptide linker sequence GGGSGGGSGGGS (SEQ ID NO: 124)
Peptide linker sequence GGGS (SEQ ID NO: 125)
Peptide linker sequence GSSGGSGGSGGSG (SEQ ID NO: 126)
Peptide linker sequence GSSGT (SEQ ID NO: 127)
Peptide linker sequence GGGGSGGGGSGGGS (SEQ ID NO: 128)

Peptide linker sequence AEAAAKEAAAKEAAAKA (SEQ ID NO: 129)
Peptide linker sequence GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 130)
Peptide linker sequence GGGSGGGS (SEQ ID NO: 131)
Peptide linker sequence GSGST (SEQ ID NO: 132)
Peptide linker sequence GGSS (SEQ ID NO: 133)
Peptide linker sequence GGGGS (SEQ ID NO: 134)
Peptide linker sequence GGSG (SEQ ID NO: 135)
Peptide linker sequence SGGG (SEQ ID NO: 136)
Peptide linker sequence GSGS (SEQ ID NO: 137)
Peptide linker sequence GSGSGS (SEQ ID NO:138)
Peptide linker sequence GSGSGSGS (SEQ ID NO: 139)
Peptide linker sequence GSGSGSGSGS (SEQ ID NO: 140)
Peptide linker sequence GSGSGSGSGSGS (SEQ ID NO: 141)
Peptide linker sequence GGGGSGGGGS (SEQ ID NO: 142)
Peptide linker sequence GGGGSGGGGSGGGGS (SEQ ID NO: 143)

What is claimed is:

1. An isolated multispecific antagonist comprising a first antigen-binding molecule that specifically binds to Activin or Activin-related ligand and a second antigen-binding molecule that specifically binds to TGF-β ligand, wherein the multispecific antagonist molecule simultaneously neutralizes Activin signaling and TGF-β signaling in a potent manner.

2. An isolated multispecific antagonist according to claim 1, wherein the first antigen-binding molecule specifically binds an Activin or Activin-related ligand selected from the group consisting of the Activin or Activin-related ligands comprising an amino acid sequence set forth in SEQ ID NOs: 1-9, and wherein the second antigen-binding molecule specifically binds a TGF-β ligand selected from the group consisting of the TGF-β family ligands comprising an amino acid sequence set forth in SEQ ID NOs: 18-21.

3. An isolated multispecific antagonist according to any one of claims 1 to 2, wherein the first antigen-binding polypeptide that specifically binds to Activin or Activin-related ligand ("Activin-binding polypeptide") is selected from the group consisting of an anti-Activin antibody (including anti-Activin A antibody and anti-Activin B antibody), a fragment of anti-Activin antibody, wild-type Activin Type 2A Receptor (ActRIIA) or Activin Type 2B Receptor (ActRIIB) extracellular domains (ECDs), modified ActRIIA and ActRIIB extracellular domains, wild-type and modified native Activin-binding proteins such as follistatin, follistatin-like protein and pro-peptide, and a phage display-derived polypeptide targeting Activin or Activin-related ligand; and wherein the second antigen-binding polypeptide that specifically binds to TGF-β ligand ("TGF-β-binding polypeptide") is selected from the group consisting of an anti-TGF-β antibody, a fragment of anti-TGF-β antibody, wild-type TGF-β type-2 receptors (including TGFβRIIA and TGFβRIIB) extracellular domains (ECDs), modified TGFβRIIA and TGFβRIIB extracellular domains, and a phage display-derived antagonistic polypeptide targeting TGF-β ligand.

4. An isolated multispecific antagonist molecule according to any one of claims 1 to 3, wherein the Activin-binding polypeptide is selected from the group of polypeptides comprising the amino acid sequence set forth in SEQ ID NOs: 1-17, and the TGF-β-binding polypeptide is selected from the group of polypeptides comprising the amino acid sequence set forth in SEQ ID NOs: 18-25.

5. An isolated multispecific antagonist molecule according to any one of claims 1 to 4, wherein the Activin-binding polypeptide comprises an isolated anti-Activin antibody, or antigen-binding fragment thereof, and wherein the TGF-β-binding polypeptide comprises an isolated anti-TGF-β antibody, or antigen-binding fragment thereof.

6. An isolated multispecific antagonist molecule according to claim 5, wherein the isolated anti-Activin antibody or antigen-binding fragment thereof and isolated anti-TGF-β antibody or antigen-binding fragment thereof is selected from the group consisting of monoclonal Abs (mAbs), polyclonal Abs, Ab fragments (e.g., Fab, Fab', F(ab')2, Fv, Fc, etc.), chimeric Abs, mini-Abs or domain Abs (dAbs), dual specific Abs, bispecific Abs, heteroconjugate Abs, single chain Abs (SCA), single chain variable region fragments (ScFv), humanized Abs, fully human Abs, and any other modified configuration of the immunoglobulin (Ig) molecule that comprises an antigen recognition site of the required specificity.

7. An isolated multispecific antagonist molecule according to any one of claims 5-6, wherein the isolated antibody or antigen-binding fragment thereof is selected from the group consisting of a fully human, humanized and chimeric antibody.

8. An isolated multispecific antagonist molecule according to any one of claims 5-7, wherein the Activin-binding polypeptide is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 10; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 11; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 10 and the light chain amino acid sequence set forth in SEQ ID NO: 11; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 12; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 13; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 12 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 13; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 14; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 15; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 14 and the light chain amino acid sequence set forth in SEQ ID NO: 15; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 16; an antibody comprising

the light chain variable region amino acid sequence set forth in SEQ ID NO: 17; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 16 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 17.

9. An isolated multispecific antagonist molecule according to any one of claims 5-8, wherein the TGF-β-binding polypeptide is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 22; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 23; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 22 and the light chain amino acid sequence set forth in SEQ ID NO: 23; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 24; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 25; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 24 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 25.

10. An isolated multispecific antagonist molecule according to any one of claims 1-2, wherein the multispecific antagonist molecule comprises an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NOs: 54-71.

11. An isolated multispecific antagonist molecule according to any one of claims 1-2, wherein the multispecific antagonist polypeptide is a polypeptide molecule comprising a heavy chain selected from the group consisting of a heavy chain comprising the amino acid sequence set forth in SEQ ID NOs: 72-84 and a light chain selected from the group consisting of a light chain comprising the amino acid sequence set forth in SEQ ID NOs: 11, 13, 15 , 17, 19, 21, 23 and 25.

12. An isolated bifunctional multispecific antagonist polypeptide comprising a first antigen-binding polypeptide that specifically binds to Activin ligand or Activin-related ligand (“Activin-Binding Polypeptide”) and a second antigen-binding polypeptide that specifically binds to TGF-β ligand (“TGF-β-Binding Polypeptide”) and a third antigen-binding polypeptide that specifically binds to either T-cell immune checkpoint PD-1 ligand, PD-L1 ligand or CTLA-4 ligand (“PD-1/PD-L1/CTLA-4-Binding Polypeptide”), wherein the bifunctional multispecific antagonist molecule simultaneously inhibits TGF-β, Activin, and the T-cell immune checkpoint.

13. An isolated bifunctional multispecific antagonist molecule according to claim 12, wherein the bifunctional multispecific antagonist molecule comprises a third antigen-binding polypeptide that specifically binds to PD-1 ligand ("PD-1-binding polypeptide"); wherein the PD-1-binding polypeptide is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 26; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 27; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 26 and the light chain amino acid sequence set forth in SEQ ID NO: 27; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 28; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 29; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 28 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 29; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 31; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 30 and the light chain amino acid sequence set forth in SEQ ID NO: 31; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 32; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 33; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 32 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 33; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 38; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 39; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 38 and the light chain amino acid sequence set forth in SEQ ID NO: 39; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 40; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 41; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 40 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 41; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 42; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 43; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 42 and the light chain amino acid sequence set forth in SEQ ID NO: 43; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 44; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 45; and an antibody comprising the heavy chain

variable region amino acid sequence set forth in SEQ ID NO: 44 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 45.

14. An isolated bifunctional multispecific antagonist molecule according to claim 12, wherein the bifunctional multispecific antagonist molecule comprises a third antigen-binding polypeptide that specifically binds to CTLA-4 ligand ("CTLA-4-binding polypeptide"); wherein the CTLA-4-binding polypeptide is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 34; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 35; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 34 and the light chain amino acid sequence set forth in SEQ ID NO: 35; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 36; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 37; and an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 36 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 37.

15. An isolated bifunctional multispecific antagonist molecule according to claim 12, wherein the bifunctional multispecific antagonist molecule comprises a third antigen-binding polypeptide that specifically binds to PD-L1 ligand ("PD-L1-binding polypeptide"); wherein the PD-L1-binding polypeptide is an isolated antibody selected from the group consisting of an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 46; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 47; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 46 and the light chain amino acid sequence set forth in SEQ ID NO: 47; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 48; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 49; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 48 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 49; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 50; an antibody comprising the light chain amino acid sequence set forth in SEQ ID NO: 51; an antibody comprising the heavy chain amino acid sequence set forth in SEQ ID NO: 50 and the light chain amino acid sequence set forth in SEQ ID NO: 51; an antibody comprising the heavy chain variable region amino acid sequence set forth in SEQ ID NO: 52; an antibody comprising the light chain variable region amino acid sequence set forth in SEQ ID NO: 53; and an antibody comprising the heavy chain

variable region amino acid sequence set forth in SEQ ID NO: 52 and the light chain variable region amino acid sequence set forth in SEQ ID NO: 53.

16. An isolated bifunctional multispecific antagonist molecule according to claim 12, wherein the bifunctional multispecific molecule is selected from the group consisting of: a bifunctional multispecific antagonist molecule comprising a heavy chain selected from a heavy chain comprising the amino acid sequence set forth in SEQ ID NOs: 85-120 and a light chain selected from a light chain comprising the amino acid sequence set forth in SEQ ID NOs: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51 and 53.

17. An isolated bifunctional multispecific antagonist molecule according to claim 16, wherein the bifunctional multispecific molecule is selected from the group consisting of: a bifunctional multispecific antagonist molecule comprising a heavy chain selected from a heavy chain comprising the amino acid sequence set forth in SEQ ID NOs: 85-102 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 27.

18. An isolated bifunctional multispecific antagonist molecule according to claim 16, wherein the bifunctional multispecific molecule is selected from the group consisting of: a bifunctional multispecific antagonist molecule comprising a heavy chain selected from a heavy chain comprising the amino acid sequence set forth in SEQ ID NOs: 103-120 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 35.

19. A pharmaceutical composition comprising a therapeutically effective amount of the multispecific antagonist molecule or bifunctional multispecific antagonist molecule according to any one of claims 1-18 in admixture with a pharmaceutically acceptable carrier.

20. A method of treating or preventing a disease condition whose pathogenesis involves the activation of both TNF-α-mediated NF-κB signaling pathway and Activin-mediated Smad2/3 signaling pathway, comprising administering to said subject a therapeutically effective amount of the composition of claim 19 to the subject.

21. A method according to claim 20, wherein the disease condition is selected from the group consisting of: blood disorders, ineffective erythropoiesis, anemia, pancytopenia, myelodysplastic syndromes; fibrotic diseases: NASH, liver fibrosis, pulmonary fibrosis, renal

fibrosis, polycystic kidney disease, cardiac fibrosis, muscle fibrosis, myelo fibrosis, skin fibrosis, fibrosis of the eye, multiple myeloma, acute myeloid leukemia, melanoma, muscular dystrophy, spinal muscular atrophy, spinal cord injury, stroke, nociceptive pain, neuropathic pain, sarcopenia, cancer cachexia, anorexia nervosa, bone metastasis, bone fragility, fracture, osteopenia, osteoporosis, pulmonary hypertension, myocardial infarction, heart failure, insulin resistance, diabetic nephropathy, chronic kidney disease, rheumatoid arthritis, inflammatory bowel disease, SARS-CoV, cytokine storm syndrome, sepsis, and burn injury.

22. A method of treating or preventing cancer, comprising administering to said subject a therapeutically effective amount of the composition of claim 19 to the subject, wherein the cancer is selected from the group consisting of melanoma, multiple myeloma, lung cancer, pancreatic cancer, colorectal cancer, liver cancer, gastric cancer, kidney cancer, bladder cancer, head and neck cancer, thyroid cancer, breast cancer, ovarian cancer, endometrial cancer, testicular cancer, prostate cancer and brain cancer.

23. A method according to claim 22, wherein the method further comprises co-therapy in combination with and immune checkpoint inhibitor selected from the group consisting of an anti-PD1, anti-PDL1, and anti-CTL4 antibodies.

24. An isolated nucleic acid molecule comprising a polynucleotide encoding a multispecific antagonist molecule or bifunctional multispecific antagonist molecule according to any one of claims 1-18.

25. A recombinant vector comprising the nucleic acid molecule of claim 24.

26. A host cell comprising the recombinant vector of claim 25.

27. A method for producing a multispecific antagonist molecule or bifunctional multispecific antagonist molecule of any one of claims 1-18, comprising the steps of a) transforming a host cell with vectors comprising polynucleotides encoding said multispecific antagonist molecule or bifunctional multispecific antagonist molecule, b) culturing the host cell according under conditions suitable for the expression of the multispecific antagonist molecule or bifunctional multispecific antagonist molecule and c) recovering the multispecific antagonist molecule or bifunctional multispecific antagonist molecule from the culture.

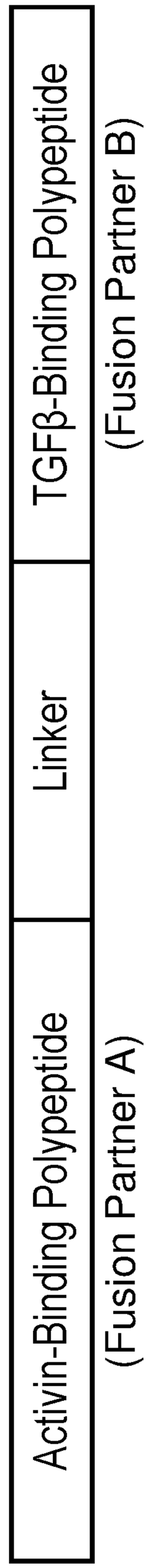

Activin-Binding Polypeptide
(Fusion Partner A)
Linker
TGFβ-Binding Polypeptide
(Fusion Partner B)

FIG. 1

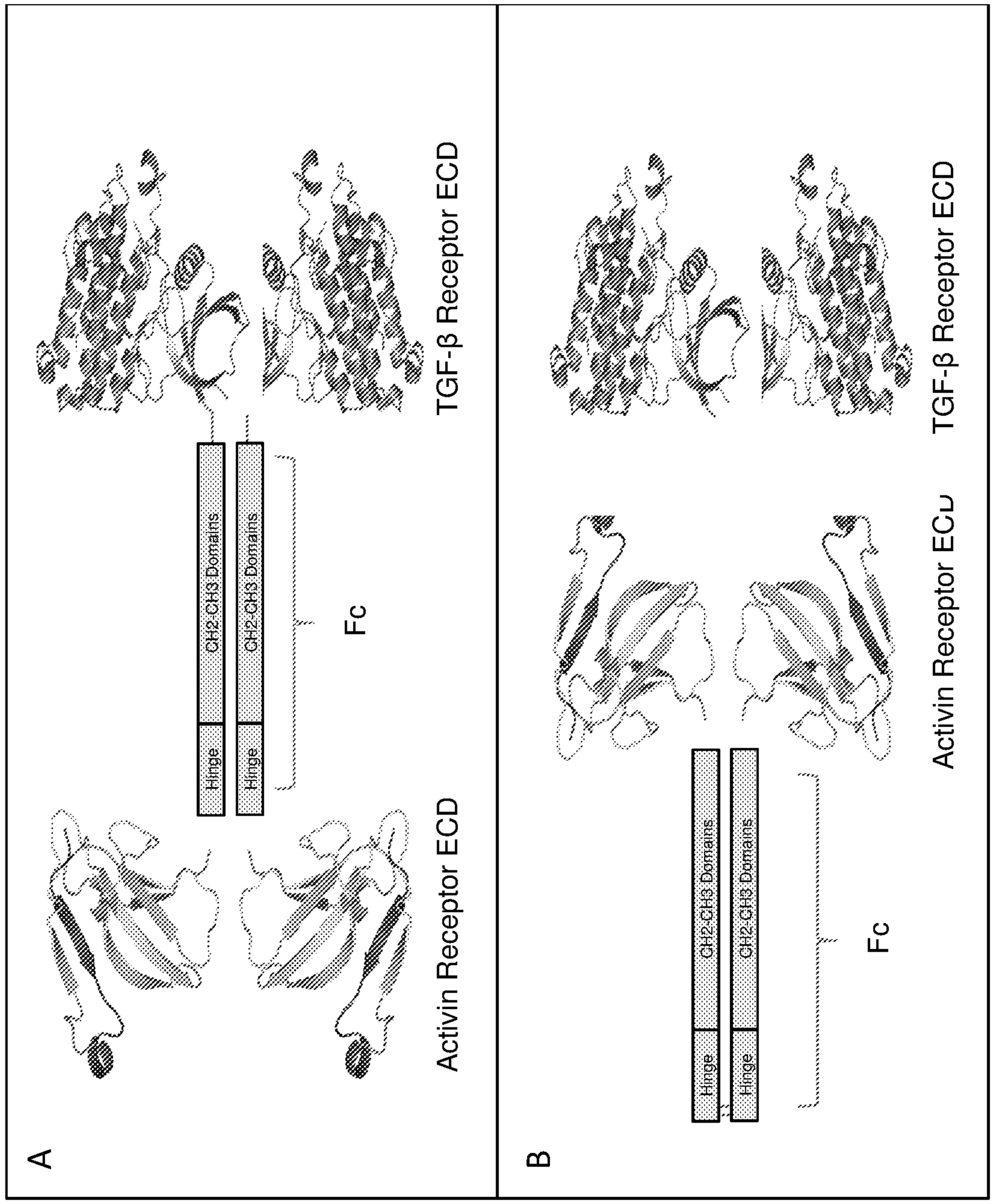

A
TGF-β Receptor ECD
Hinge
CH2-CH3 Domains
Hinge
CH2-CH3 Domains
Fc
Activin Receptor ECD
B
TGF-β Receptor ECD
Hinge
CH2-CH3 Domains
Hinge
CH2-CH3 Domains
Fc
Activin Receptor ECD

