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DESCRIPTION

[0001] The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is 910180_422PC_SEQUENCE_LISTING.txt. The text file is 839 KB, was created on December 29, 2010, and is being submitted electronically via EFS-Web, concurrent with the filing of the specification.

BACKGROUND

Technical Field

[0002] The present disclosure generally provides polypeptide heterodimers, compositions thereof, and methods for making and using such polypeptide heterodimers. More specifically, the polypeptide heterodimers provided herein are formed, in part, via natural heterodimerization between an immunoglobulin CH1 region and an immunoglobulin light chain constant region (CL). In addition, the polypeptide heterodimers provided herein comprise two or more binding domains that specifically bind one or more targets. Furthermore, both single chain polypeptides of the polypeptide heterodimers provided herein each comprise an Fc region portion (e.g., immunoglobulin CH2 and CH3 domains).

Description of the Related Art

[0003] The process of signal transduction often involves receptor proteins that have extracellular domains, transmembrane domains, and intracellular domains. During ligand binding, cell surface receptor molecules often oligomerize or multimerize (also referred to as "cross-link") to effectively transmit a signal to the intracellular compartment of the cell. The stimulation or blockade of this interaction between a receptor and a ligand or of the subsequent oligomerization or multimerization of receptors has important therapeutic implications for a wide variety of diseases.

[0004] Exemplary molecules useful in modulating receptor and ligand interactions include antibodies or molecules derived from antibodies. For instance, an antibody or its derivative may function as a receptor antagonist that binds to a cell surface receptor and inactivates it by blocking the binding site of an activating ligand or preventing receptor dimerization or multimerization required for activation. In certain other cases, an antibody or its derivative may function as an agonist by binding to and cross-linking multiple membrane receptors, mimicking the function of a natural ligand. Another example is a bispecific antibody derivative that may be used to direct cytotoxic agents or immune effector cells to target sites, such as tumors.

[0005] Bispecific antibodies are antibody-based molecules that can simultaneously bind two separate and distinct antigens (or different epitopes of the same antigen). One use of bispecific antibodies has been to redirect cytotoxic immune effector cells for enhanced killing of tumor cells by antibody dependent cellular cytotoxicity (ADCC). In this context, one arm of the bispecific antibody binds an antigen on the tumor cell, and the other binds a determinant expressed on effector cells. By cross-linking tumor and effector cells, the bispecific antibody not only brings the effector cells within the proximity of the tumor cells but also simultaneously triggers their activation, leading to effective tumor cell-killing. Bispecific antibodies have also been used to enrich chemo- or radiotherapeutic agents in tumor tissues to minimize detrimental effects to normal tissue. In this setting, one arm of the bispecific antibody binds an antigen expressed on the cell targeted for destruction, and the other arm delivers a chemotherapeutic drug, radioisotope, or toxin.

[0006] A major obstacle in the general development of bispecific antibodies has been the difficulty of producing materials of sufficient quality and quantity for both preclinical and clinical studies. Initially, the main route to the production of bispecific antibodies was by co-expression of both the light chains and both the heavy chains of two parent antibodies of different specificities in a single cell. However, the desired binding-competent bispecific antibodies are a minor product, and purification from the other products is very difficult. Another traditional method for bispecific antibody production is chemical conjugation of two antibodies or their fragments having different specificities. However, this method is also complicated, and the chemical modification process may inactivate the antibody or promote aggregation. Because purification from undesired products remains difficult, the resulting low yield and poor quality of bispecific antibody make this process unsuitable for the large scale production required for clinical development.

[0007] Recently, various heterodimerization techniques have been used to improve the production of bispecific antibodies. However, fusion of simple heterodimerization domains like the Jun/Fos coiled-coil to scFv domains lead to a mixture of homo- and heterodimers and need to be assembled by refolding (de Kruif and Logtenberg, J. Biol. Chem. 271 : 7630-4, 1996). Fusion of scFv fragments to whole antibodies was also used as a dimerization device (Coloma and Morrison, Nat. Biotechnol. 15 : 159-63, 1997). However, such fusion results in a large molecule with poor solid tissue penetration capabilities. Fusion of two scFv fragments together has also been used to generate bispecific proteins (e.g., BITE® antibodies by Micromet Inc., Bethesda, MD, U.S. Patent No. 7,635,472). However, such proteins do not contain Fc regions, and thus do not allow manipulation of their activities via Fc regions. In addition, these proteins are small (~55 kDa) and thus have relatively short half lives in serum.

[0008] WO 2006/074399 A2 discloses multispecific binding molecules comprising synthetic connecting peptides.

[0009] WO 02/02781 A1 relates to the production of bispecific or multispecific, bi- or tetravalent antibodies using recombinant DNA methods and recombinant production methods. The resulting antibody consists of one or two diabody molecules that are heterodimerized by creating a fusion protein with the CL and CH1 immunoglobulin constant domains.

[0010] US 6 809 185 B1 discloses a class of molecules specified as novel multipurpose antibody derivatives.

[0011] US 2007/014794 A1 discloses a method of preparing heteromultimeric polypeptides such as bispecific antibodies, bispecific immunoadhesins and antibody-immunoadhesin chimeras.

[0012] To date, immunoglobulin fusion technology has not provided commercially viable heterodimeric proteins or methods for making them. Thus, there remains a need in the art for alternative multispecific heterodimeric proteins as well as efficient methods for producing the same.

[0013] In a first aspect of the present invention there is provided a polypeptide heterodimer, comprising:

1. (a) a first single chain polypeptide (SCP-I) comprising from one to four binding domains that specifically bind from one to four targets, a hinge (H-I), an immunoglobulin heterodimerization domain (HD-I), and an immunoglobulin CH2 and CH3 domain of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, or any combination thereof (CH2CH3-I); and
2. (b) a second single chain polypeptide (SCP-II) comprising from zero to four binding domains that specifically bind from zero to four targets, a hinge (H-II), an immunoglobulin 3 heterodimerization domain (HD-II), and an immunoglobulin CH2 and CH3 domain of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, or any combination thereof (CH2CH3-II);

wherein

1. (i) the immunoglobulin heterodimerization domain of the first single chain polypeptide (HD-I) and the immunoglobulin heterodimerization domain of the second single chain polypeptide (HD-II) preferentially associate with each other to form a polypeptide heterodimer comprised of the first single chain polypeptide (SCP-I) and the second single chain polypeptide (SCP-II), and
 1. (1) the immunoglobulin heterodimerization domain of the first single chain polypeptide (HD-I) comprises a first immunoglobulin CH1 region, and the immunoglobulin heterodimerization domain of the second single chain polypeptide (HD-II) comprises a first immunoglobulin CL region, or
 2. (2) the immunoglobulin heterodimerization domain of the first single chain polypeptide (HD-I) comprises a first immunoglobulin CL region, and the immunoglobulin heterodimerization domain of the second single chain polypeptide (HD-II) comprises a first immunoglobulin CH1 region;
2. (ii) wherein the first immunoglobulin CL region is an altered human immunoglobulin C κ region with one or more amino acids of a wild type human C κ region substituted at N29, N30, Q52, V55, T56, S68, or T70,

provided that the polypeptide heterodimer comprises at least two binding domains that specifically bind at least two different targets.

[0014] In a further aspect of the invention there is also provided a composition comprising the polypeptide heterodimer of the present invention and a pharmaceutically acceptable excipient.

[0015] In another aspect of the present invention there is also provided the polypeptide heterodimer of the present invention for use in a) a method for directing T cell activation, wherein the polypeptide heterodimer comprises a binding domain that specifically binds TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ or a combination thereof, and a second binding domain that specifically binds a different target; or

b) inhibiting growth, metastasis or metastatic growth of a malignancy, wherein the polypeptide heterodimer comprises a binding domain that specifically binds TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ , c-Met or Ron.

c) treating an autoimmune or inflammatory condition, wherein the polypeptide heterodimer comprises a binding domain that specifically binds TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ , or CD28.

[0016] In another aspect of the present invention there is provided an expression effector capable of expressing the polypeptide heterodimer of the present invention comprising an expression vector capable of expressing the polypeptide heterodimer of the present invention, comprising a first polynucleotide encoding the first single chain polypeptide and a second polynucleotide encoding the second single chain polypeptide.

[0017] The present invention also provides a host cell comprising the expression vector of the present invention and a host cell comprising first and second expression vectors capable of expressing the first and second single chain polypeptides, respectively, of the polypeptide heterodimer of the present invention.

[0018] In another aspect of the present invention there is provided a method for making a polypeptide heterodimer, comprising

1. (a) culturing a host cell in accordance with the present invention under conditions suitable to express first and second single chain polypeptides, and
2. (b) optionally isolating or purifying the heterodimers formed from the first and second single chain polypeptides from the culture.

[0019] The present disclosure provides polypeptide heterodimers formed between two different single chain polypeptides via natural heterodimerization of an immunoglobulin CH1 region and an immunoglobulin light chain constant region (CL). The present disclosure also provides nucleic acids, vectors, host cells and methods for making polypeptide heterodimers as well as methods for using such polypeptide heterodimers, such as in directed T cell activation, inhibiting solid malignancy growth, treating autoimmune or inflammatory conditions, or treating B-cell associated disorders or diseases.

[0020] In one aspect, the present disclosure provides a polypeptide heterodimer that comprises (a) a first single chain polypeptide (SCP-I) comprising from one to four binding domains that specifically bind from one to four targets, a hinge (H-I), an immunoglobulin heterodimerization domain (HD-I), and an Fc region portion (FRP-I); and (b) a second single chain polypeptide (SCP-II) comprising from zero to four binding domains that specifically bind from zero to four targets, a hinge (H-II), an immunoglobulin heterodimerization domain (HD-II), and an Fc region portion (FRP-II); wherein (i) the immunoglobulin HD-I and the immunoglobulin HD-II preferentially associate with each other to form a polypeptide heterodimer comprised of SCP-I and SCP-II, and (1) the immunoglobulin heterodimerization domain of the first single chain polypeptide (HD-I) comprises a first immunoglobulin CH1 region, and the immunoglobulin heterodimerization domain of the second single chain polypeptide (HD-II) comprises a first immunoglobulin CL region, or (2) the immunoglobulin heterodimerization domain of the first single chain polypeptide (HD-I) comprises a first immunoglobulin CL region, and the immunoglobulin heterodimerization domain of the second single chain polypeptide (HD-II) comprises a first immunoglobulin CH1 region; and (ii) the Fc region portion of SCP-I and the Fc region portion of SCP-II comprise an immunoglobulin CH2 and CH3 domain of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, or any combination thereof; one or two immunoglobulin CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, IgM, or any combination thereof; or an immunoglobulin CH3 and CH4 domain of IgE, IgM, or any combination thereof, provided that the polypeptide heterodimer comprises at least two binding domains that specifically bind a target, for instance, at least two different targets.

[0021] In certain embodiments, the binding domains of the polypeptide heterodimers are single chain Fv (scFv) polypeptides.

[0022] In certain embodiments, the polypeptide heterodimer comprises two binding domains (BD1 and BD2). In one embodiment, the two binding domains (BD1 and BD2) are both on the first single chain polypeptide (SCP-I) and wherein the HD-I and FRP-I are disposed between BD1 and BD2. In another embodiment, the first binding domain (BD1) is on the first single chain polypeptide (SCP-I) and the second binding domain (BD2) is on the second single chain polypeptide (SCP-II). For example, the first binding domain (BD1) may be amino terminal to the Fc region portion of the first single chain polypeptide (FRP-I), and the second binding domain (BD2) may be amino terminal to the Fc region portion of the second single chain polypeptide (FRP-II). Alternatively, the first binding domain (BD1) may be amino terminal to the Fc region portion of the first single chain polypeptide (FRP-I), and the second binding domain (BD2) may be carboxyl terminal to the Fc region portion of the second single chain polypeptide (FRP-II). Also alternatively, the first binding domain (BD1) may be carboxyl terminal to the Fc region portion of the first single chain polypeptide

(FRP-I), and the second binding domain (BD2) may be carboxyl terminal to the Fc region portion of the second single chain polypeptide (FRP-II).

[0023] In certain embodiments, the polypeptide heterodimer comprises three binding domains (BD1, BD2 and BD3). In one embodiment, the HD-I and FRP-I are disposed between BD1 and BD2, and the third binding domain (BD3) is amino terminal to the Fc region portion of the second single chain polypeptide (FRP-II). In an alternative embodiment, the HD-I and FRP-I are disposed between BD1 and BD2, and the third binding domain (BD3) is carboxyl terminal to the Fc region portion of the second single chain polypeptide (FRP-II).

[0024] In certain embodiments, the polypeptide heterodimer comprises four binding domains (BD1, BD2, BD3, and BD4). For instance, the HD-I and FRP-I may be disposed between BD1 and BD2, and the HD-II and FRP-II may be disposed between BD3 and BD4.

[0025] In certain embodiments, the polypeptide heterodimer comprises five to eight binding domains (e.g., 5, 6, 7 or 8 binding domains).