FIG. 2

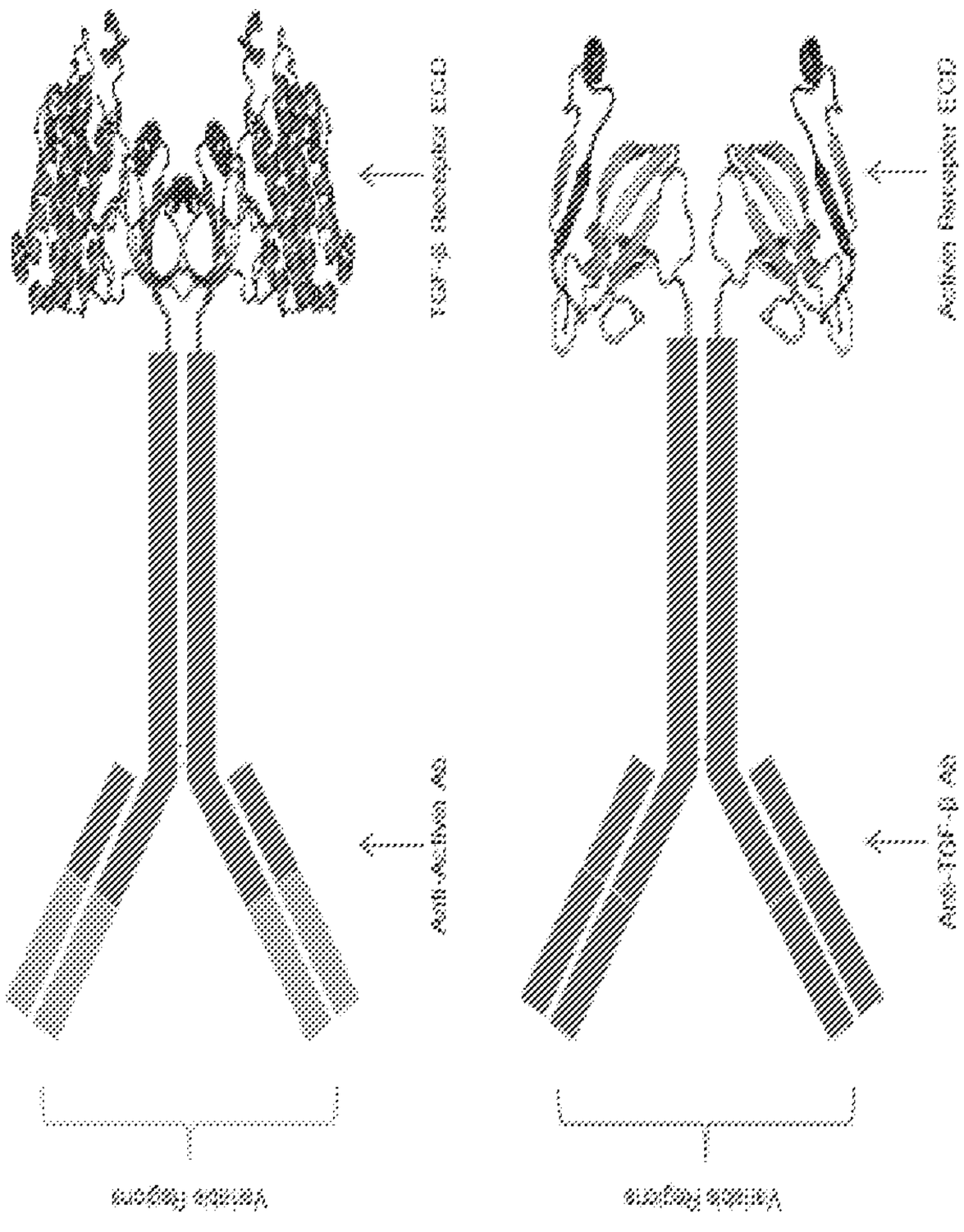

Anti-TROP-2 Ab
Anti-drug antibody Ab
Variable Region
Anti-TROP-2 Ab
Anti-drug antibody Ab
Variable Region

FIG. 3

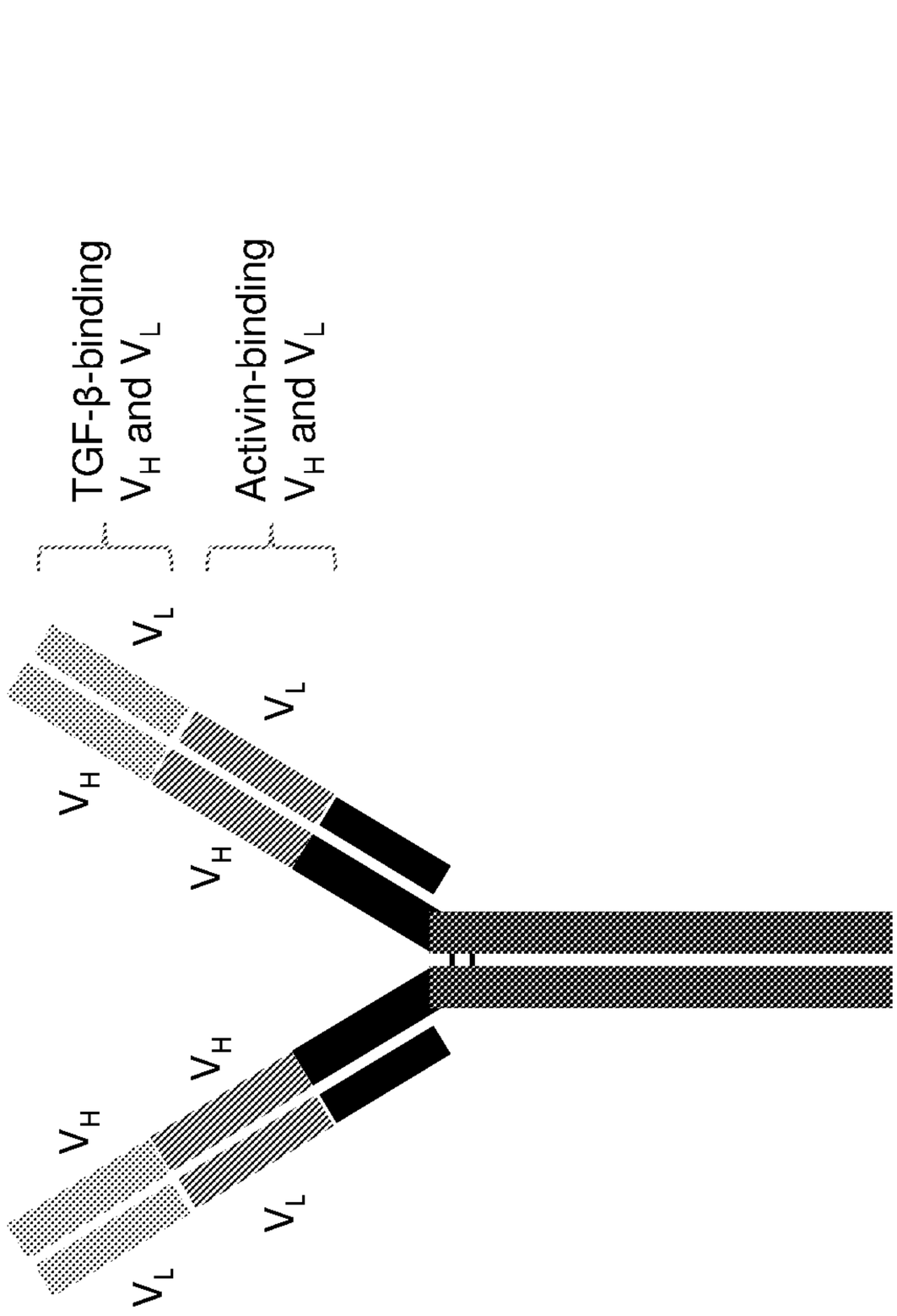

TGF-β-binding
V_H and V_L
Activin-binding
V_H and V_L
V_L
V_H
V_H
V_H
V_H
V_L
V_L
V_L

FIG. 4


TGFβ-Binding Polypeptide
(Fusion Partner C)
Linker
Activin-Binding Polypeptide
(Fusion Partner B)
Linker
Immune Checkpoint Inhibitor Polypeptide
(Fusion Partner A)

FIG. 5

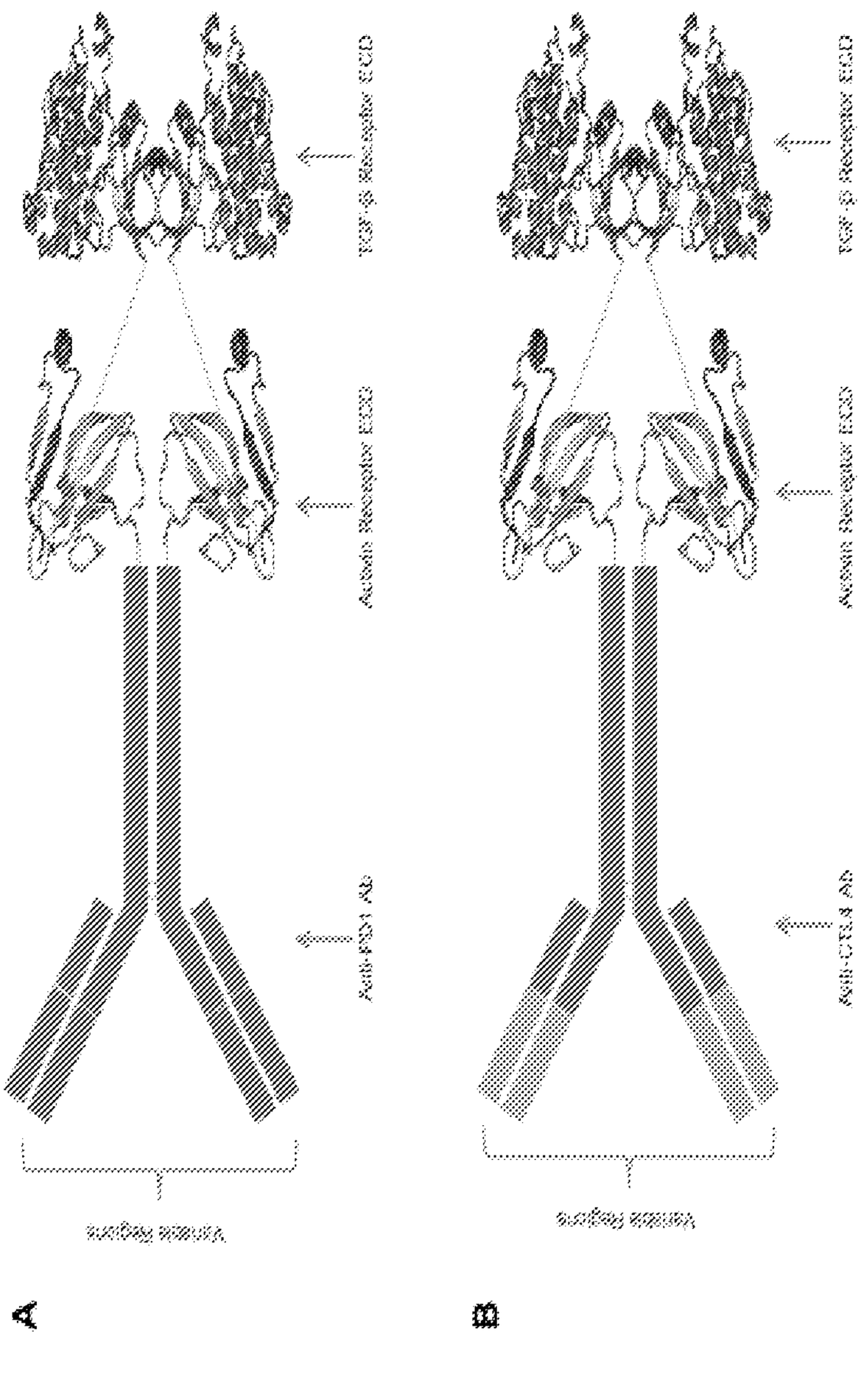

FGF-9 Receptor ECD
Anti-FGF-9 Ab
Variable Region
A
FGF-9 Receptor ECD
Anti-CD3 Ab
Variable Region
B

FIG. 6

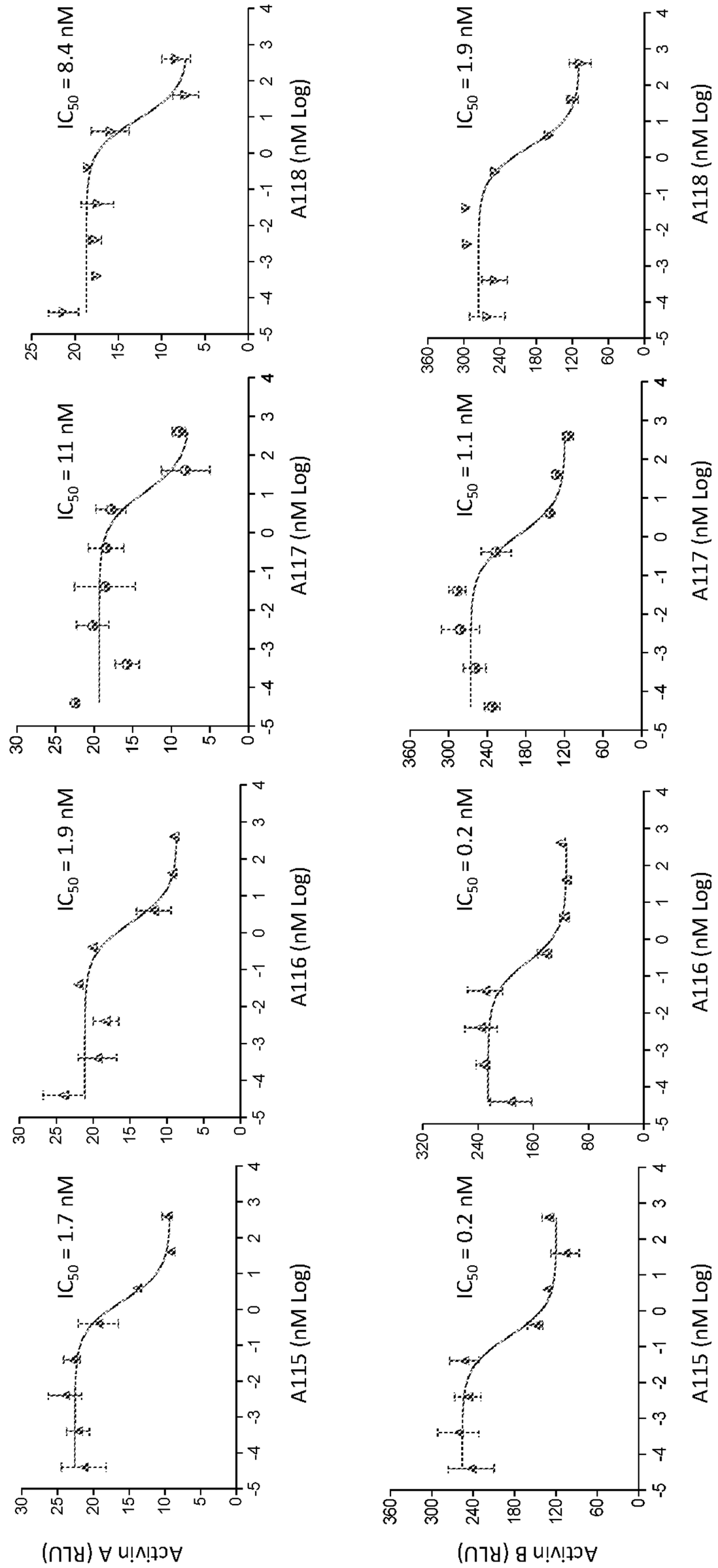

Activin A (RLU)
Activin B (RLU)
A115 (nM Log)
A116 (nM Log)
A117 (nM Log)
A118 (nM Log)
IC50 = 1.7 nM
IC50 = 0.2 nM
IC50 = 1.9 nM
IC50 = 0.2 nM
IC50 = 11 nM
IC50 = 1.1 nM
IC50 = 8.4 nM
IC50 = 1.9 nM

FIG. 7

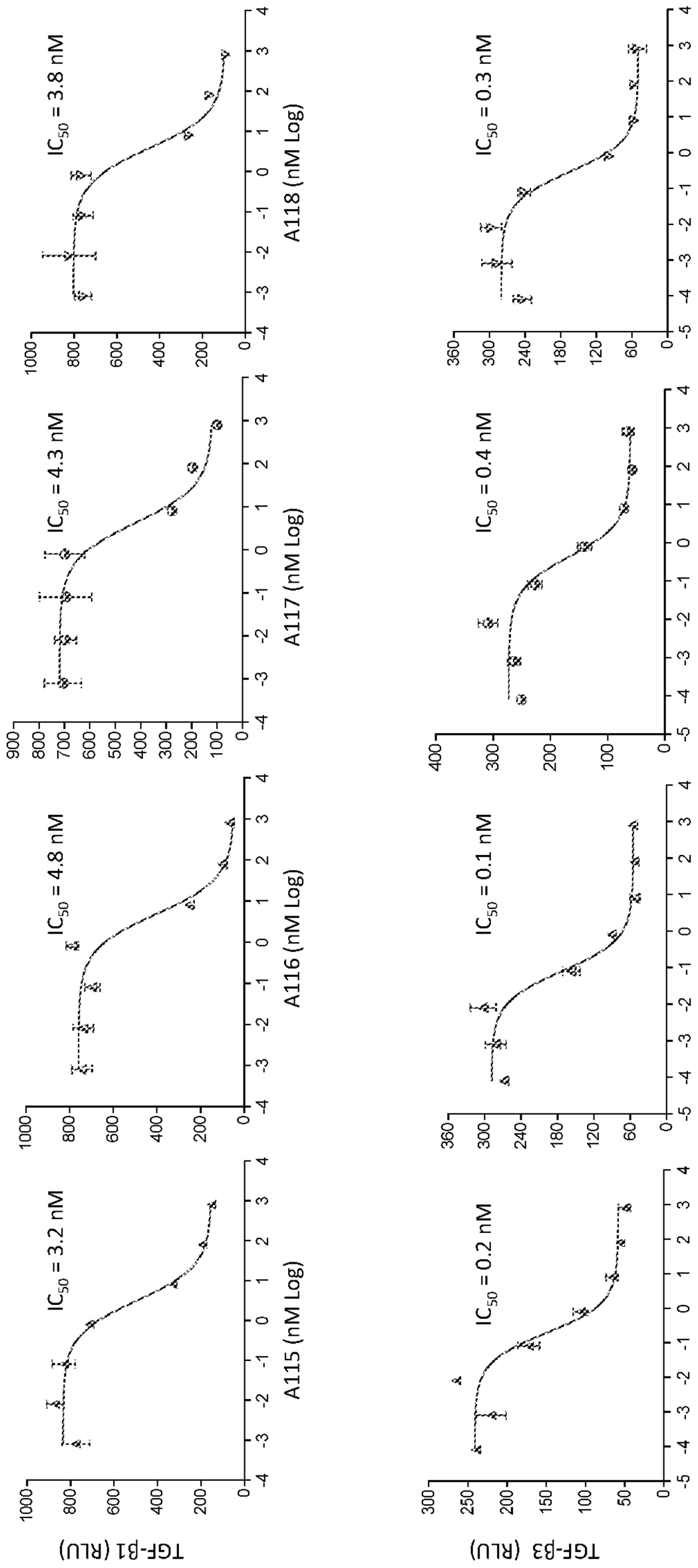

IC50 = 3.8 nM
A118 (nM Log)
IC50 = 0.3 nM
A118 (nM Log)
IC50 = 4.3 nM
A117 (nM Log)
IC50 = 0.4 nM
A117 (nM Log)
IC50 = 4.8 nM
A116 (nM Log)
IC50 = 0.1 nM
A116 (nM Log)
IC50 = 3.2 nM
A115 (nM Log)
IC50 = 0.2 nM
A115 (nM Log)
TGF-β1 (RLU)
TGF-β3 (RLU)