[0026] In certain embodiments, at least one of the binding domains of the polypeptide heterodimers provided herein specifically binds to, or is an antagonist of, TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ , CD28, CD79b, hyperIL-6, monoIL-10, CD86, CD20, PSMA, CD19, HLA-DR, Ron, c-Met, CEACAM-6, LIGHT, GITRL, CD40, PDL1, PDL2, HVEM, LTBR, EGFR, EGFRvIII, ErbB2, ErbB3, ErbB4, IGF1R, EphA2, PDGFR, VEGFR1-4, Angiopoietin 2, CD64, CD32A, CD16, CD71, TNFR1, TNFR2, TWEAKR, TACI, BAFF-R, BCMA, FAS, CD32B, CD21, CD22, CD30, CD33, CD37, CD38, CD70, TNF α , IL-6, hyperIL-6, IL-2, IL-1, IL-7, IL-8, IL-17A/C, IP-10, IFN γ , IFN α , RANKL, FASL, EGF β , IL10, IL17A/F, CSF2, IGF1, IGF2, BLyS/APRIL, , HGF, MSP, EGF (including epregeulin, herregulin, β -regulin, neuregulin), HIF-1 α , VEGFA, VEGFB, VEGFC, VEGFD, TNF α , Wnt, SHH, EGF β , PDGF, TWEAK, EpCAM, CEA, PCTA-1, STEAP-1, PSCA, ALCAM (CD166), EphA2, CD151, CA-125, MUC-1, MAGE-1, TROP2, CCR5, HER-3, HER-4, EGFR, CEA, MUC2, MUC3, MUC4, MUC5_{AC}, MUC5_B, MUC7, β hCG, Lewis-Y, ganglioside GD3, 9-O-Acetyl-GD3, GM2, Globo H, fucosyl GM1, Poly SA, GD2, Carboanhydrase IX (MN/CA IX), CD44v6, Sonic Hedgehog (Shh), Wue-1, Plasma Cell Antigen, (membrane-bound) IgE, Melanoma Chondroitin Sulfate Proteoglycan (MCSP), CCR8, TNF-alpha precursor, STEAP, mesothelin, A33 Antigen, Prostate Stem Cell Antigen (PSCA), Ly-6; desmoglein 4, E-cadherin neoepitope, Fetal Acetylcholine Receptor, CD25, CA19-9 marker, CA-125 marker and Muellierian Inhibitory Substance (MIS) Receptor type II, sTn (sialylated Tn antigen; TAG-72), FAP (fibroblast activation antigen), endosialin, EGFRvIII, LG, SAS, CD63, IGF1R, CD151, TGFB2, GHRHR, GHR, IL-6R, gp130, TNFR2, OSMR β , Patched-1, Frizzled, Robo1, CD80, CD81, CD86, OX40, CD40, CD137, LIFER β , TLR7 or TLR9.

[0027] In certain other embodiments, at least one of the binding domains of the polypeptide heterodimer is an agonist of IL-10, HLA-G, HGF, IL-35, PD-1, BTLA, TNFR1, TNFR2, DR4, DR5, TWEAKR, or FAS.

[0028] In certain polypeptide heterodimers provided herein, at least one binding domain specifically binds a TCR complex or a component thereof, and at least another binding domain specifically binds to PSMA, CD79b, CD19, HLA-DR, CD20, RON, c-Met, or CEACAM-6.

[0029] In certain other polypeptide heterodimers provided herein, at least one binding domain specifically binds to CD28, and at least another binding domain specifically binds to, or is an antagonist of, CD79b, hyperIL-6, PDL2, monoIL-10, CD86, LIGHT, GITRL, CD40, PDL1, HVEM, or LTBR.

[0030] In certain other polypeptide heterodimers provided herein, at least one binding domain specifically binds to CD28, and at least another binding domain is an agonist of IL-10, HLA-G, HGF, IL-35, PD-1, or BTLA.

[0031] In certain embodiments, the immunoglobulin heterodimerization domain of the first single chain polypeptide (HD-I) comprises the first immunoglobulin CH1 region and the immunoglobulin heterodimerization domain of the second single chain polypeptide (HD-II) comprises the first immunoglobulin CL region. In one embodiment, the first CH1 region is amino terminal to the Fc region portion of the first single chain polypeptide, and the first CL region is amino terminal to the Fc region portion of the second single chain polypeptide. In another embodiment, the first CH1 region is carboxyl terminal to the Fc region portion of the first single chain polypeptide, and the first CL region is carboxyl terminal to the Fc region portion of the second single chain polypeptide.

[0032] In certain embodiments in which the immunoglobulin heterodimerization domain of the first single chain polypeptide (HD-I) comprises the first immunoglobulin CH1 region and the immunoglobulin heterodimerization domain of the second single chain polypeptide (HD-II) comprises the first immunoglobulin CL region, the first single chain polypeptide further comprises a second

CH1 region and the second single chain polypeptide further comprises a second CL region, and the second CH1 region of the first single chain polypeptide and the second CL region of the second single chain polypeptide associate with each other in the polypeptide heterodimer. For instance, the Fc region portion of the first single chain polypeptide may be disposed between the first and second CH1 regions, and the Fc region portion of the second single chain polypeptide may be disposed between the first and second CL regions. Alternatively, both the first and second CH1 regions may be amino terminal to the Fc region portion of the first single chain polypeptide, and both the first and second CL regions may be amino terminal to the Fc region portion of the second single chain polypeptide. Also alternatively, both the first and second CH1 regions may be carboxyl terminal to the Fc region portion of the first single chain polypeptide, and both the first and second CL regions may be carboxyl terminal to the Fc region portion of the second single chain polypeptide.

[0033] In certain other embodiments in which the immunoglobulin heterodimerization domain of the first single chain polypeptide (HD-I) comprises the first immunoglobulin CH1 region and the immunoglobulin heterodimerization domain of the second single chain polypeptide (HD-II) comprises the first immunoglobulin CL region, the first single chain polypeptide further comprises a second CL region and the second single chain polypeptide further comprises a second CH1 region, and the second CL region of the first single chain polypeptide and the second CH1 region of the second single chain polypeptide associate with each other in the polypeptide heterodimer. For instance, in one embodiment, in the first single chain polypeptide, the first CH1 region is amino terminal to the Fc region portion and the second CL region is carboxyl terminal to the Fc region portion; and in the second single chain polypeptide, the first CL region is amino terminal to the Fc region portion, and the second CH1 region is carboxyl terminal to the Fc region portion. In another embodiment, in the first single chain polypeptide, the first CH1 region is carboxyl terminal to the Fc region portion, and the second CL region is amino terminal to the Fc region portion; and in the second single chain polypeptide, the first CL region is carboxyl terminal to the Fc region portion, and the second CH1 region is amino terminal to the Fc region portion. In yet another embodiment, in the first single chain polypeptide, both the first CH1 region and the second CL regions are amino terminal to the Fc region portion, and the first CH1 region is amino terminal to the second CL region; and in the second single chain polypeptide, both the first CL region and the second CH1 region are amino terminal to the Fc region portion, and the first CL region is amino terminal to the second CH1 region. In yet another embodiment, in the first single chain polypeptide, both the first CH1 region and the second CL regions are amino terminal to the Fc region portion, and the second CL region is amino terminal to the first CH1 region; and in the second single chain polypeptide, both the first CL region and the second CH1 region are amino terminal to the Fc region portion, and the second CH1 region is amino terminal to the first CL region. In a further embodiment, in the first single chain polypeptide, both the first CH1 region and the second CL regions are carboxyl terminal to the Fc region portion, and the first CH1 region is amino terminal to the second CL region; and in the second single chain polypeptide, both the first CL region and the second CH1 region are carboxyl terminal to the Fc region portion, and the first CL region is amino terminal to the second CH1 region. In another embodiment, in the first single chain polypeptide, both the first CH1 region and the second CL regions are carboxyl terminal to the Fc region portion, and the second CL region is amino terminal to the first CH1 region; and in the second single chain polypeptide, both the first CL region and the second CH1 region are carboxyl terminal to the Fc region portion, and the second CH1 region is amino terminal to the first CL region.

[0034] In certain embodiments, the immunoglobulin heterodimerization domain of the first single chain polypeptide (HD-I) comprises a first immunoglobulin CL region, and the immunoglobulin heterodimerization domain of the second single chain polypeptide (HD-II) comprises a first immunoglobulin CH1 region. In one embodiment, the first CL region is amino terminal to the Fc region portion of the first single chain polypeptide, and the first CH1 region is amino terminal to the Fc region portion of the second single chain polypeptide. In another embodiment, the first CL region is carboxyl terminal to the Fc region portion of the first single chain polypeptide, and the first CH1 region is carboxyl terminal to the Fc region portion of the second single chain polypeptide. In yet another embodiment, the first single chain polypeptide further comprises a second CL region and the second single chain polypeptide further comprises a second CH1 region, and the second CL region of the first single chain polypeptide and the second CH1 region of the second single chain polypeptide associate with each other in the polypeptide heterodimer. For instance, the Fc region portion of the first single chain polypeptide may be disposed between the first and second CL regions, and the Fc region portion of the second single chain polypeptide may be disposed between the first and second CH1 regions. Alternatively, both the first and second CL regions may be amino terminal to the Fc region portion of the first single chain polypeptide, and both the first and second CH1 regions may be amino terminal to the Fc region portion of the second single chain polypeptide. Also alternatively, both the first and second CL regions may be carboxyl terminal to the Fc region portion of the first single chain polypeptide, and both the first and second CH1 regions may be carboxyl terminal to the Fc region portion of the second single chain polypeptide.

[0035] In certain embodiments, the first CL region is a C κ region. In other embodiments, the first CL region is a C λ region.

[0036] In certain embodiments, the second CL region is a C κ region. In other embodiments, the second CL region is a C λ region.

[0037] In certain embodiments, the C κ region is a wild type human immunoglobulin C κ region. In certain other embodiments, the

Ck region is an altered human immunoglobulin Ck region with one or more amino acids of a wild type human Ck region substituted at N29, N30, Q52, V55, T56, S68, or T70. For example, the one or more amino acid substitutions may be selected from Ala (A), Arg (R), Trp (W), Tyr (Y), Glu (E), Gln (Q), Lys (K), Asp (D), Met (M), Ser (S), and Phe (F).

[0038] In certain embodiments, the CH1 region is an altered human immunoglobulin CH1 region comprising an amino acid substitution by which Val (V) at position 68 is substituted by Lys (K), Arg (R) or His (H), and wherein the Ck region is an altered human immunoglobulin Ck region comprising an amino acid substitution by which Leu (L) at position 29 is substituted by Asp (D) or Glu (E). In certain other embodiments, the CH1 region is an altered human immunoglobulin CH1 region comprising an amino acid substitution by which Val (V) at position 68 is changed to Asp (D) or Glu (E), and wherein the Ck region is an altered human immunoglobulin Ck region comprising an amino acid substitution by which Leu (L) at position 29 is changed to Lys (K), Arg (R) or His (H).

[0039] In certain embodiments, the Cλ region is a wild type human immunoglobulin Cλ region.

[0040] In certain embodiments, the first CH1 region or the second CH1 region when present is a wild type human immunoglobulin CH1 region, such as a wild type human IgG1 CH1 region.

[0041] In certain embodiments, the first CH1 region or the second CH1 region when present is an altered human immunoglobulin CH1 region, such as an altered human IgG1 CH1 region, with the cysteine of a wild type human immunoglobulin CH1 region that is involved in forming a disulfide bond with a wild type human immunoglobulin CL region deleted or substituted.

[0042] In certain embodiments, the Ck region is an altered human immunoglobulin Ck region, such as an with the cysteine residue of a wild type human Ck region that is involved in forming a disulfide bond with a wild type human immunoglobulin CH1 region deleted or substituted.

[0043] In certain embodiments, the Cλ region is an altered human immunoglobulin Cλ region with the cysteine residue of a wild type human Cλ region that is involved in forming a disulfide bond with a wild type human immunoglobulin CH1 region deleted or substituted.

[0044] In certain embodiments, the first CH1 region and the second CH1 region when present is a polypeptide comprising SEQ ID NO:114, 844 or 845.

[0045] In certain embodiments, the Ck region when present is selected from any one of the polypeptides comprising SEQ NOS:141-178, 202, and 838-843.

[0046] In certain embodiments, the Cλ region when present is a polypeptide comprising SEQ ID NO:140.

[0047] In certain embodiments, the Fc region portion of the first single chain polypeptide (FRP-I) and the Fc region portion of the second single chain polypeptide (FRP-II) each comprise an immunoglobulin CH2 domain, such as an IgG1 CH2 domain or an IgG2, IgG3, IgG4, IgA1, IgA2, or IgD CH2 domain.

[0048] In certain embodiments, the Fc region portion of the first single chain polypeptide (FRP-I) and the Fc region portion of the second single chain polypeptide (FRP-II) each comprise an immunoglobulin CH3 domain, such as an IgG1 CH3 domain or an IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE or IgM CH3 domain.

[0049] In certain embodiments, the Fc region portion of the first single chain polypeptide (FRP-I) and the Fc region portion of the second single chain polypeptide (FRP-II) each comprise an immunoglobulin CH2 domain and an immunoglobulin CH3 domain, such as are IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, or IgD CH2 and CH3 domains.

[0050] In some embodiments in which the Fc region portion comprises an immunoglobulin CH3 domain that is immediately amino terminal to an immunoglobulin heterodimerization domain (e.g., a CH1 domain or a Ck domain), the immunoglobulin CH3 domain is linked to the CH1 domain immediately carboxyl terminal to the immunoglobulin CH3 domain in one single chain polypeptide via a peptide comprising SEQ ID NOS:846, 847, 848, or 849; and the immunoglobulin CH3 domain is linked to the Ck domain immediately carboxyl terminal to the immunoglobulin CH3 domain in the other single chain polypeptide via a peptide comprising SEQ ID NOS:846, 850, 951, or 852.