FIG. 8

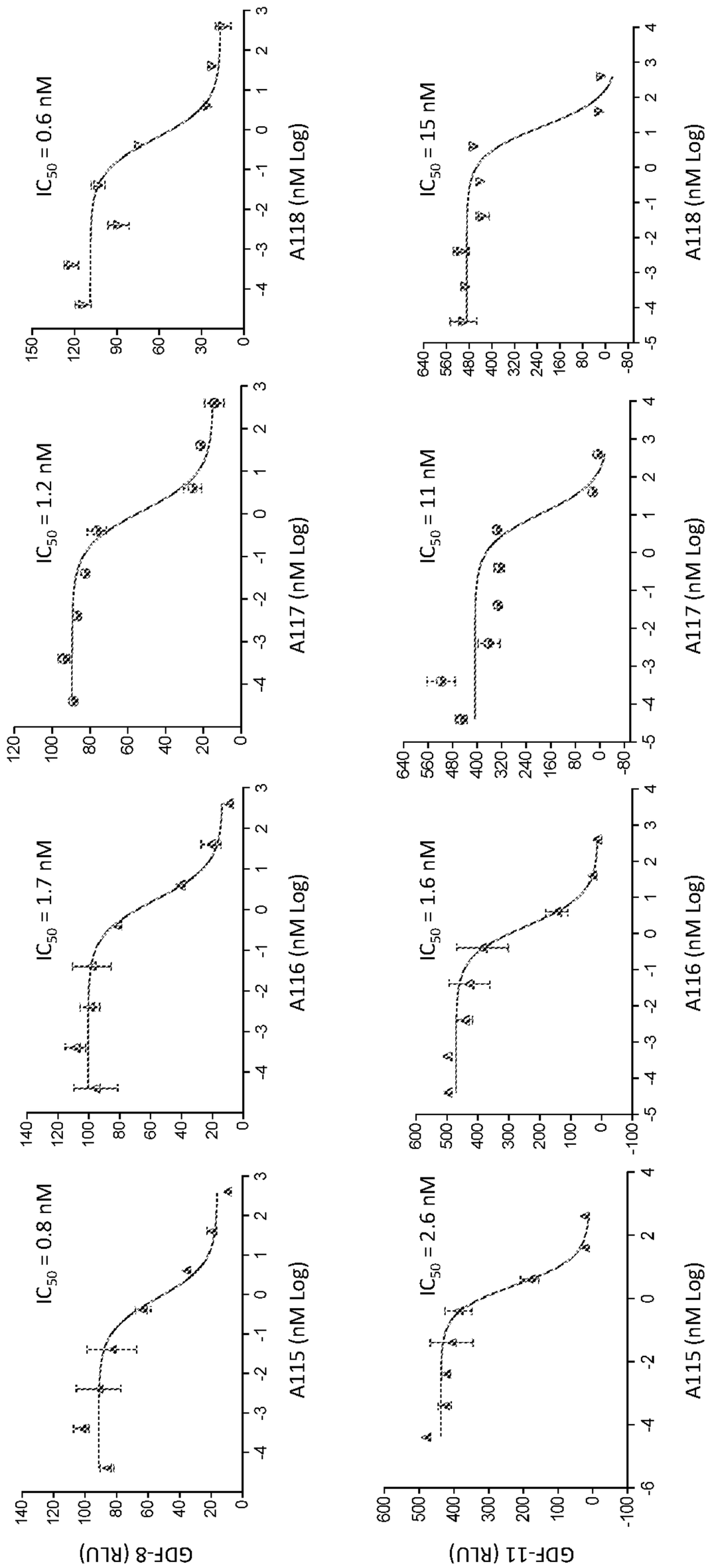

GDF-8 (RLU)
GDF-11 (RLU)
A115 (nM Log)
A116 (nM Log)
A117 (nM Log)
A118 (nM Log)
IC50 = 0.8 nM
IC50 = 2.6 nM
IC50 = 1.7 nM
IC50 = 1.6 nM
IC50 = 1.2 nM
IC50 = 11 nM
IC50 = 0.6 nM
IC50 = 15 nM

FIG.9

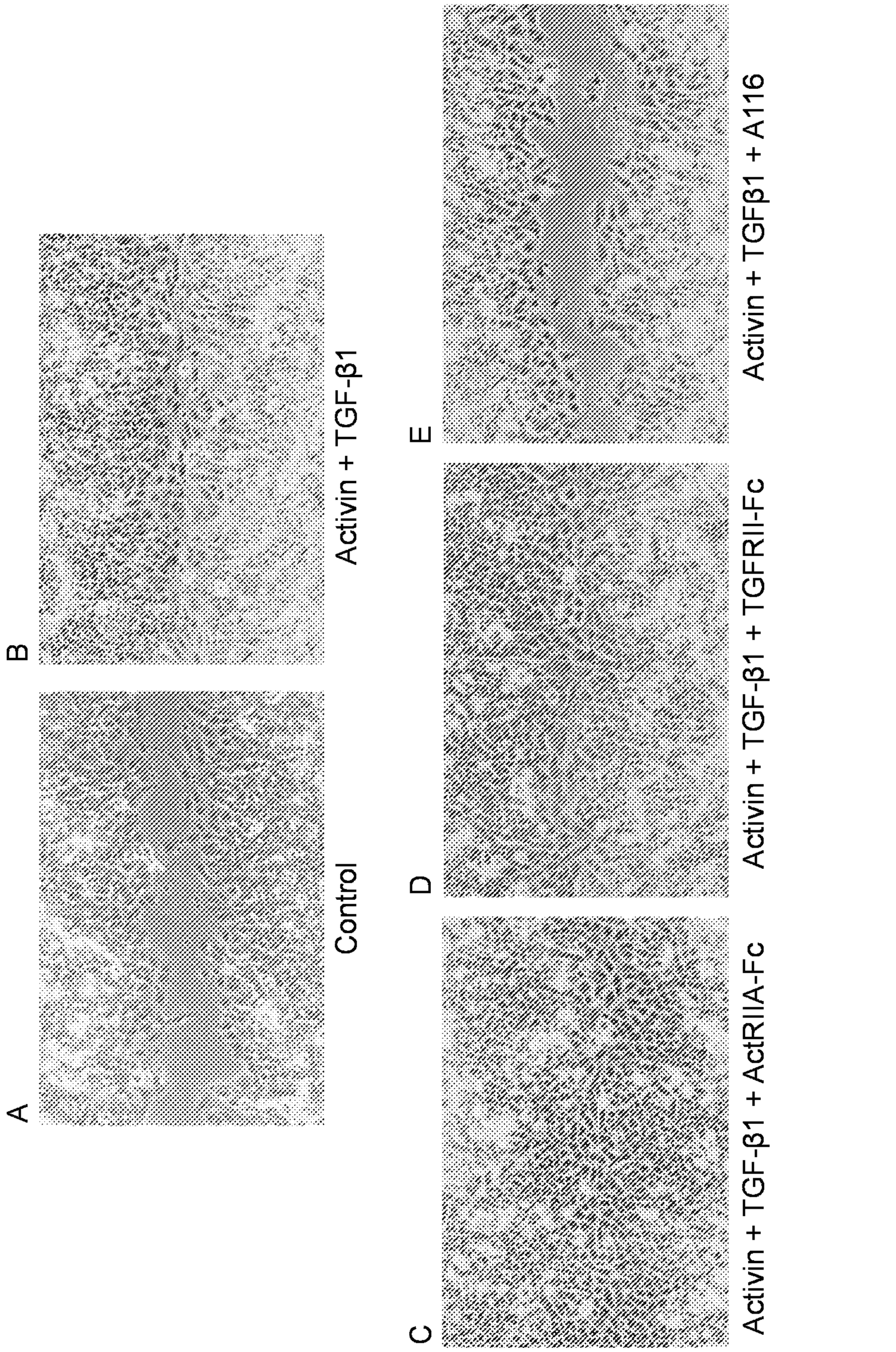

A
Control
B
Activin + TGF-β1
C
Activin + TGF-β1 + ActRIIA-Fc
D
Activin + TGF-β1 + TGFRII-Fc
E
Activin + TGFβ1 + A116

FIG.10

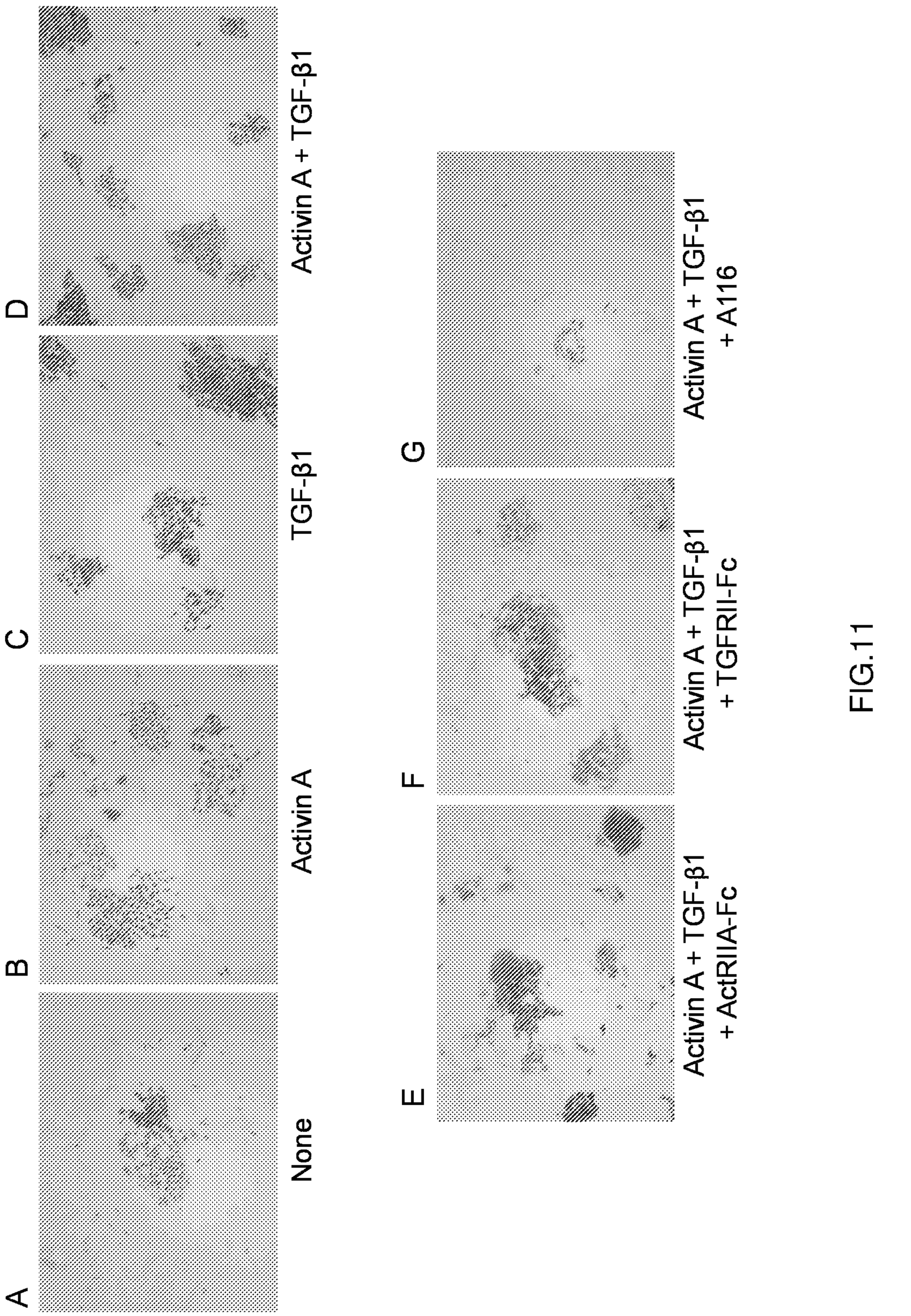

A
None
B
Activin A
C
TGF-β1
D
Activin A + TGF-β1
E
Activin A + TGF-β1 + ActRIIA-Fc
F
Activin A + TGF-β1 + TGFRII-Fc
G
Activin A + TGF-β1 + A116

FIG.11

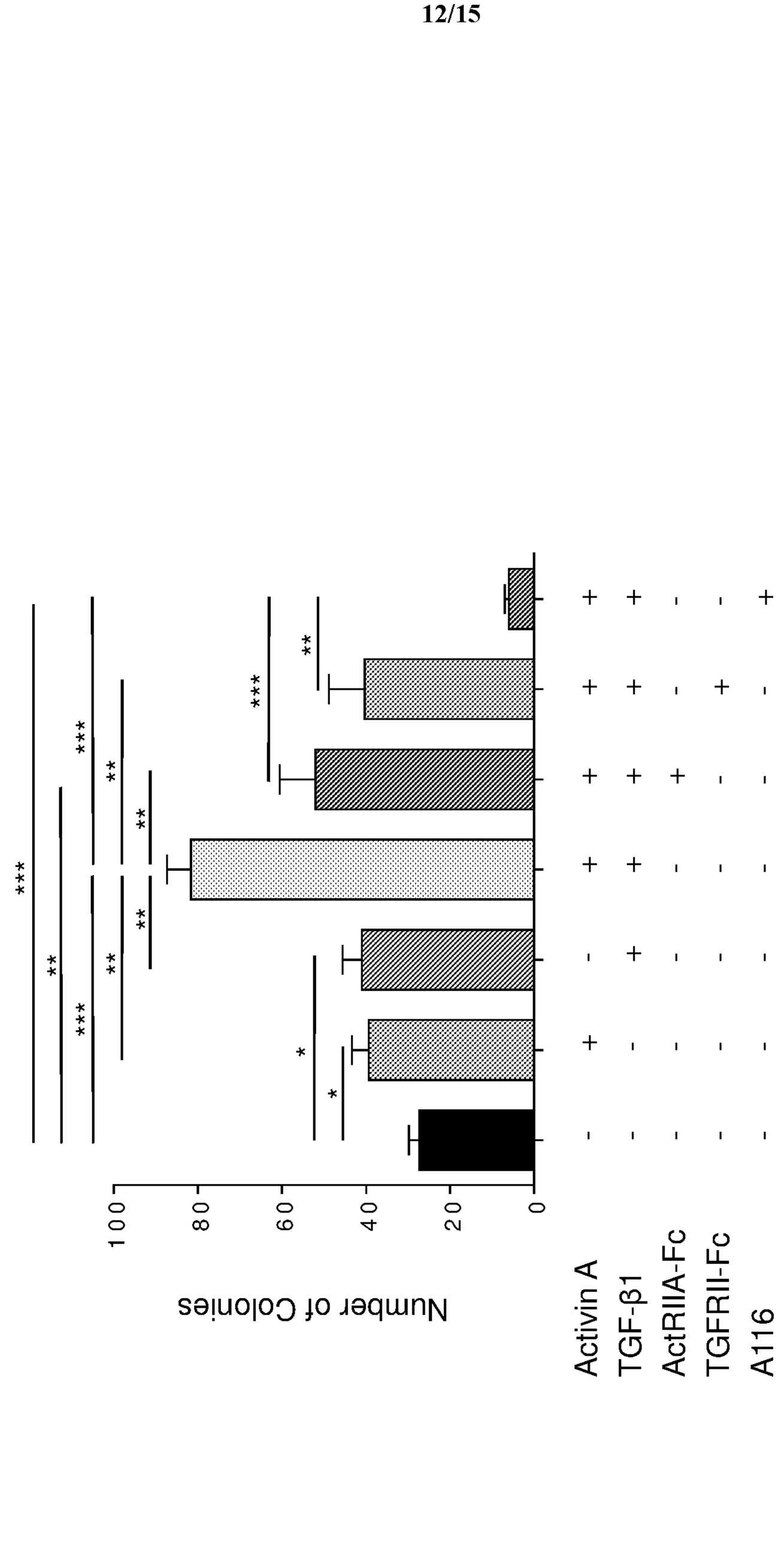

Number of Colonies
0
20
40
60
80
100
*
*
**
***
**
**
**
***
**
***
***
Activin A
TGF-β1
ActRIIA-Fc
TGFRII-Fc
A116
- + + + + + -
- - - - + - +
- - - + - - -
- + + + + + -
*: P<0.05; **: p<0.01; ***: p<0.001