[0051] In certain embodiments, the Fc region portion of the first single chain polypeptide (FRP-I) and the Fc region portion of the

second chain polypeptide (FRP-II) comprise IgM or IgE CH3 and CH4 domains.

[0052] In certain embodiments in which the Fc region portion comprises an immunoglobulin CH2 domain, the CH2 domain may be an altered human IgG1, IgG2, IgG3, or IgG4 CH2 domain. Exemplary altered human IgG1, IgG2, IgG3 or IgG4 CH2 domain include those that comprise (a) an amino acid substitution at position 297 and at least one additional substitution or deletion at positions 234 to 238; (b) one or more amino acid mutations at positions 234-238 and at least one substitution at position 253, 310, 318, 320, 322, or 331; or (c) an amino acid substitution at the asparagine of position 297, one or more substitutions or deletions at positions 234 to 238, and at least one substitution at position 253, 310, 318, 320, 322, or 331. Another exemplary CH2 domain is an altered human IgG1 CH2 domain that comprises amino acid substitutions at positions L234, L235, G237, E318, K320 and K322.

[0053] In certain embodiments, the CH3 domain of the first single chain polypeptide is an altered human IgG1, IgG2, IgG3, or IgG4 CH3 domain that comprises a T366W, and the CH3 domain of the second single chain polypeptide is an altered human IgG1, IgG2, IgG3 or IgG4 CH3 domain that comprises a Y407A substitution. In certain other embodiments, the CH3 domain of the first single chain polypeptide is an altered human IgG1, IgG2, IgG3, or IgG4 CH3 domain that comprises a T366Y substitution, and the CH3 domain of the second single chain polypeptide is an altered human IgG1, IgG2, IgG3 or IgG4 CH3 domain that comprises a Y407T substitution. In certain other embodiments, the CH3 domain of the first single chain polypeptide is an altered human IgG1, IgG2, IgG3, or IgG4 CH3 domain that comprises a T366W substitution, and the CH3 domain of the second single chain polypeptide is an altered human IgG1, IgG2, IgG3 or IgG4 CH3 domain that comprises T366S, L368A and Y407V substitutions. In certain other embodiments, the CH3 domain of the first single chain polypeptide is an altered human IgG1, IgG2, IgG3, or IgG4 CH3 domain that comprises a Y407A substitution, and the CH3 domain of the second single chain polypeptide is an altered human IgG1, IgG2, IgG3 or IgG4 CH3 domain that comprises a T366W substitution. In certain other embodiments, the CH3 domain of the first single chain polypeptide is an altered human IgG1, IgG2, IgG3, or IgG4 CH3 domain that comprises a Y407T substitution, and the CH3 domain of the second single chain polypeptide is an altered human IgG1, IgG2, IgG3 or IgG4 CH3 domain that comprises a T366Y substitution. In certain other embodiments, the CH3 domain of the first single chain polypeptide is an altered human IgG1, IgG2, IgG3, or IgG4 CH3 domain that comprises T366S, L368A and Y407W substitutions, and the CH3 domain of the second single chain polypeptide is an altered human IgG1, IgG2, IgG3 or IgG4 CH3 domain that comprises a T366W substitution.

[0054] In certain embodiments, the hinge of both the first and second single chain polypeptides is an immunoglobulin hinge region, such as an IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, or IgE hinge. In certain embodiments, the immunoglobulin hinge is a wild type immunoglobulin hinge. In certain other embodiments, the immunoglobulin hinge is an altered immunoglobulin hinge selected from SEQ ID NOS:232, 234, 240, 664-673, 675 and 676.

[0055] In certain embodiments, the hinge region is (a) at the amino terminal to the Fc region portion, (b) disposed between the binding domain and the immunoglobulin heterodimerization domain, (c) disposed between the immunoglobulin heterodimerization domain and the Fc region portion, (d) at the amino terminus of the first or second single chain polypeptide, (e) disposed between the Fc region portion and a binding domain, or (f) at the carboxyl terminus of the first or second single chain polypeptide.

[0056] In certain embodiments, at least one of the first and second single chain polypeptide hinges is a C-type lectin hinge region, such as an NKg2A or NKg2D peptide, or a derivative thereof.

[0057] In certain embodiments, the hinges of the first and second single chain polypeptides are identical. In certain other embodiments, the hinges of the first and second single chain polypeptides are different.

[0058] In certain embodiments, the first single chain polypeptide comprises a binding domain that specifically binds a TCR complex or a component thereof, and the second single chain polypeptide comprises a binding domain that specifically binds CD 19, CD79b, HLA-DR or CD20.

[0059] In certain embodiments, the first single chain polypeptide comprises a binding domain that specifically binds CD28, and the second single chain polypeptide comprises a binding domain (a) that specifically binds CD79b, hyperIL-6, or CD86 or (b) that comprises a PDL ectodomain or a monIL-10.

[0060] In certain embodiments, the first single chain polypeptide comprises a binding domain that specifically binds c-Met, and the second single chain polypeptide comprises a binding domain that specifically binds RON.

[0061] In certain embodiments, the first and second single chain polypeptides comprise SEQ ID NOS: SEQ ID NOS:2 and 4, SEQ ID NOS:6 and 8, SEQ ID NOS:10 and 12, SEQ ID NOS: 14 and 16, SEQ ID NOS:18 and 20, SEQ ID NOS:20 and 22, SEQ ID

NOS:20 and 24, SEQ ID NOS:30 and 32, SEQ ID NOS:29 and 31, SEQ ID NOS:29 and 32, SEQ ID NOS:30 and 72, SEQ ID NOS:53 and 72, SEQ ID NOS:54 and 72, SEQ ID NOS:55 and 72, SEQ ID NOS:70 and 72, SEQ ID NOS:71 and 72, SEQ ID NOS:63 and 56, SEQ ID NOS:64 and 57, SEQ ID NOS:65 and 60, SEQ ID NOS:66 and 58, SEQ ID NOS:67 and 59, SEQ ID NOS:68 and 61, SEQ ID NOS:69 and 62, SEQ ID NOS:54 and 811, SEQ ID NOS:54 and 812, SEQ ID NOS:54 and 813, SEQ ID NOS:814 and 818, SEQ ID NOS:815 and 818, SEQ ID NOS:816 and 818, SEQ ID NOS:817 and 818, SEQ ID NOS:814 and 820, SEQ ID NOS:814 and 821, SEQ ID NOS:54 and 819, SEQ ID NOS:814 and 826, SEQ ID NOS:814 and 822, SEQ ID NOS:814 and 823, SEQ ID NOS:814 and 824, SEQ ID NOS:859 and 862, SEQ ID NOS:860 and 863, SEQ ID NOS:861 and 864, SEQ ID NOS:874 and 825, SEQ ID NOS:875 and 879, SEQ ID NOS:876 and 880, SEQ ID NOS:877 and 881, or SEQ ID NOS:878 and 882.