FIG.12

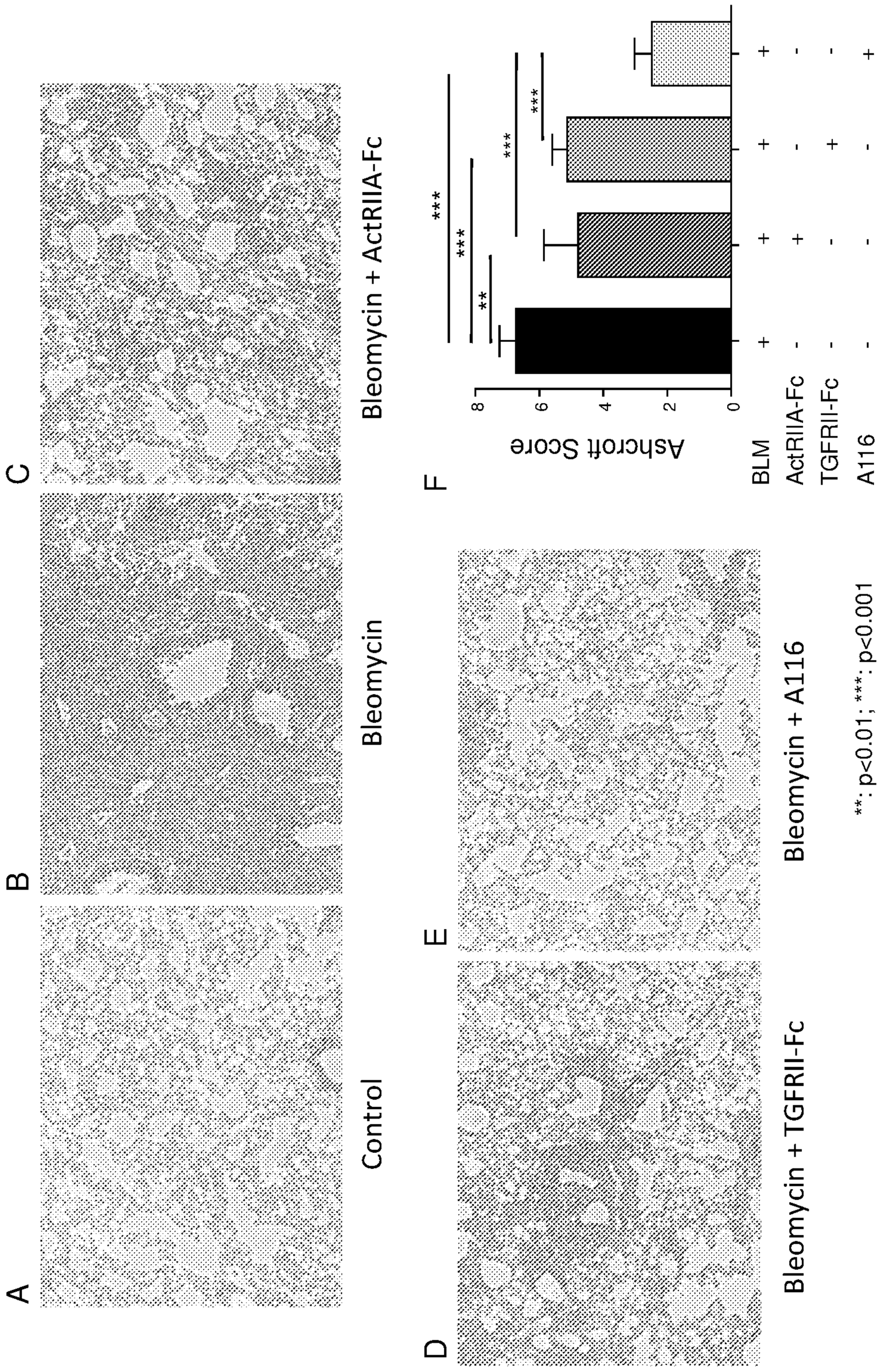
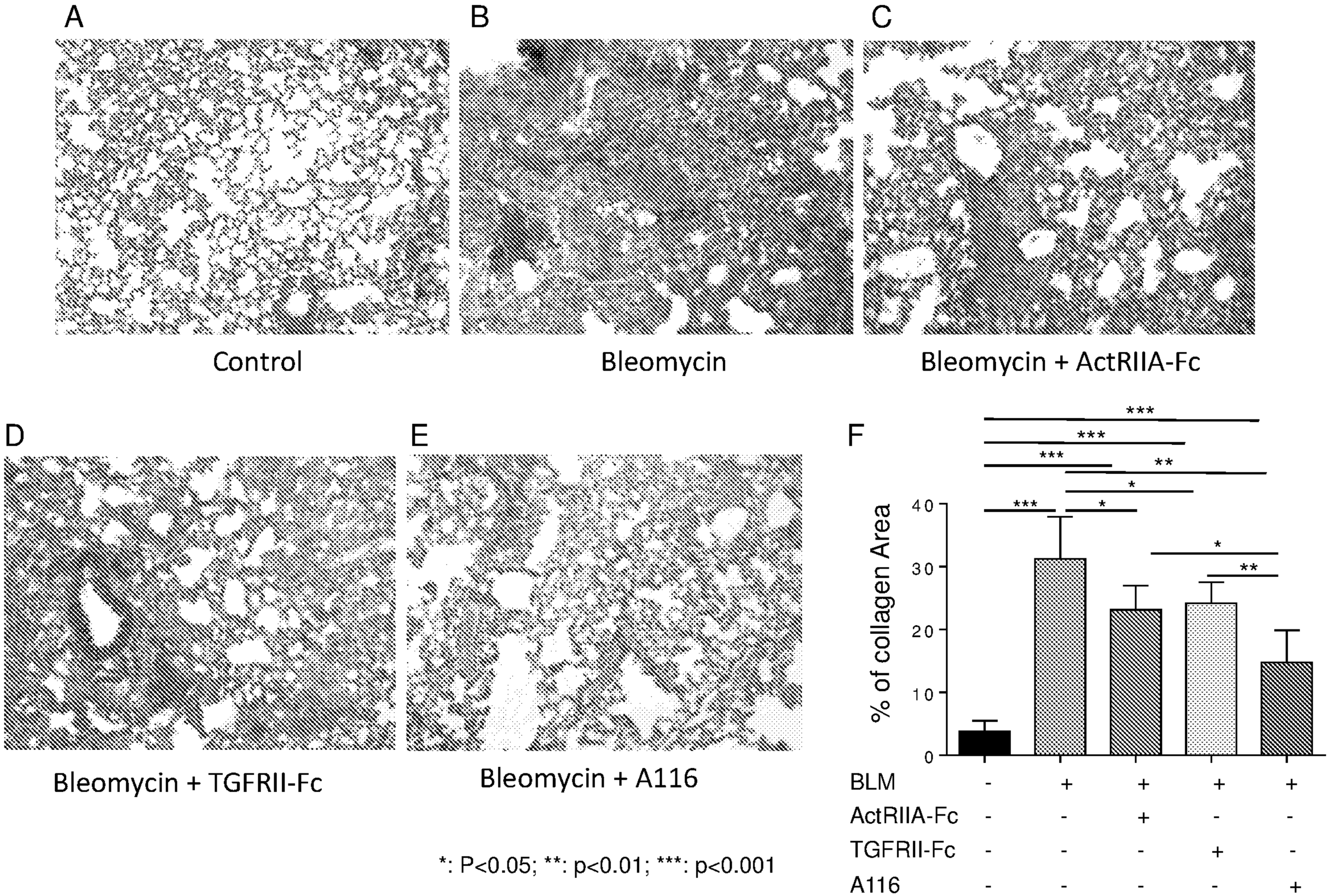

A
Control
B
Bleomycin
C
Bleomycin + ActRIIA-Fc
D
Bleomycin + TGFRII-Fc
E
Bleomycin + A116
F
Ashcroft Score
0
2
4
6
8
**
***
***
***
***
BLM + + + +
ActRIIA-Fc - + - -
TGFRII-Fc - - + -
A116 - - - +
**: p<0.01; ***: p<0.001

FIG.13



*: P<0.05; **: p<0.01; ***: p<0.001

FIG.14

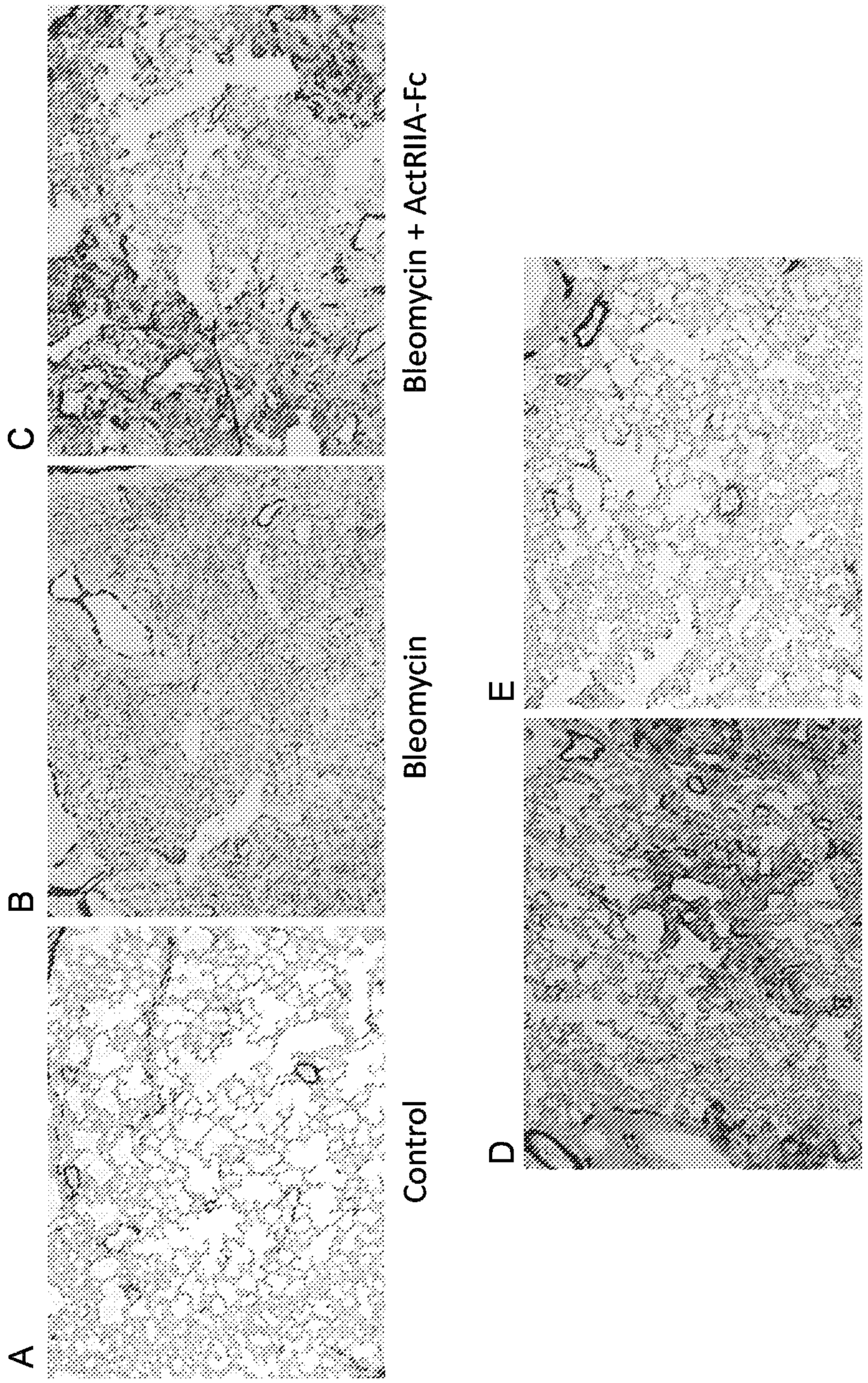

A
Control
B
Bleomycin
C
Bleomycin + ActRIIA-Fc
D
Bleomycin + TGFRII-Fc
E
Bleomycin + A116

FIG.15

SEQUENCE LISTING

<110> HAN, HQ
ZHOU, XIAOLAN

<120> NOVEL BIFUNCTIONAL MULTISPECIFIC ANTAGONISTS CAPABLE OF INHIBITING MULTIPLE LIGANDS OF TGF-BETA FAMILY AND USES THEREOF

<130> CACAG1.0009WO

<160> 143

<170> PatentIn version 3.5

<210> 1
<211> 110
<212> PRT
<213> Homo sapiens

<400> 1

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1 5 10 15

Thr Asn Gln Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg
20 25 30

Arg His Cys Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile
35 40 45

Val Lys Gln Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr
50 55 60

Asp Cys Val Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys
65 70 75 80

Glu Gly Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro Glu Met Glu
85 90 95

Val Thr Gln Pro Thr Ser Asn Pro Val Thr Pro Lys Pro Pro
100 105 110

<210> 2

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<213> Homo sapiens

<400> 2

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1 5 10 15

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20 25 30

Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
35 40 45

Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
50 55 60

Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65 70 75 80

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
85 90 95

Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr
100 105 110

<210> 3
<211> 315
<212> PRT
<213> Homo sapiens

<400> 3

Gly Asn Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu
1 5 10 15

Tyr Lys Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu
20 25 30

Ser Thr Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys

```
        35                  40                  45

Trp Met Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu
    50                  55                  60

Thr Cys Glu Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn
65                  70                  75                  80

Lys Lys Asn Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile
                85                  90                  95

Thr Trp Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn
            100                 105                 110

Glu Cys Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu
        115                 120                 125

Val Gln Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys
    130                 135                 140

Pro Gly Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys
145                 150                 155                 160

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

Leu Cys Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg
            180                 185                 190

Lys Ala Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly
        195                 200                 205

Lys Cys Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly
    210                 215                 220

Lys Lys Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu
225                 230                 235                 240
```

```
Cys Asp Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala
                245                 250                 255


Ser Asp Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala
            260                 265                 270


Cys Ser Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
        275                 280                 285


Ser Ile Ser Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp
    290                 295                 300


Tyr Ser Phe Pro Ile Ser Ser Ile Leu Glu Trp
305                 310                 315


<210>  4
<211>  315
<212>  PRT
<213>  Homo sapiens

<400>  4

Gly Asn Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu
1               5                   10                  15


Tyr Lys Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu
            20                  25                  30


Ser Thr Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys
        35                  40                  45


Trp Met Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu
    50                  55                  60


Thr Cys Glu Asn Val Asp Cys Gly Pro Gly Gln Ser Cys Val Val Asp
65                  70                  75                  80


Gln Thr Gly Ser Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile
                85                  90                  95
```

```
Thr Trp Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn
            100                 105                 110

Glu Cys Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu
        115                 120                 125

Val Gln Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys
    130                 135                 140

Pro Gly Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys
145                 150                 155                 160

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

Leu Cys Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg
            180                 185                 190

Lys Ala Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly
        195                 200                 205

Lys Cys Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly
    210                 215                 220

Lys Lys Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu
225                 230                 235                 240

Cys Asp Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala
                245                 250                 255

Ser Asp Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala
            260                 265                 270

Cys Ser Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
        275                 280                 285
```

```
Ser Ile Ser Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp
    290                 295                 300

Tyr Ser Phe Pro Ile Ser Ser Ile Leu Glu Trp
305                 310                 315
```

<210> 5
<211> 288
<212> PRT
<213> Homo sapiens

<400> 5

```
Gly Asn Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu
1               5                   10                  15

Tyr Lys Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu
            20                  25                  30

Ser Thr Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys
        35                  40                  45

Trp Met Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu
    50                  55                  60

Thr Cys Glu Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn
65                  70                  75                  80

Lys Lys Asn Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile
                85                  90                  95

Thr Trp Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn
            100                 105                 110

Glu Cys Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu
        115                 120                 125

Val Gln Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys
    130                 135                 140
```

```
Pro Gly Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys
145                 150                 155                 160


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


Leu Cys Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg
            180                 185                 190


Lys Ala Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly
        195                 200                 205


Lys Cys Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly
    210                 215                 220


Lys Lys Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu
225                 230                 235                 240


Cys Asp Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala
                245                 250                 255


Ser Asp Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala
            260                 265                 270


Cys Ser Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
        275                 280                 285


<210>  6
<211>  110
<212>  PRT
<213>  Artificial

<220>
<223>  Modified human ActRIIB ECD

<400>  6

Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1               5                   10                  15
```

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

Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45

Val Lys Lys Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Gln
    50                  55                  60

Glu Cys Val Ala Thr Lys Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95

Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr
            100                 105                 110
```

<210> 7
<211> 110
<212> PRT
<213> Artificial

<220>
<223> Modified human ActRIIB ECD

<400> 7

```
Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1               5                   10                  15

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

Arg His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45

Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60
```

```
Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80


Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95


Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr
            100                 105                 110


<210>  8
<211>  107
<212>  PRT
<213>  Artificial

<220>
<223>  Modified human ActRIIB ECD

<400>  8

Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1               5                   10                  15


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


Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45


Val Lys Lys Gly Cys Trp Asp Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60


Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80


Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95


Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr
            100                 105
```

<210> 9
<211> 109
<212> PRT
<213> Artificial

<220>
<223> Modified human ActRIIA ECD

<400> 9

Gly Ala Ile Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Tyr Asn
1 5 10 15

Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Thr Gly Val Glu Pro Cys
20 25 30

Glu Gly Glu Lys Asp Lys Arg Leu His Cys Tyr Ala Thr Trp Arg Asn
35 40 45

Ile Ser Gly Ser Ile Glu Ile Val Lys Lys Gly Cys Trp Leu Asp Asp
50 55 60

Phe Asn Cys Tyr Asp Arg Thr Asp Cys Val Glu Thr Glu Glu Asn Pro
65 70 75 80

Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe
85 90 95

Ser Tyr Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser
100 105

<210> 10
<211> 452
<212> PRT
<213> Artificial

<220>
<223> Anti-Activin antibody heavy chain amino acid sequence

<400> 10

Gln Val Gln Leu Val Gln Ser Gly Ala 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 Ser Tyr
            20                  25                  30

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

Gly Trp Ile Ile Pro Tyr Asn Gly Asn Thr Asn Ser Ala Gln Lys Leu
    50                  55                  60

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

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

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

Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

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

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

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205
```

```
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

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

His Glu Asp Pro Glu Val Lys Phe Asn Val Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

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

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

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

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
```

405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly Lys
450

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

<220>
<223> Anti-Activin A antibody light chain amino acid sequence

<400> 11

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

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

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

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg Thr Val Ala Ala Pro

```
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

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

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205

Asn Arg Gly Glu Cys
    210


<210>  12
<211>  122
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-Activin A antibody heavy chain variable region amino acid
       sequence

<400>  12

Gln Val Gln Leu Val Gln Ser Gly Ala 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 Ser Tyr
            20                  25                  30
```

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


Gly Trp Ile Ile Pro Tyr Asn Gly Asn Thr Asn Ser Ala Gln Lys Leu
    50                  55                  60


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


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


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


Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120
```

<210> 13
<211> 106
<212> PRT
<213> Artificial

<220>
<223> Anti-Activin A antibody light chain variable region amino acid sequence

<400> 13

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


Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
            20                  25                  30


Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
        35                  40                  45


Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60
```

```
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65                  70                  75                  80


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


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


<210>  14
<211>  453
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-Activin A antibody heavy chain amino acid sequence

<400>  14

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


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Phe Ser Ser His
            20                  25                  30


Phe Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Leu Tyr Thr Gly Gly Thr Ser Phe Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Ser Met Ser Val Gly Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Ala Arg Ser Gly Ile Thr Phe Thr Gly Ile Ile Val Pro Gly Ser
            100                 105                 110
```

```
Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser
        115                 120                 125

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

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

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

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

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

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

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

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

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

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
```

305 310 315 320

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

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

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

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
370 375 380

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385 390 395 400

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
420 425 430

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

Leu Ser Leu Gly Lys
450

<210> 15
<211> 215
<212> PRT
<213> Artificial

<220>
<223> Anti-Activin A antibody light chain amino acid sequence

<400> 15

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 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> 16
<211> 126
<212> PRT
<213> Artificial

<220>
<223> Anti-Activin A antibody heavy chain variable region amino acid
       sequence

<400> 16

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Phe Ser Ser His
            20   25   30

Phe Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

Gly Tyr Ile Leu Tyr Thr Gly Gly Thr Ser Phe Asn Pro Ser Leu Lys
    50   55   60

Ser Arg Val Ser Met Ser Val Gly Thr Ser Lys Asn Gln Phe Ser Leu
65   70   75   80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Arg Ala Arg Ser Gly Ile Thr Phe Thr Gly Ile Ile Val Pro Gly Ser
            100   105   110

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

<210> 17
<211> 108

<212> PRT
<213> Artificial

<220>
<223> Anti-Activin A antibody light chain variable region amino acid sequence

<400> 17

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 Ser Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 18
<211> 567
<212> PRT
<213> Homo sapiens