[0062] In another aspect, the present disclosure provides a composition comprising a polypeptide heterodimer provided herein and a pharmaceutically acceptable excipient.

[0063] In another aspect, the present disclosure provides an expression vector capable of expressing a polypeptide heterodimer provided herein, comprising a first polynucleotide encoding the first single chain polypeptide and a second polynucleotide encoding the second single chain polypeptide.

[0064] In another aspect, the present disclosure provides a host cell comprising the above expression vector.

[0065] In another aspect, the present disclosure provides a host cell comprising first and second expression vectors capable of expressing the first and second single chain polypeptides, respectively, of the polypeptide heterodimer provided herein.

[0066] In another aspect, the present disclosure provides a method for making a polypeptide heterodimer, comprising (a) culturing a host cell provided herein under conditions suitable to express first and second single chain polypeptides, and (b) optionally isolating or purifying the heterodimers formed from the first and second single chain polypeptides from the culture.

[0067] In another aspect, the present disclosure provides a method for directing T cell activation, comprising administering to a patient in need thereof an effective amount of a polypeptide heterodimer that comprises a binding domain that specifically binds TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ , or a combination thereof, and a second binding domain that specifically binds a different target, for instance, a tumor-specific antigen or other antigen of choice at a site or cell where T cell activation is desired.

[0068] In another aspect, the present disclosure provides a method for inhibiting growth, metastasis, or metastatic growth of a malignancy, comprising administering to a patient in need thereof an effective amount of a polypeptide heterodimer that comprises a binding domain that specifically binds TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ , c-Met, RON, or a combination thereof. In certain embodiments, the method further comprises administering to a patient in need thereof a chemotherapeutic agent or ionizing radiation.

[0069] In another aspect, the present disclosure provides a method for treating an autoimmune or inflammatory condition, comprising administering to a patient in need thereof an effective amount of a polypeptide heterodimer that comprises a binding domain that specifically binds TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ , or CD28.

[0070] In another aspect, the present disclosure provides a method for treating a B-cell associated disorder or disease comprising administering to a patient in need thereof an effective amount of a polypeptide heterodimer that comprises a binding domain that specifically binds TCR α , TCR β , CD3 γ , CD3 δ , or CD3 ϵ , and a second binding domain that specifically binds to CD 19, CD20, CD79b or HLA-DR.

[0071] In certain embodiments, the methods for using the polypeptide heterodimers provided herein may further comprise administering to a patient in need thereof a second active agent, such as a second polypeptide heterodimer, a monoclonal antibody, or an immunoglobulin-derived fusion protein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0072]

Figure 1 is a schematic representation of bivalent anti-CD28 polypeptide heterodimer X0172 (left) and SDS-PAGE analysis of X0172 (right). "NR" stands for "Non-Reduced," and "Red" stands for "Reduced."

Figure 2 shows that both a monovalent (X0124) and a bivalent (X0172) anti-CD28 polypeptide heterodimer synergize with a suboptimal concentration of PMA in stimulating purified human T cells when compared to an anti-CD28 scFv (2E12 scFv) but less than a bivalent anti-CD28 SMIP protein (2E12 SMIP).

Figure 3 shows that bivalent polypeptide heterodimer X0172 binds to CD4⁺ T cells better than 2E12 scFv and monovalent polypeptide heterodimer X0124.

Figure 4 shows cation exchange chromatography of polypeptide heterodimers X0251, X0252 and X0253 (left) and SDS-PAGE electrophoresis analysis of the same polypeptide heterodimers under non-reduced (NR) and reduced (Red) conditions (right).

Figure 5 shows the mass spectra of polypeptide heterodimer X0252, which demonstrates that the heterodimer is the predominant species.

Figure 6 shows SDS-PAGE electrophoresis analysis of polypeptide heterodimers X0283 and X0284 under non-reduced (NR) and reduced (Red) conditions (left) and cation exchange chromatography analysis of polypeptide heterodimer X0283.

Figure 7 shows direct binding to CD86 by polypeptide heterodimer X0283 as examined by BIAcore® analysis, with response units (Ru) plotted against time (left) and a schematic representation of X0283.

Figures 8A and 8B show binding of bispecific anti-RON and anti-CD3 constructs (polypeptide heterodimer S0268 and Scorpion protein S0266) to MDA-MB-453 cells (A) and to isolated T cells (B).

Figures 9A and 9B show specificity of binding to (A) Rec1 (CD19⁺, CD20⁺) cells or (B) Jurkat (CD3⁺) cells by bispecific heterodimers having either anti-CD19 and anti-CD3 binding domains (TSC020) or having anti-CD20 and anti-CD3 binding domains (TSC021).

Figures 10A-10D show proliferation of CD4⁺ and CD8⁺ T-cells in response to bispecific polypeptide heterodimers TSC054, TSC078, TSC079, and bsc19x3 (TSC036) with (A and B) Daudi (CD19⁺) cells or (C and D) MDA-MB-453 (CD19⁻) cells.

Figures 11A and 11B shows T-cell directed cytotoxicity induced by bispecific polypeptide heterodimers TSC054, TSC078, TSC079, and S0268 in a chromium (⁵¹Cr) release assay with (A) Daudi (RON⁺, CD19⁺) cells or (B) BxPC-3 (RON⁺, CD19⁻) cells.

Figure 12 shows target-dependent T-cell proliferation induced by a CD 19⁺ cell line (Daudi) using bispecific polypeptide heterodimers TSC165, TSC166, TSC167, TSC168 and TSC100 at concentrations from 0.1 pM to 10000 pM.

Figure 13 shows target-dependent T-cell proliferation induced by a CD19⁺ cell line (Daudi) using bispecific polypeptide heterodimers TSC127 and TS165 with bsc19x3 BITE as a control at concentrations from 0.001 pM to 1000 pM.

Figure 14 shows target-dependent redirected T-cell cytotoxicity on a CD 19⁺ cell line (Daudi) using bispecific polypeptide heterodimers TSC100, TSC165, TC166, TSC167, and TSC168.

DETAILED DESCRIPTION

[0073] The present disclosure provides polypeptide heterodimers formed between two different single chain polypeptides via natural heterodimerization of an immunoglobulin CH1 region and an immunoglobulin light chain constant region (CL). The polypeptide heterodimer has two or more binding domains that specifically bind one or more targets (e.g., an antigen, a receptor, or a ligand). In addition, both chains of a heterodimer each further comprise an Fc region portion (e.g., immunoglobulin CH2 and/or CH3 domains). The present disclosure also provides nucleic acids, vectors, host cells and methods for making polypeptide heterodimers.

[0074] The heterodimerization technology described herein has one or more of the following advantages: (1) potential for minimal immunogenicity of the polypeptide heterodimers because the dimers are formed via natural heterodimerization of an immunoglobulin CH1 region and an immunoglobulin CL region; (2) efficient production and purification of polypeptide heterodimers of the present disclosure is possible by co-expressing the two different single chain polypeptides, as shown in the examples; (3) the ability to mediate Fc effector functions (e.g., CDC, ADCC, ADCP), which can be modulated up or down by mutagenesis, and a longer serum half life because each chain of a polypeptide heterodimer according to the present disclosure has an Fc region portion (e.g., immunoglobulin CH2 and CH3 domains); and (4) polypeptide heterodimers of the present disclosure have a size that is typically smaller than an antibody molecule, which can allow for better tissue penetration, such as

into a solid malignancy.

[0075] The polypeptide heterodimers provided herein are useful to direct therapeutic agents or immune effector cells to target cells. For instance, in certain embodiments, the polypeptide heterodimers may comprise a binding domain that specifically binds a TCR complex or a component thereof (e.g., TCR α , TCR β , CD3 γ , CD3 δ , and CD3 ϵ) and another binding domain that specifically binds a second different target, such as an oncology target (e.g., c-Met, RON, CEACAM-6, and PSMA) or a B-cell target (e.g., CD19, CD79b, HLA-DR and CD20). The binding domain specific for the second different target may have a higher affinity for its target than the affinity of the binding domain for the TCR complex or component thereof, such as CD3. Such polypeptide heterodimers will preferably bind to the oncology target or the B-cell target first and subsequently recruit T cells to the tumor or cancer cells expressing the oncology target or B-cell target and are useful in inhibiting growth, metastasis or metastatic growth of a malignancy (including B-cell cancers). Additional uses of polypeptide heterodimers provided herein include directed T cell activation and treating autoimmune or inflammatory conditions.

[0076] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited herein, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose. In the event that one or more of the incorporated documents or portions of documents defines a term that contradicts that term's definition in the application, the definition that appears in this application controls.

[0077] In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. As used herein, "about" means $\pm$ 20% of the indicated range, value, sequence, or structure, unless otherwise indicated. It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components unless otherwise indicated or dictated by its context. The use of the alternative (e.g., "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the terms "include" and "comprise" are used synonymously. In addition, it should be understood that the individual single chain polypeptides or heterodimers derived from various combinations of the structures and substituents (e.g., domains, regions, hinges, and linkers) described herein are disclosed by the present application to the same extent as if each single chain polypeptide or heterodimer were set forth individually. Thus, selection of particular components to form individual single chain polypeptides or heterodimers is within the scope of the present disclosure.

[0078] As used herein, a protein "consists essentially of" several domains (e.g., a binding domain that specifically binds a target, a hinge, an immunoglobulin heterodimerization domain, and an Fc region portion) if the other portions of the protein (e.g., amino acids at the amino- or carboxy-terminus or between two domains), in combination, contribute to at most 20% (e.g., at most 15%, 10%, 8%, 6%, 5%, 4%, 3%, 2% or 1 %) of the length of the protein and do not substantially affect (i.e., do not reduce the activity by more than 50%, such as more than 40%, 30%, 25%, 20%, 15%, 10%, or 5%) the activities of various domains (e.g., the target binding affinity of the binding domain, the activities of the Fc region portion, and the capability of the immunoglobulin heterodimerization domain in facilitating heterodimerization). In certain embodiments, a protein (e.g., a single chain polypeptide) consists essentially of a binding domain that specifically binds a target, an immunoglobulin heterodimerization domain, a hinge, and an Fc region portion may comprise junction amino acids at the amino- and/or carboxy-terminus of the protein and/or between two different domains (e.g., between the binding domain and the immunoglobulin heterodimerization domain, between the immunoglobulin heterodimerization domain and the hinge, and/or between the hinge and the Fc region portion).

[0079] A "polypeptide heterodimer" or "heterodimer," as used herein, refers to a dimer formed from two different single chain polypeptides. This term does not include an antibody formed from four single chain polypeptides (i.e., two light chains and two heavy chains). A "dimer" refers to a biological entity that consists of two subunits associated with each other via one or more forms of intramolecular forces, including covalent bonds (e.g., disulfide bonds) and other interactions (e.g., electrostatic interactions, salt bridges, hydrogen bonding, and hydrophobic interactions), and is stable under appropriate conditions (e.g., under physiological conditions, in an aqueous solution suitable for expressing, purifying, and/or storing recombinant proteins, or under conditions for non-denaturing and/or non-reducing electrophoresis).

[0080] A "single chain polypeptide" is a single, linear and contiguous arrangement of covalently linked amino acids. It does not include two polypeptide chains that link together in a non-linear fashion, such as via an interchain disulfide bond (e.g., a half immunoglobulin molecule in which a light chain links with a heavy chain via a disulfide bond). In certain embodiments, a single chain polypeptide may have or form one or more intrachain disulfide bonds.

[0081] An "immunoglobulin heterodimerization domain," as used herein, refers to an immunoglobulin domain of a single chain

polypeptide that preferentially interacts or associates with a different immunoglobulin domain of another single chain polypeptide wherein the interaction of the different heterodimerization domains substantially contributes to or efficiently promotes heterodimerization of the first and second single chain polypeptides (*i.e.*, the formation of a dimer between two different single chain polypeptides, which is also referred to as a "heterodimer"). The interaction(s) between heterodimerization domains "substantially contributes to or efficiently promotes" the heterodimerization of first and second single chain polypeptides if there is a statistically significant reduction in the dimerization between the first and second single chain polypeptides in the absence of the heterodimerization domain of the first single chain polypeptide (HD-I) and/or the heterodimerization domain of the second single chain polypeptide (HD-II). In certain embodiments, when the first and second single chain polypeptides are co-expressed, at least 60%, at least about 60% to about 70%, at least about 70% to about 80%, at least about 80% to about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, and at least about 90% to about 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the first and second single chain polypeptides form heterodimers with each other. Representative immunoglobulin heterodimerization domains of the present disclosure include an immunoglobulin CH1 region, an immunoglobulin CL region (*e.g.*, C κ or C λ isotypes), or derivatives thereof, including wild type immunoglobulin CH1 and CL regions and altered (or mutated) immunoglobulin CH1 and CL regions, as provided herein.

[0082] A "binding domain" or "binding region," as used herein, refers to a protein, polypeptide, oligopeptide, or peptide that possesses the ability to specifically recognize and bind to a target (*e.g.*, CD3, TCR, CD28, c-Met, RON). A binding domain includes any naturally occurring, synthetic, semi-synthetic, or recombinantly produced binding partner for a biological molecule or another target of interest. Exemplary binding domains include single chain antibody variable regions (*e.g.*, domain antibodies, sFv, scFv, Fab), receptor ectodomains (*e.g.*, c-Met, RON), or ligands (*e.g.*, cytokines, chemokines). A variety of assays are known for identifying binding domains of the present disclosure that specifically bind a particular target, including Western blot, ELISA, and Biacore analysis.