<400> 18

Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu
1 5 10 15

Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Val
20 25 30

```
Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
        35                  40                  45

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
    50                  55                  60

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
65                  70                  75                  80

Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
                85                  90                  95

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

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
        115                 120                 125

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
    130                 135                 140

Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Leu
145                 150                 155                 160

Leu Leu Val Ile Phe Gln Val Thr Gly Ile Ser Leu Leu Pro Pro Leu
                165                 170                 175

Gly Val Ala Ile Ser Val Ile Ile Ile Phe Tyr Cys Tyr Arg Val Asn
            180                 185                 190

Arg Gln Gln Lys Leu Ser Ser Thr Trp Glu Thr Gly Lys Thr Arg Lys
        195                 200                 205

Leu Met Glu Phe Ser Glu His Cys Ala Ile Ile Leu Glu Asp Asp Arg
    210                 215                 220
```

```
Ser Asp Ile Ser Ser Thr Cys Ala Asn Asn Ile Asn His Asn Thr Glu
225                 230                 235                 240

Leu Leu Pro Ile Glu Leu Asp Thr Leu Val Gly Lys Gly Arg Phe Ala
                245                 250                 255

Glu Val Tyr Lys Ala Lys Leu Lys Gln Asn Thr Ser Glu Gln Phe Glu
            260                 265                 270

Thr Val Ala Val Lys Ile Phe Pro Tyr Glu Glu Tyr Ala Ser Trp Lys
        275                 280                 285

Thr Glu Lys Asp Ile Phe Ser Asp Ile Asn Leu Lys His Glu Asn Ile
    290                 295                 300

Leu Gln Phe Leu Thr Ala Glu Glu Arg Lys Thr Glu Leu Gly Lys Gln
305                 310                 315                 320

Tyr Trp Leu Ile Thr Ala Phe His Ala Lys Gly Asn Leu Gln Glu Tyr
                325                 330                 335

Leu Thr Arg His Val Ile Ser Trp Glu Asp Leu Arg Lys Leu Gly Ser
            340                 345                 350

Ser Leu Ala Arg Gly Ile Ala His Leu His Ser Asp His Thr Pro Cys
        355                 360                 365

Gly Arg Pro Lys Met Pro Ile Val His Arg Asp Leu Lys Ser Ser Asn
    370                 375                 380

Ile Leu Val Lys Asn Asp Leu Thr Cys Cys Leu Cys Asp Phe Gly Leu
385                 390                 395                 400

Ser Leu Arg Leu Asp Pro Thr Leu Ser Val Asp Asp Leu Ala Asn Ser
                405                 410                 415

Gly Gln Val Gly Thr Ala Arg Tyr Met Ala Pro Glu Val Leu Glu Ser
            420                 425                 430
```

Arg Met Asn Leu Glu Asn Val Glu Ser Phe Lys Gln Thr Asp Val Tyr
        435   440   445

Ser Met Ala Leu Val Leu Trp Glu Met Thr Ser Arg Cys Asn Ala Val
    450   455   460

Gly Glu Val Lys Asp Tyr Glu Pro Pro Phe Gly Ser Lys Val Arg Glu
465   470   475   480

His Pro Cys Val Glu Ser Met Lys Asp Asn Val Leu Arg Asp Arg Gly
                485   490   495

Arg Pro Glu Ile Pro Ser Phe Trp Leu Asn His Gln Gly Ile Gln Met
            500   505   510

Val Cys Glu Thr Leu Thr Glu Cys Trp Asp His Asp Pro Glu Ala Arg
        515   520   525

Leu Thr Ala Gln Cys Val Ala Glu Arg Phe Ser Glu Leu Glu His Leu
    530   535   540

Asp Arg Leu Ser Gly Arg Ser Cys Ser Glu Glu Lys Ile Pro Glu Asp
545   550   555   560

Gly Ser Leu Asn Thr Thr Lys
                565

<210> 19
<211> 137
<212> PRT
<213> Homo sapiens

<400> 19

Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
1   5   10   15

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys

```
            20                  25                  30

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
        35                  40                  45

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
    50                  55                  60

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
65                  70                  75                  80

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
                85                  90                  95

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
            100                 105                 110

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
        115                 120                 125

Glu Glu Tyr Asn Thr Ser Asn Pro Asp
    130                 135
```

<210> 20
<211> 592
<212> PRT
<213> Homo sapiens

<400> 20

```
Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu
1               5                   10                  15

Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp
            20                  25                  30

Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn
        35                  40                  45
```

```
Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr
    50                  55                  60

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
65                  70                  75                  80

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
                85                  90                  95

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
            100                 105                 110

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
        115                 120                 125

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
    130                 135                 140

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
145                 150                 155                 160

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
                165                 170                 175

Glu Tyr Asn Thr Ser Asn Pro Asp Leu Leu Leu Val Ile Phe Gln Val
            180                 185                 190

Thr Gly Ile Ser Leu Leu Pro Pro Leu Gly Val Ala Ile Ser Val Ile
        195                 200                 205

Ile Ile Phe Tyr Cys Tyr Arg Val Asn Arg Gln Gln Lys Leu Ser Ser
    210                 215                 220

Thr Trp Glu Thr Gly Lys Thr Arg Lys Leu Met Glu Phe Ser Glu His
225                 230                 235                 240

Cys Ala Ile Ile Leu Glu Asp Asp Arg Ser Asp Ile Ser Ser Thr Cys
                245                 250                 255
```

```
Ala Asn Asn Ile Asn His Asn Thr Glu Leu Leu Pro Ile Glu Leu Asp
            260                 265                 270

Thr Leu Val Gly Lys Gly Arg Phe Ala Glu Val Tyr Lys Ala Lys Leu
        275                 280                 285

Lys Gln Asn Thr Ser Glu Gln Phe Glu Thr Val Ala Val Lys Ile Phe
    290                 295                 300

Pro Tyr Glu Glu Tyr Ala Ser Trp Lys Thr Glu Lys Asp Ile Phe Ser
305                 310                 315                 320

Asp Ile Asn Leu Lys His Glu Asn Ile Leu Gln Phe Leu Thr Ala Glu
                325                 330                 335

Glu Arg Lys Thr Glu Leu Gly Lys Gln Tyr Trp Leu Ile Thr Ala Phe
            340                 345                 350

His Ala Lys Gly Asn Leu Gln Glu Tyr Leu Thr Arg His Val Ile Ser
        355                 360                 365

Trp Glu Asp Leu Arg Lys Leu Gly Ser Ser Leu Ala Arg Gly Ile Ala
    370                 375                 380

His Leu His Ser Asp His Thr Pro Cys Gly Arg Pro Lys Met Pro Ile
385                 390                 395                 400

Val His Arg Asp Leu Lys Ser Ser Asn Ile Leu Val Lys Asn Asp Leu
                405                 410                 415

Thr Cys Cys Leu Cys Asp Phe Gly Leu Ser Leu Arg Leu Asp Pro Thr
            420                 425                 430

Leu Ser Val Asp Asp Leu Ala Asn Ser Gly Gln Val Gly Thr Ala Arg
        435                 440                 445
```

```
Tyr Met Ala Pro Glu Val Leu Glu Ser Arg Met Asn Leu Glu Asn Val
    450                 455                 460

Glu Ser Phe Lys Gln Thr Asp Val Tyr Ser Met Ala Leu Val Leu Trp
465                 470                 475                 480

Glu Met Thr Ser Arg Cys Asn Ala Val Gly Glu Val Lys Asp Tyr Glu
                485                 490                 495

Pro Pro Phe Gly Ser Lys Val Arg Glu His Pro Cys Val Glu Ser Met
            500                 505                 510

Lys Asp Asn Val Leu Arg Asp Arg Gly Arg Pro Glu Ile Pro Ser Phe
        515                 520                 525

Trp Leu Asn His Gln Gly Ile Gln Met Val Cys Glu Thr Leu Thr Glu
    530                 535                 540

Cys Trp Asp His Asp Pro Glu Ala Arg Leu Thr Ala Gln Cys Val Ala
545                 550                 555                 560

Glu Arg Phe Ser Glu Leu Glu His Leu Asp Arg Leu Ser Gly Arg Ser
                565                 570                 575

Cys Ser Glu Glu Lys Ile Pro Glu Asp Gly Ser Leu Asn Thr Thr Lys
            580                 585                 590
```

<210> 21
<211> 162
<212> PRT
<213> Homo sapiens

<400> 21

```
Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln
1               5                   10                  15

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

```
Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val
        35                  40                  45

Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys
    50                  55                  60

Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys
65                  70                  75                  80

Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu
                85                  90                  95

Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His
            100                 105                 110

Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu
        115                 120                 125

Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp
    130                 135                 140

Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn
145                 150                 155                 160

Pro Asp
```

<210> 22
<211> 447
<212> PRT
<213> Artificial

<220>
<223> Anti-TGF-Beta antibody heavy chain amino acid sequence

<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 Tyr Thr Phe Ser Ser Asn
            20                  25                  30

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

Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu 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 Ser 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>  23
<211>  215
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-TGF-Beta antibody light chain amino acid sequence

<400>  23

Glu Thr 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 Leu 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 Ser Ser Arg Ala Pro 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 Ala Asp Ser Pro
                85                  90                  95


Ile Thr Phe Gly Gln Gly Thr Arg Leu 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> 24
<211> 120
<212> PRT
<213> Artificial

<220>
<223> Anti-TGF-Beta antibody heavy chain variable region amino acid sequence

<400> 24

```
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 Tyr Thr Phe Ser Ser Asn
            20                  25                  30

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

Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60
```

```
Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  25
<211>  108
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-TGF-Beta antibody light chain variable region amino acid
       sequence

<400>  25

Glu Thr 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 Leu 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 Ser Ser Arg Ala Pro 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 Ala Asp Ser Pro
```

85 90 95

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 26
<211> 447
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody heavy chain amino acid sequence

<400> 26

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> 27
<211> 218
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody light chain amino acid sequence

<400> 27

```
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> 28
<211> 120
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody heavy chain variable region amino acid sequence

<400> 28

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
        115   120

<210> 29
<211> 111
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody light chain variable region amino acid sequence

<400> 29

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
            100   105   110

<210> 30
<211> 440
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody heavy chain amino acid sequence

<400> 30

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> 31
<211> 214
<212> PRT

<213> Artificial

<220>
<223> Anti-PD1 antibody light chain amino acid sequence

<400> 31

```
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> 32
<211> 113
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody heavy chain variable region amino acid sequence

<400> 32

```
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

<210> 33
<211> 107
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody light chain variable region amino acid sequence

<400> 33

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
100 105

<210> 34
<211> 448
<212> PRT
<213> Artificial

<220>
<223> Anti-CTLA-4 antibody heavy chain amino acid sequence

<400> 34

```
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 Lys
435 440 445

<210> 35
<211> 215
<212> PRT
<213> Artificial

<220>
<223> Anti-CTLA-4 antibody light chain amino acid sequence

<400> 35

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>  36
<211>  118
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-CTLA-4 antibody heavy chain variable region amino acid
       sequence

<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 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
        115


<210>  37
<211>  108
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-CTLA-4 antibody light chain variable region amino acid
       sequence

<400>  37

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
            100                 105


<210>  38
<211>  444
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-PD1 antibody heavy chain amino acid sequence

<400>  38

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


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


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


Ser Gly Ile Ser Gly Gly Gly Arg Asp Thr Tyr Phe 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 Lys Gly Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Val Lys Trp Gly Asn Ile Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110
```

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

Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

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

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

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

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

Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
225                 230                 235                 240

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

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
            260                 265                 270

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        275                 280                 285

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

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
```

305 310 315 320

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

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
340 345 350

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365

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

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

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

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> 39
<211> 214
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody light chain amino acid sequence

<400> 39

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Ser Ile Thr Ile Thr Cys Arg Ala Ser Leu Ser Ile Asn Thr Phe

```
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu His Gly Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Asn Thr Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Val Val Asp Phe Arg 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> 40
<211> 117
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody heavy chain variable region amino acid sequence

<400> 40

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

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

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

Ser Gly Ile Ser Gly Gly Gly Arg Asp Thr Tyr Phe 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 Lys Gly Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Val Lys Trp Gly Asn Ile Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

<210> 41
<211> 107
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody light chain variable region amino acid sequence

<400> 41

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu His Gly Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Asn Thr Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Val Val Asp Phe Arg
100 105

<210> 42
<211> 450
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody heavy chain amino acid sequence

<400> 42

Glu Val Gln Leu Leu 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 Ser Tyr
20 25 30

Ile Met Met Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

```
        35                  40                  45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr 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 Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly 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 Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240
```

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

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

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
```

435 440 445

Gly Lys
450

<210> 43
<211> 216
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody light chain amino acid sequence

<400> 43

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr

```
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145                 150                 155                 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210>  44
<211>  120
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-PD1 antibody heavy chain variable region amino acid sequence

<400>  44

Glu Val Gln Leu Leu 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 Ser Tyr
            20                  25                  30

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

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr 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 Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 45
<211> 110
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody light chain variable region amino acid sequence

<400> 45

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 46
<211> 448
<212> PRT
<213> Artificial

<220>
<223> Anti-PD-L1 antibody heavy chain amino acid sequence

<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>  214
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-PD-L1 antibody light chain amino acid sequence

<400>  47

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> 48
<211> 118
<212> PRT
<213> Artificial

<220>
<223> Anti-PD-L1 antibody heavy chain variable region amino acid sequence

<400> 48

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
115

<210> 49
<211> 107
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody light chain variable region amino acid sequence

<400> 49

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
            100   105

<210> 50
<211> 451
<212> PRT
<213> Artificial

<220>
<223> Anti-PD-L1 antibody heavy chain amino acid sequence

<400> 50

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 Arg Tyr
            20   25   30

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

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

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

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

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270
```

```
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

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

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile
                325                 330                 335

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

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

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly Lys
    450
```

<210> 51
<211> 215

<212> PRT
<213> Artificial

<220>
<223> Anti-PD-L1 antibody light chain amino acid sequence

<400> 51

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 Arg 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 Asp 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 Leu 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>  52
<211>  121
<212>  PRT
<213>  Artificial

<220>
<223>  Anti-PD-L1 antibody heavy chain variable region amino acid
       sequence

<400>  52

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 Arg Tyr
            20                  25                  30


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


Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
```

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 53
<211> 108
<212> PRT
<213> Artificial

<220>
<223> Anti-PD1 antibody light chain variable region amino acid sequence

<400> 53

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 Arg 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 Asp 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 Leu Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 54
<211> 509
<212> PRT
<213> Artificial

<220>
<223> A115 amino acid sequence

<400> 54

```
Glu Thr Gln Glu Cys Leu Phe Phe Asn Ala Asn Trp Glu Lys Asp Arg
1               5                  10                  15


Thr Asn Gln Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg
            20                  25                  30


Arg His Cys Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile
        35                  40                  45


Val Lys Gln Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr
    50                  55                  60


Asp Cys Val Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys
65                  70                  75                  80


Glu Gly Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro Glu Met Glu
                85                  90                  95


Val Thr Gln Pro Thr Ser Asn Pro Val Thr Pro Lys Pro Pro Gly Gly
            100                 105                 110


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys
        115                 120                 125


Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
    130                 135                 140


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


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
```

```
            180                 185                 190

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

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

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

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

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

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

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

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

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

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        355                 360                 365

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
    370                 375                 380
```

```
Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
385                 390                 395                 400


Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
                405                 410                 415


Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
            420                 425                 430


Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
        435                 440                 445


Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
    450                 455                 460


Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
465                 470                 475                 480


Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
                485                 490                 495


Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            500                 505


<210>  55
<211>  534
<212>  PRT
<213>  Artificial

<220>
<223>  A116 amino acid sequence

<400>  55

Glu Thr Gln Glu Cys Leu Phe Phe Asn Ala Asn Trp Glu Lys Asp Arg
1               5                   10                  15


Thr Asn Gln Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg
            20                  25                  30
```

```
Arg His Cys Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile
        35                  40                  45

Val Lys Gln Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr
    50                  55                  60

Asp Cys Val Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

Glu Gly Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro Glu Met Glu
                85                  90                  95

Val Thr Gln Pro Thr Ser Asn Pro Val Thr Pro Lys Pro Pro Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys
        115                 120                 125

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
    130                 135                 140

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

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

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

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
```

```
225                 230                 235                 240

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

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

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

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

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

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

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

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        355                 360                 365

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
    370                 375                 380

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
385                 390                 395                 400

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
                405                 410                 415

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            420                 425                 430
```

```
Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        435                 440                 445


Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    450                 455                 460


Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
465                 470                 475                 480


Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                485                 490                 495


Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
            500                 505                 510


Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
        515                 520                 525


Asn Thr Ser Asn Pro Asp
    530


<210>  56
<211>  509
<212>  PRT
<213>  Artificial

<220>
<223>  A140 amino acid sequence

<400>  56

Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1               5                   10                  15


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


Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45
```

```
Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60

Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95

Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys
        115                 120                 125

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
    130                 135                 140

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

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

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

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

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

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
```

```
                245                 250                 255

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

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

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

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

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

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

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        355                 360                 365

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
    370                 375                 380

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
385                 390                 395                 400

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
                405                 410                 415

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
            420                 425                 430

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
        435                 440                 445
```

```
Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
    450                 455                 460

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
465                 470                 475                 480

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
                485                 490                 495

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            500                 505
```

<210> 57
<211> 534
<212> PRT
<213> Artificial

<220>
<223> A141 amino acid sequence

<400> 57

```
Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1               5                   10                  15

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

Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45

Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60

Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95
```

```
Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys
        115                 120                 125

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
    130                 135                 140

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

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

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

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

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

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

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

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

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

```
    290                 295                 300

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

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

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

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        355                 360                 365

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
    370                 375                 380

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
385                 390                 395                 400

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
                405                 410                 415

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            420                 425                 430

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        435                 440                 445

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    450                 455                 460

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
465                 470                 475                 480

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                485                 490                 495
```

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
500 505 510

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
515 520 525

Asn Thr Ser Asn Pro Asp
530

<210> 58
<211> 714
<212> PRT
<213> Artificial

<220>
<223> A142 amino acid sequence

<400> 58

Gly Asn Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu
1 5 10 15

Tyr Lys Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu
20 25 30

Ser Thr Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys
35 40 45

Trp Met Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu
50 55 60

Thr Cys Glu Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn
65 70 75 80

Lys Lys Asn Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile
85 90 95

Thr Trp Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn
100 105 110

```
Glu Cys Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu
        115                 120                 125

Val Gln Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys
    130                 135                 140

Pro Gly Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys
145                 150                 155                 160

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

Leu Cys Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg
            180                 185                 190

Lys Ala Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly
        195                 200                 205

Lys Cys Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly
    210                 215                 220

Lys Lys Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu
225                 230                 235                 240

Cys Asp Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala
                245                 250                 255

Ser Asp Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala
            260                 265                 270

Cys Ser Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
        275                 280                 285

Ser Ile Ser Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp
    290                 295                 300

Tyr Ser Phe Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser
```

```
305                 310                 315                 320

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys Ser Cys Asp
                325                 330                 335

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
            340                 345                 350

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        355                 360                 365

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    370                 375                 380

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
385                 390                 395                 400

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                405                 410                 415

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            420                 425                 430

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        435                 440                 445

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    450                 455                 460

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
465                 470                 475                 480

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                485                 490                 495

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            500                 505                 510
```

```
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        515                 520                 525

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    530                 535                 540

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
545                 550                 555                 560

Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                565                 570                 575

Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
            580                 585                 590

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
        595                 600                 605

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
    610                 615                 620

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
625                 630                 635                 640

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
                645                 650                 655

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
            660                 665                 670

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
        675                 680                 685

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
    690                 695                 700

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
```

705 710

<210> 59
<211> 739
<212> PRT
<213> Artificial

<220>
<223> A143 amino acid sequence

<400> 59

Gly Asn Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu
1 5 10 15

Tyr Lys Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu
20 25 30

Ser Thr Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys
35 40 45

Trp Met Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu
50 55 60

Thr Cys Glu Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn
65 70 75 80

Lys Lys Asn Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile
85 90 95

Thr Trp Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn
100 105 110

Glu Cys Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu
115 120 125

Val Gln Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys
130 135 140

Pro Gly Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys

```
145                 150                 155                 160

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

Leu Cys Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg
            180                 185                 190

Lys Ala Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly
        195                 200                 205

Lys Cys Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly
    210                 215                 220

Lys Lys Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu
225                 230                 235                 240

Cys Asp Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala
                245                 250                 255

Ser Asp Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala
            260                 265                 270

Cys Ser Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
        275                 280                 285

Ser Ile Ser Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp
    290                 295                 300

Tyr Ser Phe Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser
305                 310                 315                 320

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys Ser Cys Asp
                325                 330                 335

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
            340                 345                 350
```

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        355                 360                 365

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    370                 375                 380

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
385                 390                 395                 400

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                405                 410                 415

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            420                 425                 430

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        435                 440                 445

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    450                 455                 460

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
465                 470                 475                 480

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                485                 490                 495

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            500                 505                 510

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        515                 520                 525

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    530                 535                 540

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
```

```
545                 550                 555                 560

Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                565                 570                 575

Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala
            580                 585                 590

Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro
        595                 600                 605

Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
    610                 615                 620

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
625                 630                 635                 640

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
                645                 650                 655

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
            660                 665                 670

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
        675                 680                 685

His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
    690                 695                 700

Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
705                 710                 715                 720

Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
                725                 730                 735

Asn Pro Asp
```

<210> 60
<211> 714
<212> PRT
<213> Artificial

<220>
<223> A117 amino acid sequence

<400> 60

```
Gly Asn Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu
1               5                  10                  15


Tyr Lys Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu
            20                  25                  30


Ser Thr Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys
        35                  40                  45


Trp Met Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu
    50                  55                  60


Thr Cys Glu Asn Val Asp Cys Gly Pro Gly Gln Ser Cys Val Val Asp
65                  70                  75                  80


Gln Thr Gly Ser Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile
                85                  90                  95


Thr Trp Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn
            100                 105                 110


Glu Cys Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu
        115                 120                 125


Val Gln Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys
    130                 135                 140


Pro Gly Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys
145                 150                 155                 160
```

```
Val Thr Cys Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr
                165                 170                 175

Leu Cys Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg
            180                 185                 190

Lys Ala Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly
        195                 200                 205

Lys Cys Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly
    210                 215                 220

Lys Lys Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu
225                 230                 235                 240

Cys Asp Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala
                245                 250                 255

Ser Asp Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala
            260                 265                 270

Cys Ser Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
        275                 280                 285

Ser Ile Ser Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp
    290                 295                 300

Tyr Ser Phe Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser
305                 310                 315                 320

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys Ser Cys Asp
                325                 330                 335

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
            340                 345                 350

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
```

```
        355                 360                 365

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    370                 375                 380

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
385                 390                 395                 400

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                405                 410                 415

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            420                 425                 430

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        435                 440                 445

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    450                 455                 460

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
465                 470                 475                 480

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                485                 490                 495

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            500                 505                 510

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        515                 520                 525

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    530                 535                 540

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
545                 550                 555                 560
```

```
Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                565                 570                 575


Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
            580                 585                 590


Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
        595                 600                 605


Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
    610                 615                 620


Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
625                 630                 635                 640


Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
                645                 650                 655


His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
            660                 665                 670


Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
        675                 680                 685


Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
    690                 695                 700


Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
705                 710
```

<210> 61
<211> 739
<212> PRT
<213> Artificial

<220>
<223> A118 amino acid sequence

<400> 61

```
Gly Asn Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu
1               5                  10                  15

Tyr Lys Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu
            20                  25                  30

Ser Thr Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys
        35                  40                  45

Trp Met Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu
    50                  55                  60

Thr Cys Glu Asn Val Asp Cys Gly Pro Gly Gln Ser Cys Val Val Asp
65                  70                  75                  80

Gln Thr Gly Ser Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile
                85                  90                  95

Thr Trp Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn
            100                 105                 110

Glu Cys Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu
        115                 120                 125

Val Gln Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys
    130                 135                 140

Pro Gly Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys
145                 150                 155                 160

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

Leu Cys Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg
            180                 185                 190

Lys Ala Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly
```

```
        195                 200                 205

Lys Cys Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly
    210                 215                 220

Lys Lys Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu
225                 230                 235                 240

Cys Asp Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala
                245                 250                 255

Ser Asp Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala
            260                 265                 270

Cys Ser Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
        275                 280                 285

Ser Ile Ser Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp
    290                 295                 300

Tyr Ser Phe Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser
305                 310                 315                 320

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys Ser Cys Asp
                325                 330                 335

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
            340                 345                 350

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        355                 360                 365

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    370                 375                 380

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
385                 390                 395                 400
```

```
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                405                 410                 415

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            420                 425                 430

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        435                 440                 445

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    450                 455                 460

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
465                 470                 475                 480

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                485                 490                 495

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            500                 505                 510

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        515                 520                 525

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    530                 535                 540

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
545                 550                 555                 560

Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                565                 570                 575

Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala
            580                 585                 590

Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro
```

595 600 605

Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
610 615 620

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
625 630 635 640

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
645 650 655

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
660 665 670

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
675 680 685

His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
690 695 700

Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
705 710 715 720

Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
725 730 735

Asn Pro Asp

<210> 62
<211> 687
<212> PRT
<213> Artificial

<220>
<223> A144 amino acid sequence

<400> 62

Gly Asn Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu

```
1               5                   10                  15

Tyr Lys Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu
            20                  25                  30

Ser Thr Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys
        35                  40                  45

Trp Met Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu
    50                  55                  60

Thr Cys Glu Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn
65                  70                  75                  80

Lys Lys Asn Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile
                85                  90                  95

Thr Trp Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn
            100                 105                 110

Glu Cys Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu
        115                 120                 125

Val Gln Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys
    130                 135                 140

Pro Gly Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys
145                 150                 155                 160

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

Leu Cys Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg
            180                 185                 190

Lys Ala Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly
        195                 200                 205
```

```
Lys Cys Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly
    210                 215                 220

Lys Lys Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu
225                 230                 235                 240

Cys Asp Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala
                245                 250                 255

Ser Asp Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala
            260                 265                 270

Cys Ser Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
        275                 280                 285

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    290                 295                 300

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
305                 310                 315                 320

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                325                 330                 335

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            340                 345                 350

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        355                 360                 365

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
    370                 375                 380

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
385                 390                 395                 400

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
```

```
                405                 410                 415

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            420                 425                 430

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        435                 440                 445

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    450                 455                 460

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
465                 470                 475                 480

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                485                 490                 495

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            500                 505                 510

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        515                 520                 525

Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
    530                 535                 540

Ser Gly Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val
545                 550                 555                 560

Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
                565                 570                 575

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
            580                 585                 590

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
        595                 600                 605
```

```
Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
    610                 615                 620

Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
625                 630                 635                 640

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
                645                 650                 655

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
            660                 665                 670

Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        675                 680                 685
```

<210> 63
<211> 712
<212> PRT
<213> Artificial

<220>
<223> A145 amino acid sequence

<400> 63

```
Gly Asn Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu
1               5                   10                  15

Tyr Lys Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu
            20                  25                  30

Ser Thr Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys
        35                  40                  45

Trp Met Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu
    50                  55                  60

Thr Cys Glu Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn
65                  70                  75                  80
```

```
Lys Lys Asn Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile
                85                  90                  95

Thr Trp Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn
            100                 105                 110

Glu Cys Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu
        115                 120                 125

Val Gln Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys
    130                 135                 140

Pro Gly Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys
145                 150                 155                 160

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

Leu Cys Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg
            180                 185                 190

Lys Ala Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly
        195                 200                 205

Lys Cys Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly
    210                 215                 220

Lys Lys Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu
225                 230                 235                 240

Cys Asp Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala
                245                 250                 255

Ser Asp Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala
            260                 265                 270

Cys Ser Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
```

```
        275                 280                 285

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    290                 295                 300

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
305                 310                 315                 320

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                325                 330                 335

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            340                 345                 350

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        355                 360                 365

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
    370                 375                 380

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
385                 390                 395                 400

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                405                 410                 415

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            420                 425                 430

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        435                 440                 445

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    450                 455                 460

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
465                 470                 475                 480
```

```
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                485                 490                 495

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            500                 505                 510

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        515                 520                 525

Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
    530                 535                 540

Ser Gly Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp
545                 550                 555                 560

Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn
                565                 570                 575

Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr
            580                 585                 590

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
        595                 600                 605

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
    610                 615                 620

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
625                 630                 635                 640

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
                645                 650                 655

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
            660                 665                 670

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
```

675 680 685

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
690 695 700

Glu Tyr Asn Thr Ser Asn Pro Asp
705 710

<210> 64
<211> 509
<212> PRT
<213> Artificial

<220>
<223> A146 amino acid sequence

<400> 64

Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1 5 10 15

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

Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
35 40 45

Val Lys Lys Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Gln
50 55 60

Glu Cys Val Ala Thr Lys Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65 70 75 80

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
85 90 95

Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
100 105 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys

```
        115                 120                 125

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
    130                 135                 140

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

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

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

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

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

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

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

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

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

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

```
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

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

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        355                 360                 365

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
    370                 375                 380

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
385                 390                 395                 400

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
                405                 410                 415

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
            420                 425                 430

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
        435                 440                 445

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
    450                 455                 460

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
465                 470                 475                 480

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
                485                 490                 495

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            500                 505
```

<210> 65

<211> 534
<212> PRT
<213> Artificial

<220>
<223> A147 amino acid sequence

<400> 65

Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1 5 10 15

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

Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
35 40 45

Val Lys Lys Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Gln
50 55 60

Glu Cys Val Ala Thr Lys Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65 70 75 80

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
85 90 95

Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
100 105 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys
115 120 125

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
130 135 140

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

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val

```
                165                 170                 175

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

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

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

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

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

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

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

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

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

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

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        355                 360                 365
```

```
Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
    370                 375                 380

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
385                 390                 395                 400

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
                405                 410                 415

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            420                 425                 430

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        435                 440                 445

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    450                 455                 460

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
465                 470                 475                 480

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                485                 490                 495

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
            500                 505                 510

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
        515                 520                 525

Asn Thr Ser Asn Pro Asp
    530
```

<210> 66
<211> 509
<212> PRT
<213> Artificial

<220>
<223> A148 amino acid sequence

<400> 66

```
Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1               5                   10                  15


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


Arg His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45


Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60


Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80


Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95


Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
            100                 105                 110


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys
        115                 120                 125


Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
    130                 135                 140


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


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
```

```
            180                 185                 190

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

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

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

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

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

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

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

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

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

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        355                 360                 365

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
    370                 375                 380
```

```
Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
385                 390                 395                 400


Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
                405                 410                 415


Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
            420                 425                 430


Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
        435                 440                 445


Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
    450                 455                 460


Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
465                 470                 475                 480


Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
                485                 490                 495


Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            500                 505


<210>  67
<211>  534
<212>  PRT
<213>  Artificial

<220>
<223>  A149 amino acid sequence

<400>  67

Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1               5                   10                  15


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

```
Arg His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45

Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60

Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95

Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys
        115                 120                 125

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
    130                 135                 140

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

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

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

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
```

```
225                 230                 235                 240

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

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

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

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

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

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

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

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        355                 360                 365

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
    370                 375                 380

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
385                 390                 395                 400

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
                405                 410                 415

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            420                 425                 430
```

```
Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        435                 440                 445

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    450                 455                 460

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
465                 470                 475                 480

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                485                 490                 495

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
            500                 505                 510

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
        515                 520                 525

Asn Thr Ser Asn Pro Asp
    530
```

<210> 68
<211> 506
<212> PRT
<213> Artificial

<220>
<223> A150 amino acid sequence

<400> 68

```
Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1               5                   10                  15

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

Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45
```

```
Val Lys Lys Gly Cys Trp Asp Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60

Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95

Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys Ser Cys Asp
        115                 120                 125

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

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

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

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

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

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

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

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
```

```
                245                 250                 255

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

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

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

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

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

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

Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        355                 360                 365

Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
    370                 375                 380

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
385                 390                 395                 400

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
                405                 410                 415

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
            420                 425                 430

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
        435                 440                 445
```

```
His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
    450                 455                 460

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
465                 470                 475                 480

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
                485                 490                 495

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            500                 505
```

<210> 69
<211> 531
<212> PRT
<213> Artificial

<220>
<223> A151 amino acid sequence

<400> 69

```
Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg
1               5                   10                  15

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

Leu His Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu
        35                  40                  45

Val Lys Lys Gly Cys Trp Asp Asp Asp Phe Asn Cys Tyr Asp Arg Gln
    50                  55                  60

Glu Cys Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys
65                  70                  75                  80

Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly
                85                  90                  95
```

```
Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys Ser Cys Asp
        115                 120                 125

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

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

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

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

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

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

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

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

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

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

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

```
    290                 295                 300

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

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

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

Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        355                 360                 365

Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala
    370                 375                 380

Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro
385                 390                 395                 400

Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
                405                 410                 415

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
            420                 425                 430

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
        435                 440                 445

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
    450                 455                 460

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
465                 470                 475                 480

His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
                485                 490                 495
```

```
Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
            500                 505                 510


Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
        515                 520                 525


Asn Pro Asp
    530


<210>  70
<211>  508
<212>  PRT
<213>  Artificial

<220>
<223>  A152 amino acid sequence

<400>  70

Gly Ala Ile Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Tyr Asn
1               5                   10                  15


Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Thr Gly Val Glu Pro Cys
            20                  25                  30


Glu Gly Glu Lys Asp Lys Arg Leu His Cys Tyr Ala Thr Trp Arg Asn
        35                  40                  45


Ile Ser Gly Ser Ile Glu Ile Val Lys Lys Gly Cys Trp Leu Asp Asp
    50                  55                  60


Phe Asn Cys Tyr Asp Arg Thr Asp Cys Val Glu Thr Glu Glu Asn Pro
65                  70                  75                  80


Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe
                85                  90                  95


Ser Tyr Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser Gly Gly Gly
            100                 105                 110
```

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys Ser
        115                 120                 125

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

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

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
                165                 170                 175

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

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

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
    210                 215                 220

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

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

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

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

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

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
```

```
305                 310                 315                 320

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

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

Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        355                 360                 365

Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
    370                 375                 380

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
385                 390                 395                 400

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
                405                 410                 415

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
            420                 425                 430

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
        435                 440                 445

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
    450                 455                 460

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
465                 470                 475                 480

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
                485                 490                 495

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            500                 505
```

<210> 71
<211> 533
<212> PRT
<213> Artificial

<220>
<223> A153 amino acid sequence

<400> 71

```
Gly Ala Ile Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Tyr Asn
1               5                  10                  15


Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Thr Gly Val Glu Pro Cys
            20                  25                  30


Glu Gly Glu Lys Asp Lys Arg Leu His Cys Tyr Ala Thr Trp Arg Asn
        35                  40                  45


Ile Ser Gly Ser Ile Glu Ile Val Lys Lys Gly Cys Trp Leu Asp Asp
    50                  55                  60


Phe Asn Cys Tyr Asp Arg Thr Asp Cys Val Glu Thr Glu Glu Asn Pro
65                  70                  75                  80


Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe
                85                  90                  95


Ser Tyr Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser Gly Gly Gly
            100                 105                 110


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Pro Lys Ser
        115                 120                 125


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


Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
145                 150                 155                 160
```

```
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
                165                 170                 175

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

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

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
    210                 215                 220

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

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

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

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

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

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

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

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

Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
```

```
        355                 360                 365

Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met
    370                 375                 380

Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala
385                 390                 395                 400

His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn
                405                 410                 415

Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe
            420                 425                 430

Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr
        435                 440                 445

Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys
    450                 455                 460

Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu
465                 470                 475                 480

Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile
                485                 490                 495

Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys
            500                 505                 510

Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn
        515                 520                 525

Thr Ser Asn Pro Asp
    530
```

<210> 72
<211> 604
<212> PRT

<213> Artificial

<220>
<223> A154 Heavy chain amino acid sequence

<400> 72

```
Gln Val Gln Leu Val Gln Ser Gly Ala 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 Ser Tyr
            20                  25                  30


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


Gly Trp Ile Ile Pro Tyr Asn Gly Asn Thr Asn Ser Ala Gln Lys Leu
    50                  55                  60


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


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


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


Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125


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


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


Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175
```

```
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

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

His Glu Asp Pro Glu Val Lys Phe Asn Val Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

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

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

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

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
```

```
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

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

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    450                 455                 460

Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
465                 470                 475                 480

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
                485                 490                 495

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
            500                 505                 510

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
        515                 520                 525

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
    530                 535                 540

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
545                 550                 555                 560

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                565                 570                 575
```

```
Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            580                 585                 590


Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        595                 600


<210>  73
<211>  629
<212>  PRT
<213>  Artificial

<220>
<223>  A155 Heavy chain amino acid sequence

<400>  73

Gln Val Gln Leu Val Gln Ser Gly Ala 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 Ser Tyr
            20                  25                  30


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


Gly Trp Ile Ile Pro Tyr Asn Gly Asn Thr Asn Ser Ala Gln Lys Leu
    50                  55                  60


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


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


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


Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125
```

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

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

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

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

His Glu Asp Pro Glu Val Lys Phe Asn Val Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

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

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
```

```
                325                 330                 335

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

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

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

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    450                 455                 460

Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met
465                 470                 475                 480

Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala
                485                 490                 495

His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn
            500                 505                 510

Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe
        515                 520                 525
```

```
Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr
    530                 535                 540

Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys
545                 550                 555                 560

Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu
                565                 570                 575

Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile
            580                 585                 590

Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys
        595                 600                 605

Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn
    610                 615                 620

Thr Ser Asn Pro Asp
625
```

<210> 74
<211> 605
<212> PRT
<213> Artificial

<220>
<223> A156 Heavy chain amino acid sequence

<400> 74

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Phe Ser Ser His
            20                  25                  30

Phe Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45
```

```
Gly Tyr Ile Leu Tyr Thr Gly Gly Thr Ser Phe Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Ser Met Ser Val Gly Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Ala Arg Ser Gly Ile Thr Phe Thr Gly Ile Ile Val Pro Gly Ser
            100                 105                 110

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser
        115                 120                 125

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

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

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

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

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

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

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
```

```
                245                 250                 255

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

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

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320

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

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

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

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
                405                 410                 415

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
            420                 425                 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445
```

```
Leu Ser Leu Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    450                 455                 460

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
465                 470                 475                 480

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
                485                 490                 495

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
            500                 505                 510

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
        515                 520                 525

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
    530                 535                 540

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
545                 550                 555                 560

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
                565                 570                 575

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
            580                 585                 590

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        595                 600                 605
```

<210> 75
<211> 630
<212> PRT
<213> Artificial

<220>
<223> A157 Heavy chain amino acid sequence

<400> 75

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Phe Ser Ser His
            20                  25                  30

Phe Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Leu Tyr Thr Gly Gly Thr Ser Phe Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Ser Met Ser Val Gly Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Ala Arg Ser Gly Ile Thr Phe Thr Gly Ile Ile Val Pro Gly Ser
            100                 105                 110

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser
        115                 120                 125

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

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

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

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

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr
```

```
        195                 200                 205

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

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

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

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

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320

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

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

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

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400
```

```
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
                405                 410                 415

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
            420                 425                 430

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

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

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
465                 470                 475                 480

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
                485                 490                 495

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
            500                 505                 510

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
        515                 520                 525

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
    530                 535                 540

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
545                 550                 555                 560

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
                565                 570                 575

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
            580                 585                 590

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
```

595 600 605

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
610 615 620

Asn Thr Ser Asn Pro Asp
625 630

<210> 76
<211> 572
<212> PRT
<213> Artificial

<220>
<223> A158 Heavy chain amino acid sequence

<400> 76

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 Tyr Thr Phe Ser Ser Asn
20 25 30

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

Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu 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 Ser 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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Thr
    450                 455                 460

Gln Glu Cys Leu Phe Phe Asn Ala Asn Trp Glu Lys Asp Arg Thr Asn
465                 470                 475                 480

Gln Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg Arg His
                485                 490                 495

Cys Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile Val Lys
            500                 505                 510

Gln Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr Asp Cys
```

```
        515                 520                 525

Val Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys Glu Gly
    530                 535                 540

Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro Glu Met Glu Val Thr
545                 550                 555                 560

Gln Pro Thr Ser Asn Pro Val Thr Pro Lys Pro Pro
                565                 570

<210>  77
<211>  572
<212>  PRT
<213>  Artificial

<220>
<223>  A159 Heavy chain amino acid sequence

<400>  77

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 Tyr Thr Phe Ser Ser Asn
            20                  25                  30

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

Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
```

```
            100                 105                 110

Gly Thr Leu 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 Ser 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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Thr
    450                 455                 460

Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn
465                 470                 475                 480

Gln Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His
                485                 490                 495

Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys
```

```
            500                 505                 510


Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys
        515                 520                 525


Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly
    530                 535                 540


Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro
545                 550                 555                 560


Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr
                565                 570


<210>  78
<211>  777
<212>  PRT
<213>  Artificial

<220>
<223>  A160 Heavy chain amino acid sequence

<400>  78

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 Tyr Thr Phe Ser Ser Asn
            20                  25                  30


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


Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60


Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu 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 Ser 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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Asn
    450                 455                 460

Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys
465                 470                 475                 480

Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr
```

```
                485                 490                 495

Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met
            500                 505                 510

Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys
        515                 520                 525

Glu Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys
    530                 535                 540

Asn Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp
545                 550                 555                 560

Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys
                565                 570                 575

Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln
            580                 585                 590

Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly
        595                 600                 605

Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr
    610                 615                 620

Cys Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys
625                 630                 635                 640

Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala
                645                 650                 655

Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys
            660                 665                 670

Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys
        675                 680                 685
```

```
Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp
    690                 695                 700

Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp
705                 710                 715                 720

Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser
                725                 730                 735

Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile
            740                 745                 750

Ser Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser
        755                 760                 765

Phe Pro Ile Ser Ser Ile Leu Glu Trp
    770                 775
```

<210> 79
<211> 777
<212> PRT
<213> Artificial

<220>
<223> A161 Heavy chain amino acid sequence

<400> 79

```
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 Tyr Thr Phe Ser Ser Asn
            20                  25                  30

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

Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60
```

```
Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu 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 Ser 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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Asn
    450                 455                 460
```

```
Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys
465                 470                 475                 480

Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr
                485                 490                 495

Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met
            500                 505                 510

Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys
        515                 520                 525

Glu Asn Val Asp Cys Gly Pro Gly Gln Ser Cys Val Val Asp Gln Thr
    530                 535                 540

Gly Ser Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp
545                 550                 555                 560

Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys
                565                 570                 575

Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln
            580                 585                 590

Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly
        595                 600                 605

Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr
    610                 615                 620

Cys Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys
625                 630                 635                 640

Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala
                645                 650                 655

Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys
```

660 665 670

Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys
675 680 685

Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp
690 695 700

Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp
705 710 715 720

Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser
725 730 735

Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile
740 745 750

Ser Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser
755 760 765

Phe Pro Ile Ser Ser Ile Leu Glu Trp
770 775

<210> 80
<211> 777
<212> PRT
<213> Artificial

<220>
<223> A162 Heavy chain amino acid sequence

<400> 80

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 Tyr Thr Phe Ser Ser Asn
20 25 30

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

```
        35                  40                  45

Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu 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 Ser 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 Gly
```

```
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Asn
    450                 455                 460

Cys Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys
465                 470                 475                 480

Thr Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr
                485                 490                 495

Ser Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met
            500                 505                 510

Ile Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys
        515                 520                 525

Glu Asn Val Asp Cys Gly Pro Gly Gln Ser Cys Val Val Asp Gln Thr
    530                 535                 540

Gly Ser Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp
545                 550                 555                 560

Lys Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys
                565                 570                 575

Ala Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln
            580                 585                 590

Tyr Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly
        595                 600                 605

Ser Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr
    610                 615                 620

Cys Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys
625                 630                 635                 640
```

```
Gly Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala
                645                 650                 655

Thr Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys
            660                 665                 670

Ile Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys
        675                 680                 685

Cys Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp
    690                 695                 700

Glu Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp
705                 710                 715                 720

Asn Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser
                725                 730                 735

Ser Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile
            740                 745                 750

Ser Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser
        755                 760                 765

Phe Pro Ile Ser Ser Ile Leu Glu Trp
    770                 775
```

<210> 81
<211> 572
<212> PRT
<213> Artificial

<220>
<223> A163 Heavy chain amino acid sequence

<400> 81

```
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 Tyr Thr Phe Ser Ser Asn
            20                  25                  30

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

Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu 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 Ser 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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Thr
    450                 455                 460

Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn
465                 470                 475                 480

Gln Ser Gly Leu Glu Arg Cys Glu Gly Asp Gln Asp Lys Arg Leu His
                485                 490                 495

Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys
            500                 505                 510

Lys Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Gln Glu Cys
        515                 520                 525

Val Ala Thr Lys Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly
    530                 535                 540

Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro
545                 550                 555                 560

Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr
                565                 570
```

<210> 82
<211> 572
<212> PRT
<213> Artificial

<220>
<223> A164 Heavy chain amino acid sequence

<400> 82

```
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 Tyr Thr Phe Ser Ser Asn
            20                  25                  30

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

Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu 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 Ser 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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Thr
    450                 455                 460

Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn
465                 470                 475                 480

Gln Ser Gly Leu Glu Arg Cys Tyr Gly Asp Lys Asp Lys Arg Arg His
                485                 490                 495

Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys
            500                 505                 510

Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys
        515                 520                 525

Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly
    530                 535                 540

Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro
545                 550                 555                 560

Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr
                565                 570
```

<210> 83
<211> 569
<212> PRT
<213> Artificial

<220>
<223> A165 Heavy chain amino acid sequence

<400> 83

```
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 Tyr Thr Phe Ser Ser Asn
            20                  25                  30


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


Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60


Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu 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 Ser 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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Thr
    450                 455                 460

Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn
465                 470                 475                 480

Gln Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His
                485                 490                 495

Cys Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys
            500                 505                 510

Lys Gly Cys Trp Asp Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys
        515                 520                 525

Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly
    530                 535                 540

Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro
545                 550                 555                 560

Glu Val Thr Tyr Glu Pro Pro Pro Thr
                565
```

<210> 84

<211> 571
<212> PRT
<213> Artificial

<220>
<223> A166 Heavy chain amino acid sequence

<400> 84

```
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 Tyr Thr Phe Ser Ser Asn
            20                  25                  30


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


Gly Gly Val Ile Pro Ile Val Asp Ile Ala Asn Tyr Ala Gln Arg Phe
    50                  55                  60


Lys Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Thr 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 Ser Thr Leu Gly Leu Val Leu Asp Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu 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 Ser 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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ala
    450                 455                 460

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

Trp Glu Leu Glu Arg Thr Asn Gln Thr Gly Val Glu Pro Cys Glu Gly
                485                 490                 495

Glu Lys Asp Lys Arg Leu His Cys Tyr Ala Thr Trp Arg Asn Ile Ser
            500                 505                 510

Gly Ser Ile Glu Ile Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn
        515                 520                 525

Cys Tyr Asp Arg Thr Asp Cys Val Glu Thr Glu Glu Asn Pro Gln Val
    530                 535                 540

Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser Tyr
545                 550                 555                 560

Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser
```

565 570

<210> 85
<211> 733
<212> PRT
<213> Artificial

<220>
<223> A169 Heavy chain amino acid sequence

<400> 85

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Gln
    450                 455                 460

Glu Cys Leu Phe Phe Asn Ala Asn Trp Glu Lys Asp Arg Thr Asn Gln
465                 470                 475                 480

Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg Arg His Cys
                485                 490                 495

Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile Val Lys Gln
            500                 505                 510

Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr Asp Cys Val
        515                 520                 525

Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro Glu Met Glu Val Thr Gln
```

```
545                 550                 555                 560

Pro Thr Ser Asn Pro Val Thr Pro Lys Pro Pro Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
        595                 600                 605

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
    610                 615                 620

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
625                 630                 635                 640

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
                645                 650                 655

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
            660                 665                 670

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
        675                 680                 685

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
    690                 695                 700

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
705                 710                 715                 720

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
                725                 730
```

<210> 86
<211> 758
<212> PRT

<213> Artificial

<220>
<223> A170 Heavy chain amino acid sequence

<400> 86

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Gln
    450                 455                 460

Glu Cys Leu Phe Phe Asn Ala Asn Trp Glu Lys Asp Arg Thr Asn Gln
465                 470                 475                 480

Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg Arg His Cys
                485                 490                 495

Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile Val Lys Gln
            500                 505                 510

Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr Asp Cys Val
        515                 520                 525

Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro Glu Met Glu Val Thr Gln
545                 550                 555                 560

Pro Thr Ser Asn Pro Val Thr Pro Lys Pro Pro Gly Gly Gly Gly Ser
                565                 570                 575
```

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
        595                 600                 605

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
    610                 615                 620

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
625                 630                 635                 640

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                645                 650                 655

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            660                 665                 670

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        675                 680                 685

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    690                 695                 700

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
705                 710                 715                 720

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                725                 730                 735

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            740                 745                 750

Asn Thr Ser Asn Pro Asp
        755
```

<210> 87

<211> 733
<212> PRT
<213> Artificial

<220>
<223> A171 Heavy chain amino acid sequence

<400> 87

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
```

```
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
        595                 600                 605

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
    610                 615                 620

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
625                 630                 635                 640

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
                645                 650                 655

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
            660                 665                 670

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
        675                 680                 685

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
    690                 695                 700

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
705                 710                 715                 720

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
                725                 730
```

<210> 88
<211> 758
<212> PRT
<213> Artificial

<220>
<223> A172 Heavy chain amino acid sequence

<400> 88

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590
```

```
Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
        595                 600                 605

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
    610                 615                 620

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
625                 630                 635                 640

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                645                 650                 655

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            660                 665                 670

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        675                 680                 685

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    690                 695                 700

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
705                 710                 715                 720

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                725                 730                 735

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            740                 745                 750

Asn Thr Ser Asn Pro Asp
        755
```

<210> 89
<211> 938
<212> PRT
<213> Artificial

<220>
<223> A173 Heavy chain amino acid sequence

<400> 89

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys Asn
    530                 535                 540

Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
                565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
```

```
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile Ser
            740                 745                 750

Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser Phe
        755                 760                 765

Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser Gly Gly Gly
    770                 775                 780
```

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
785                 790                 795                 800


Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
                805                 810                 815


Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
            820                 825                 830


Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
        835                 840                 845


Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
    850                 855                 860


Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
865                 870                 875                 880


His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
                885                 890                 895


Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
            900                 905                 910


Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
        915                 920                 925


Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
    930                 935


<210>  90
<211>  963
<212>  PRT
<213>  Artificial

<220>
<223>  A174 Heavy chain amino acid sequence

<400>  90
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```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys Asn
    530                 535                 540

Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
                565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
```

```
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile Ser
            740                 745                 750

Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser Phe
        755                 760                 765

Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser Gly Gly Gly
    770                 775                 780

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
785                 790                 795                 800
```

```
Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala
                805                 810                 815

Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro
            820                 825                 830

Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
        835                 840                 845

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
    850                 855                 860

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
865                 870                 875                 880

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
                885                 890                 895

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
            900                 905                 910

His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
        915                 920                 925

Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
    930                 935                 940

Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
945                 950                 955                 960

Asn Pro Asp
```

<210> 91
<211> 938
<212> PRT
<213> Artificial

<220>
<223> A175 Heavy chain amino acid sequence

<400> 91

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Gln Ser Cys Val Val Asp Gln Thr Gly
    530                 535                 540

Ser Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
                565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
```

```
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile Ser
            740                 745                 750

Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser Phe
        755                 760                 765

Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser Gly Gly Gly
    770                 775                 780
```

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
785                 790                 795                 800


Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
                805                 810                 815


Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
            820                 825                 830


Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
        835                 840                 845


Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
    850                 855                 860


Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
865                 870                 875                 880


His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
                885                 890                 895


Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
            900                 905                 910


Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
        915                 920                 925


Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
    930                 935


<210>  92
<211>  963
<212>  PRT
<213>  Artificial

<220>
<223>  A176 Heavy chain amino acid sequence

<400>  92
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```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Gln Ser Cys Val Val Asp Gln Thr Gly
    530                 535                 540

Ser Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
                565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
```

```
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile Ser
            740                 745                 750

Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser Phe
        755                 760                 765

Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser Gly Gly Gly
    770                 775                 780

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
785                 790                 795                 800
```

```
Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala
                805                 810                 815

Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro
            820                 825                 830

Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
        835                 840                 845

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
    850                 855                 860

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
865                 870                 875                 880

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
                885                 890                 895

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
            900                 905                 910

His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
        915                 920                 925

Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
    930                 935                 940

Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
945                 950                 955                 960

Asn Pro Asp
```

<210> 93
<211> 911
<212> PRT
<213> Artificial

<220>
<223> A177 Heavy chain amino acid sequence

<400> 93

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys Asn
    530                 535                 540

Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
                565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
```

```
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Gly Gly Gly
            740                 745                 750

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        755                 760                 765

Ser Gly Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val
    770                 775                 780
```

```
Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
785                 790                 795                 800


Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
                805                 810                 815


Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
            820                 825                 830


Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
        835                 840                 845


Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
    850                 855                 860


Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
865                 870                 875                 880


Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
                885                 890                 895


Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            900                 905                 910


<210>  94
<211>  936
<212>  PRT
<213>  Artificial

<220>
<223>  A178 Heavy chain amino acid sequence

<400>  94

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys Asn
    530                 535                 540

Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
                565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
```

```
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Gly Gly Gly
            740                 745                 750

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        755                 760                 765

Ser Gly Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp
    770                 775                 780

Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn
785                 790                 795                 800

Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr
                805                 810                 815

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
            820                 825                 830
```

```
Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
        835                 840                 845


Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
    850                 855                 860


Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
865                 870                 875                 880


Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
                885                 890                 895


Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
            900                 905                 910


Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
        915                 920                 925


Glu Tyr Asn Thr Ser Asn Pro Asp
    930                 935


<210>  95
<211>  733
<212>  PRT
<213>  Artificial

<220>
<223>  A179 Heavy chain amino acid sequence

<400>  95

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 Gly
        435                 440                 445
```

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Asp Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Lys Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
        595                 600                 605

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
    610                 615                 620

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
625                 630                 635                 640

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
```

645 650 655

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
660 665 670

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
675 680 685

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
690 695 700

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
705 710 715 720

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
725 730

<210> 96
<211> 758
<212> PRT
<213> Artificial

<220>
<223> A180 Heavy chain amino acid sequence

<400> 96

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
```

```
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Asp Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Lys Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
        595                 600                 605

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
    610                 615                 620

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
625                 630                 635                 640

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                645                 650                 655

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            660                 665                 670
```

```
Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        675                 680                 685

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    690                 695                 700

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
705                 710                 715                 720

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                725                 730                 735

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            740                 745                 750

Asn Thr Ser Asn Pro Asp
        755
```

<210> 97
<211> 733
<212> PRT
<213> Artificial

<220>
<223> A181 Heavy chain amino acid sequence

<400> 97

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460
```

```
Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Tyr Gly Asp Lys Asp Lys Arg Arg His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
        595                 600                 605

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
    610                 615                 620

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
625                 630                 635                 640

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
                645                 650                 655

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
```

660 665 670

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
675 680 685

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
690 695 700

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
705 710 715 720

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
725 730

<210> 98
<211> 758
<212> PRT
<213> Artificial

<220>
<223> A182 Heavy chain amino acid sequence

<400> 98

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Tyr Gly Asp Lys Asp Lys Arg Arg His Cys
```

```
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
        595                 600                 605

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
    610                 615                 620

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
625                 630                 635                 640

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                645                 650                 655

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            660                 665                 670

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        675                 680                 685
```

```
Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    690                 695                 700

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
705                 710                 715                 720

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                725                 730                 735

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            740                 745                 750

Asn Thr Ser Asn Pro Asp
        755
```

<210> 99
<211> 730
<212> PRT
<213> Artificial

<220>
<223> A183 Heavy chain amino acid sequence

<400> 99

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480
```

```
Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Asp Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Gly Gly Gly Gly Ser Gly Gly Gly
                565                 570                 575

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            580                 585                 590

Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
        595                 600                 605

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
    610                 615                 620

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
625                 630                 635                 640

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
                645                 650                 655

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
            660                 665                 670

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
```

675 680 685

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
690 695 700

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
705 710 715 720

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
725 730

<210> 100
<211> 755
<212> PRT
<213> Artificial

<220>
<223> A184 Heavy chain amino acid sequence

<400> 100

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
```

```
            500                 505                 510

Gly Cys Trp Asp Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Gly Gly Gly Gly Ser Gly Gly Gly
                565                 570                 575

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            580                 585                 590

Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala
        595                 600                 605

Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro
    610                 615                 620

Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
625                 630                 635                 640

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
                645                 650                 655

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
            660                 665                 670

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
        675                 680                 685

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
    690                 695                 700
```

```
His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
705                 710                 715                 720


Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
                725                 730                 735


Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
            740                 745                 750


Asn Pro Asp
        755


<210>  101
<211>  732
<212>  PRT
<213>  Artificial

<220>
<223>  A185 Heavy chain amino acid sequence

<400>  101

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Ala Ile
    450                 455                 460

Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Tyr Asn Ala Asn Trp
465                 470                 475                 480

Glu Leu Glu Arg Thr Asn Gln Thr Gly Val Glu Pro Cys Glu Gly Glu
                485                 490                 495
```

```
Lys Asp Lys Arg Leu His Cys Tyr Ala Thr Trp Arg Asn Ile Ser Gly
            500                 505                 510

Ser Ile Glu Ile Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys
        515                 520                 525

Tyr Asp Arg Thr Asp Cys Val Glu Thr Glu Glu Asn Pro Gln Val Tyr
    530                 535                 540

Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe
545                 550                 555                 560

Pro Glu Met Glu Val Thr Gln Pro Thr Ser Gly Gly Gly Gly Ser Gly
                565                 570                 575

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            580                 585                 590

Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
        595                 600                 605

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
    610                 615                 620

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
625                 630                 635                 640

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
                645                 650                 655

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
            660                 665                 670

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
        675                 680                 685

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
```

690 695 700

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
705 710 715 720

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
725 730

<210> 102
<211> 757
<212> PRT
<213> Artificial

<220>
<223> A186 Heavy chain amino acid sequence

<400> 102

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Ala Ile
    450                 455                 460

Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Tyr Asn Ala Asn Trp
465                 470                 475                 480

Glu Leu Glu Arg Thr Asn Gln Thr Gly Val Glu Pro Cys Glu Gly Glu
                485                 490                 495

Lys Asp Lys Arg Leu His Cys Tyr Ala Thr Trp Arg Asn Ile Ser Gly
            500                 505                 510

Ser Ile Glu Ile Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys
```

```
        515                 520                 525

Tyr Asp Arg Thr Asp Cys Val Glu Thr Glu Glu Asn Pro Gln Val Tyr
    530                 535                 540

Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe
545                 550                 555                 560

Pro Glu Met Glu Val Thr Gln Pro Thr Ser Gly Gly Gly Gly Ser Gly
                565                 570                 575

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            580                 585                 590

Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met
        595                 600                 605

Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala
    610                 615                 620

His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn
625                 630                 635                 640

Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe
                645                 650                 655

Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr
            660                 665                 670

Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys
        675                 680                 685

Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu
    690                 695                 700

Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile
705                 710                 715                 720
```

Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys
725 730 735

Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn
740 745 750

Thr Ser Asn Pro Asp
755

<210> 103
<211> 734
<212> PRT
<213> Artificial

<220>
<223> A187 Heavy chain amino acid sequence

<400> 103

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 Lys
        435                 440                 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr
    450                 455                 460

Gln Glu Cys Leu Phe Phe Asn Ala Asn Trp Glu Lys Asp Arg Thr Asn
465                 470                 475                 480

Gln Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg Arg His
                485                 490                 495

Cys Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile Val Lys
            500                 505                 510
```

```
Gln Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr Asp Cys
        515                 520                 525

Val Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys Glu Gly
    530                 535                 540

Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro Glu Met Glu Val Thr
545                 550                 555                 560

Gln Pro Thr Ser Asn Pro Val Thr Pro Lys Pro Pro Gly Gly Gly Gly
                565                 570                 575

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
            580                 585                 590

Gly Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn
        595                 600                 605

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
    610                 615                 620

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
625                 630                 635                 640

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
                645                 650                 655

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
            660                 665                 670

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
        675                 680                 685

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
    690                 695                 700

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
```

705 710 715 720

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
725 730

<210> 104
<211> 758
<212> PRT
<213> Artificial

<220>
<223> A188 Heavy chain amino acid sequence

<400> 104

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Gln
    450                 455                 460

Glu Cys Leu Phe Phe Asn Ala Asn Trp Glu Lys Asp Arg Thr Asn Gln
465                 470                 475                 480

Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg Arg His Cys
                485                 490                 495

Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile Val Lys Gln
            500                 505                 510

Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr Asp Cys Val
        515                 520                 525

Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys Glu Gly Asn
```

```
    530                 535                 540

Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro Glu Met Glu Val Thr Gln
545                 550                 555                 560

Pro Thr Ser Asn Pro Val Thr Pro Lys Pro Pro Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
        595                 600                 605

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
    610                 615                 620

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
625                 630                 635                 640

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                645                 650                 655

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            660                 665                 670

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        675                 680                 685

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    690                 695                 700

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
705                 710                 715                 720

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                725                 730                 735
```

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
740 745 750

Asn Thr Ser Asn Pro Asp
755

<210> 105
<211> 733
<212> PRT
<213> Artificial

<220>
<223> A189 Heavy chain amino acid sequence

<400> 105

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 Lys Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525
```

```
Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
        595                 600                 605

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
    610                 615                 620

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
625                 630                 635                 640

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
                645                 650                 655

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
            660                 665                 670

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
        675                 680                 685

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
    690                 695                 700

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
705                 710                 715                 720

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
```

725 730

<210> 106
<211> 758
<212> PRT
<213> Artificial

<220>
<223> A190 Heavy chain amino acid sequence

<400> 106

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
```

```
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
        595                 600                 605

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
    610                 615                 620

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
625                 630                 635                 640

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                645                 650                 655

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            660                 665                 670

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        675                 680                 685

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    690                 695                 700

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
705                 710                 715                 720

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                725                 730                 735

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            740                 745                 750
```

Asn Thr Ser Asn Pro Asp
        755

<210> 107
<211> 938
<212> PRT
<213> Artificial

<220>
<223> A191 Heavy chain amino acid sequence

<400> 107

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 Lys Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys Asn
    530                 535                 540
```

```
Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
                565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile Ser
```

```
            740                 745                 750

Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser Phe
        755                 760                 765

Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser Gly Gly Gly
    770                 775                 780

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
785                 790                 795                 800

Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
                805                 810                 815

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
            820                 825                 830

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
        835                 840                 845

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
    850                 855                 860

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
865                 870                 875                 880

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
                885                 890                 895

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
            900                 905                 910

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
        915                 920                 925

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
    930                 935
```

<210> 108
<211> 963
<212> PRT
<213> Artificial

<220>
<223> A192 Heavy chain amino acid sequence

<400> 108

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys Asn
    530                 535                 540

Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560
```

```
Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
               565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
               645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
               725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile Ser
            740                 745                 750

Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser Phe
```

```
        755                 760                 765

Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser Gly Gly Gly
    770                 775                 780

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
785                 790                 795                 800

Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala
                805                 810                 815

Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro
            820                 825                 830

Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
        835                 840                 845

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
    850                 855                 860

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
865                 870                 875                 880

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
                885                 890                 895

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
            900                 905                 910

His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
        915                 920                 925

Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
    930                 935                 940

Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
945                 950                 955                 960
```

Asn Pro Asp

<210> 109
<211> 938
<212> PRT
<213> Artificial

<220>
<223> A193 Heavy chain amino acid sequence

<400> 109

```
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 Lys Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Gln Ser Cys Val Val Asp Gln Thr Gly
    530                 535                 540
```

```
Ser Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
                565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile Ser
```

```
            740                 745                 750

Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser Phe
        755                 760                 765

Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser Gly Gly Gly
    770                 775                 780

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
785                 790                 795                 800

Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
                805                 810                 815

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
            820                 825                 830

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
        835                 840                 845

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
    850                 855                 860

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
865                 870                 875                 880

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
                885                 890                 895

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
            900                 905                 910

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
        915                 920                 925

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
    930                 935
```

<210> 110
<211> 963
<212> PRT
<213> Artificial

<220>
<223> A194 Heavy chain amino acid sequence

<400> 110

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Gln Ser Cys Val Val Asp Gln Thr Gly
    530                 535                 540

Ser Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560
```

```
Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
               565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
               645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
               725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Ser Ile Ser
            740                 745                 750

Glu Asp Thr Glu Glu Glu Glu Glu Asp Glu Asp Gln Asp Tyr Ser Phe
```

```
        755                 760                 765

Pro Ile Ser Ser Ile Leu Glu Trp Gly Gly Gly Gly Ser Gly Gly Gly
    770                 775                 780

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
785                 790                 795                 800

Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala
                805                 810                 815

Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro
            820                 825                 830

Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
        835                 840                 845

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
    850                 855                 860

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
865                 870                 875                 880

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
                885                 890                 895

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
            900                 905                 910

His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
        915                 920                 925

Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
    930                 935                 940

Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
945                 950                 955                 960
```

Asn Pro Asp

<210> 111
<211> 911
<212> PRT
<213> Artificial

<220>
<223> A195 Heavy chain amino acid sequence

<400> 111

```
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 Lys Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
    450                 455                 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465                 470                 475                 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
                485                 490                 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
            500                 505                 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
        515                 520                 525

Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys Asn
    530                 535                 540
```

```
Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545                 550                 555                 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
                565                 570                 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
            580                 585                 590

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Gly Gly Gly
```

```
            740                 745                 750

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        755                 760                 765

Ser Gly Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val
    770                 775                 780

Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
785                 790                 795                 800

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
                805                 810                 815

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
            820                 825                 830

Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
        835                 840                 845

Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
    850                 855                 860

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
865                 870                 875                 880

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
                885                 890                 895

Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            900                 905                 910


<210>  112
<211>  936
<212>  PRT
<213>  Artificial

<220>
<223>  A196 Heavy chain amino acid sequence
```

<400> 112

```
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 Gly
435 440 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Asn Cys
450 455 460

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
465 470 475 480

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
485 490 495

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
500 505 510

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
515 520 525

Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys Asn
530 535 540

Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
545 550 555 560

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
565 570 575

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
580 585 590

```
Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
        595                 600                 605

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
    610                 615                 620

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
625                 630                 635                 640

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
                645                 650                 655

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
            660                 665                 670

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
        675                 680                 685

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
    690                 695                 700

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
705                 710                 715                 720

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
                725                 730                 735

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn Gly Gly Gly
            740                 745                 750

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        755                 760                 765

Ser Gly Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp
    770                 775                 780

Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn
```

785 790 795 800

Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr
805 810 815

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
820 825 830

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
835 840 845

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
850 855 860

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
865 870 875 880

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
885 890 895

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
900 905 910

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
915 920 925

Glu Tyr Asn Thr Ser Asn Pro Asp
930 935

<210> 113
<211> 733
<212> PRT
<213> Artificial

<220>
<223> A197 Heavy chain amino acid sequence

<400> 113

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 Lys Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Asp Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Lys Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
        595                 600                 605
```

```
Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
    610                 615                 620


Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
625                 630                 635                 640


Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
                645                 650                 655


Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
            660                 665                 670


Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
        675                 680                 685


Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
    690                 695                 700


Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
705                 710                 715                 720


Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
                725                 730


<210>  114
<211>  758
<212>  PRT
<213>  Artificial

<220>
<223>  A198 Heavy chain amino acid sequence

<400>  114

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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Asp Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Lys Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
        595                 600                 605

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
    610                 615                 620

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
```

625 630 635 640

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
645 650 655

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
660 665 670

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
675 680 685

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
690 695 700

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
705 710 715 720

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
725 730 735

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
740 745 750

Asn Thr Ser Asn Pro Asp
755

<210> 115
<211> 733
<212> PRT
<213> Artificial

<220>
<223> A199 Heavy chain amino acid sequence

<400> 115

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 Lys Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Tyr Gly Asp Lys Asp Lys Arg Arg His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
        595                 600                 605

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
    610                 615                 620
```

```
Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
625                 630                 635                 640


Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
                645                 650                 655


Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
            660                 665                 670


Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
        675                 680                 685


Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
    690                 695                 700


Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
705                 710                 715                 720


Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
                725                 730


<210>  116
<211>  758
<212>  PRT
<213>  Artificial

<220>
<223>  A200 Heavy chain amino acid sequence

<400>  116

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 Gly
        435                 440                 445
```

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Tyr Gly Asp Lys Asp Lys Arg Arg His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro Thr Gly Gly Gly Gly Ser
                565                 570                 575

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            580                 585                 590

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
        595                 600                 605

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
    610                 615                 620

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
625                 630                 635                 640

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
```

```
                645                 650                 655

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            660                 665                 670

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        675                 680                 685

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    690                 695                 700

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
705                 710                 715                 720

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                725                 730                 735

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            740                 745                 750

Asn Thr Ser Asn Pro Asp
        755


<210>  117
<211>  730
<212>  PRT
<213>  Artificial

<220>
<223>  A201 Heavy chain amino acid sequence

<400>  117

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 Lys Gly
```

```
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460

Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Asp Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Gly Gly Gly Gly Ser Gly Gly Gly
                565                 570                 575

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            580                 585                 590

Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
        595                 600                 605

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
    610                 615                 620

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
625                 630                 635                 640
```

```
Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
                645                 650                 655

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
            660                 665                 670

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
        675                 680                 685

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
    690                 695                 700

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
705                 710                 715                 720

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
                725                 730
```

<210> 118
<211> 755
<212> PRT
<213> Artificial

<220>
<223> A202 Heavy chain amino acid sequence

<400> 118

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Glu Thr Arg
    450                 455                 460
```

```
Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln
465                 470                 475                 480

Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys
                485                 490                 495

Tyr Ala Ser Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys
            500                 505                 510

Gly Cys Trp Asp Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val
        515                 520                 525

Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn
    530                 535                 540

Phe Cys Asn Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu
545                 550                 555                 560

Val Thr Tyr Glu Pro Pro Pro Thr Gly Gly Gly Gly Ser Gly Gly Gly
                565                 570                 575

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            580                 585                 590

Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala
        595                 600                 605

Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro
    610                 615                 620

Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
625                 630                 635                 640

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
                645                 650                 655

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
```

660 665 670

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
675 680 685

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
690 695 700

His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
705 710 715 720

Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
725 730 735

Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
740 745 750

Asn Pro Asp
755

<210> 119
<211> 732
<212> PRT
<213> Artificial

<220>
<223> A203 Heavy chain amino acid sequence

<400> 119

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 Lys Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Ala Ile
```

```
    450                 455                 460

Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Tyr Asn Ala Asn Trp
465                 470                 475                 480

Glu Leu Glu Arg Thr Asn Gln Thr Gly Val Glu Pro Cys Glu Gly Glu
                485                 490                 495

Lys Asp Lys Arg Leu His Cys Tyr Ala Thr Trp Arg Asn Ile Ser Gly
            500                 505                 510

Ser Ile Glu Ile Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys
        515                 520                 525

Tyr Asp Arg Thr Asp Cys Val Glu Thr Glu Glu Asn Pro Gln Val Tyr
    530                 535                 540

Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe
545                 550                 555                 560

Pro Glu Met Glu Val Thr Gln Pro Thr Ser Gly Gly Gly Gly Ser Gly
                565                 570                 575

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            580                 585                 590

Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
        595                 600                 605

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
    610                 615                 620

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
625                 630                 635                 640

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
                645                 650                 655
```

```
Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
            660                 665                 670

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
        675                 680                 685

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
    690                 695                 700

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
705                 710                 715                 720

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
                725                 730
```

<210> 120
<211> 757
<212> PRT
<213> Artificial

<220>
<223> A204 Heavy chain amino acid sequence

<400> 120

```
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 Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Ala Ile
    450                 455                 460

Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Tyr Asn Ala Asn Trp
465                 470                 475                 480
```

```
Glu Leu Glu Arg Thr Asn Gln Thr Gly Val Glu Pro Cys Glu Gly Glu
               485                 490                 495

Lys Asp Lys Arg Leu His Cys Tyr Ala Thr Trp Arg Asn Ile Ser Gly
            500                 505                 510

Ser Ile Glu Ile Val Lys Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys
        515                 520                 525

Tyr Asp Arg Thr Asp Cys Val Glu Thr Glu Glu Asn Pro Gln Val Tyr
    530                 535                 540

Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe
545                 550                 555                 560

Pro Glu Met Glu Val Thr Gln Pro Thr Ser Gly Gly Gly Gly Ser Gly
               565                 570                 575

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            580                 585                 590

Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met
        595                 600                 605

Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala
    610                 615                 620

His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn
625                 630                 635                 640

Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe
               645                 650                 655

Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr
            660                 665                 670

Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys
```

675 680 685

Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu
690 695 700

Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile
705 710 715 720

Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys
725 730 735

Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn
740 745 750

Thr Ser Asn Pro Asp
755

<210> 121
<211> 534
<212> PRT
<213> Artificial

<220>
<223> A216 amino acid sequence

<400> 121

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

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

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

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

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

```
65                  70                  75                  80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

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

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

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

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

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

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

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

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

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

Gly Ser Gly Gly Gly Gly Ser Glu Thr Gln Glu Cys Leu Phe Phe Asn
                245                 250                 255

Ala Asn Trp Glu Lys Asp Arg Thr Asn Gln Thr Gly Val Glu Pro Cys
            260                 265                 270
```

```
Tyr Gly Asp Lys Asp Lys Arg Arg His Cys Phe Ala Thr Trp Lys Asn
        275                 280                 285

Ile Ser Gly Ser Ile Glu Ile Val Lys Gln Gly Cys Trp Leu Asp Asp
    290                 295                 300

Ile Asn Cys Tyr Asp Arg Thr Asp Cys Val Glu Lys Lys Asp Ser Pro
305                 310                 315                 320

Glu Val Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe
                325                 330                 335

Ser Tyr Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser Asn Pro Val
            340                 345                 350

Thr Pro Lys Pro Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        355                 360                 365

Gly Gly Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
    370                 375                 380

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
385                 390                 395                 400

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
                405                 410                 415

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            420                 425                 430

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        435                 440                 445

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    450                 455                 460

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
```

```
465                 470                 475                 480

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                485                 490                 495

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
            500                 505                 510

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
        515                 520                 525

Asn Thr Ser Asn Pro Asp
    530


<210>  122
<211>  584
<212>  PRT
<213>  Artificial

<220>
<223>  A167 Heavy chain amino acid sequence

<400>  122

Gln Val Gln Leu Val Gln Ser Gly Ala 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 Ser Tyr
            20                  25                  30

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

Gly Trp Ile Ile Pro Tyr Asn Gly Asn Thr Asn Ser Ala Gln Lys Leu
    50                  55                  60

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

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
```

```
                85                  90                  95

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

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser
    130                 135                 140

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

Ala Ser Gly Tyr Thr Phe Ser Ser Asn Val Ile Ser Trp Val Arg Gln
                165                 170                 175

Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Gly Val Ile Pro Ile Val
            180                 185                 190

Asp Ile Ala Asn Tyr Ala Gln Arg Phe Lys Gly Arg Val Thr Ile Thr
        195                 200                 205

Ala Asp Glu Ser Thr Ser Thr Thr Tyr Met Glu Leu Ser Ser Leu Arg
    210                 215                 220

Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ser Thr Leu Gly Leu Val
225                 230                 235                 240

Leu Asp Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
                245                 250                 255

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
            260                 265                 270

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
        275                 280                 285
```

```
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
    290                 295                 300

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
305                 310                 315                 320

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
                325                 330                 335

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
            340                 345                 350

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala
        355                 360                 365

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
    370                 375                 380

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
385                 390                 395                 400

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
                405                 410                 415

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
            420                 425                 430

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
        435                 440                 445

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
    450                 455                 460

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
465                 470                 475                 480

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
```

```
                485                 490                 495

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
            500                 505                 510

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
        515                 520                 525

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
    530                 535                 540

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
545                 550                 555                 560

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
                565                 570                 575

Ser Leu Ser Leu Ser Leu Gly Lys
            580


<210>  123
<211>  337
<212>  PRT
<213>  Artificial

<220>
<223>  A167 Light chain amino acid sequence

<400>  123

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

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
            20                  25                  30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
        35                  40                  45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
```

```
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65                  70                  75                  80

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

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

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

Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
    130                 135                 140

Arg Ala Ser Gln Ser Leu Gly Ser Ser Tyr Leu Ala Trp Tyr Gln Gln
145                 150                 155                 160

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg
                165                 170                 175

Ala Pro Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            180                 185                 190

Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr
        195                 200                 205

Tyr Cys Gln Gln Tyr Ala Asp Ser Pro Ile Thr Phe Gly Gln Gly Thr
    210                 215                 220

Arg Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
225                 230                 235                 240

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                245                 250                 255
```

```
Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            260                 265                 270

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        275                 280                 285

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    290                 295                 300

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
305                 310                 315                 320

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
                325                 330                 335

Ala
```

<210> 124
<211> 12
<212> PRT
<213> Artificial

<220>
<223> Peptide linker sequence

<400> 124

```
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1               5                   10
```

<210> 125
<211> 4
<212> PRT
<213> Artificial

<220>
<223> Peptide linker sequence

<400> 125

Gly Gly Gly Ser

1

<210> 126
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Peptide linker sequence

<400> 126

Gly Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1 5 10

<210> 127
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Peptide linker sequence

<400> 127

Gly Ser Ser Gly Thr
1 5

<210> 128
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Peptide linker sequence

<400> 128

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10

<210> 129
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Peptide linker sequence

<400> 129

Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1   5   10   15

Ala

<210> 130
<211> 20
<212> PRT
<213> Artificial

<220>
<223> Peptide linker sequence

<400> 130

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> 131
<211> 8
<212> PRT
<213> Artificial

<220>
<223> Peptide linker sequence

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1   5

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