[0083] A binding domain and a fusion protein thereof "specifically binds" a target if it binds the target with an affinity or K_a (*i.e.*, an equilibrium association constant of a particular binding interaction with units of 1/M) equal to or greater than 10^5 M^{-1} , while not significantly binding other components present in a test sample. Binding domains (or fusion proteins thereof) may be classified as "high affinity" binding domains (or fusion proteins thereof) and "low affinity" binding domains (or fusion proteins thereof). "High affinity" binding domains refer to those binding domains with a K_a of at least 10^7 M^{-1} , at least 10^8 M^{-1} , at least 10^9 M^{-1} , at least 10^{10} M^{-1} , at least 10^{11} M^{-1} , at least 10^{12} M^{-1} , or at least 10^{13} M^{-1} . "Low affinity" binding domains refer to those binding domains with a K_a of up to 10^7 M^{-1} , up to 10^6 M^{-1} , up to 10^5 M^{-1} . Alternatively, affinity may be defined as an equilibrium dissociation constant (K_d) of a particular binding interaction with units of M (*e.g.*, 10^{-5} M to 10^{-13} M). Affinities of binding domain polypeptides and single chain polypeptides according to the present disclosure can be readily determined using conventional techniques (see, *e.g.*, Scatchard et al. (1949) Ann. N.Y. Acad. Sci. 51:660; and U.S. Patent Nos. 5,283,173, 5,468,614, or the equivalent).

[0084] "T cell receptor" (TCR) is a molecule found on the surface of T cells that, along with CD3, is generally responsible for recognizing antigens bound to major histocompatibility complex (MHC) molecules. It consists of a disulfide-linked heterodimer of the highly variable α and β chains in most T cells. In other T cells, an alternative receptor made up of variable γ and δ chains is expressed. Each chain of the TCR is a member of the immunoglobulin superfamily and possesses one N-terminal immunoglobulin variable domain, one immunoglobulin constant domain, a transmembrane region, and a short cytoplasmic tail at the C-terminal end (see, Abbas and Lichtman, Cellular and Molecular Immunology (5th Ed.), Editor: Saunders, Philadelphia, 2003; Janeway et al., Immunobiology: The Immune System in Health and Disease, 4th Ed., Current Biology Publications, p148, 149, and 172, 1999). TCR as used in the present disclosure may be from various animal species, including human, mouse, rat, or other mammals.

[0085] "CD3" is known in the art as a multi-protein complex of six chains (see, Abbas and Lichtman, 2003; Janeway *et al.*, p. 172 and 178, 1999). In mammals, the complex comprises a CD3 γ chain, a CD3 δ chain, two CD3 ϵ chains, and a homodimer of CD3 ζ chains. The CD3 γ , CD3 δ , and CD3 ϵ chains are highly related cell surface proteins of the immunoglobulin superfamily containing a single immunoglobulin domain. The transmembrane regions of the CD3 γ , CD3 δ , and CD3 ϵ chains are negatively charged, which is a characteristic that allows these chains to associate with the positively charged T cell receptor chains. The intracellular tails of the CD3 γ , CD3 δ , and CD3 ϵ chains each contain a single conserved motif known as an immunoreceptor tyrosine-based activation motif or ITAM, whereas each CD3 ζ chain has three. It is believed the ITAMs are important for the signaling capacity of a TCR complex. CD3 as used in the present disclosure may be from various animal species, including human, mouse, rat, or other mammals.

[0086] "TCR complex," as used herein, refers to a complex formed by the association of CD3 with TCR. For example, a TCR complex can be composed of a CD3 γ chain, a CD3 δ chain, two CD3 ϵ chains, a homodimer of CD3 ζ chains, a TCR α chain, and a TCR β chain. Alternatively, a TCR complex can be composed of a CD3 γ chain, a CD3 δ chain, two CD3 ϵ chains, a homodimer of

CD3 ζ chains, a TCR γ chain, and a TCR δ chain.

[0087] "A component of a TCR complex," as used herein, refers to a TCR chain (*i.e.*, TCR α , TCR β , TCR γ or TCR δ), a CD3 chain (*i.e.*, CD3 γ , CD3 δ , CD3 ϵ or CD3 ζ), or a complex formed by two or more TCR chains or CD3 chains (*e.g.*, a complex of TCR α and TCR β , a complex of TCR γ and TCR δ , a complex of CD3 ϵ and CD3 δ , a complex of CD3 γ and CD3 ϵ , or a sub-TCR complex of TCR α , TCR β , CD3 γ , CD3 δ , and two CD3 ϵ chains).

[0088] Terms understood by those in the art of antibody technology are each given the meaning acquired in the art, unless expressly defined differently herein. Antibodies are known to have variable regions, a hinge region, and constant domains. Immunoglobulin structure and function are reviewed, for example, in Harlow et al., Eds., *Antibodies: A Laboratory Manual*, Chapter 14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, 1988).

[0089] For example, the terms "VL" and "VH" refer to the variable binding region from an antibody light and heavy chain, respectively. The variable binding regions are made up of discrete, well-defined sub-regions known as "complementarity determining regions" (CDRs) and "framework regions" (FRs). The term "CL" refers to an "immunoglobulin light chain constant region" or a "light chain constant region," *i.e.*, a constant region from an antibody light heavy chain. The term "CH" refers to an "immunoglobulin heavy chain constant region" or a "heavy chain constant region," which is further divisible, depending on the antibody isotype into CH1, CH2, and CH3 (IgA, IgD, IgG), or CH1, CH2, CH3, and CH4 domains (IgE, IgM). A "Fab" (fragment antigen binding) is the part of an antibody that binds to antigens and includes the variable region and CH1 of the heavy chain linked to the light chain via an inter-chain disulfide bond.

[0090] As used herein, "an Fc region constant domain portion" or "Fc region portion" refers to the heavy chain constant region segment of the Fc fragment (the "fragment crystallizable" region or Fc region) from an antibody, which can include one or more constant domains, such as CH2, CH3, CH4, or any combination thereof. By way of background, the Fc region is responsible for the effector functions of an immunoglobulin, such as ADCC (antibody-dependent cell-mediated cytotoxicity), ADCP (antibody-dependent cellular phagocytosis), CDC (complement-dependent cytotoxicity) and complement fixation, binding to Fc receptors (*e.g.*, CD16, CD32, FcRn), greater half-life *in vivo* relative to a polypeptide lacking an Fc region, protein A binding, and perhaps even placental transfer (*see* Capon et al., *Nature*, 337:525 (1989)).

[0091] In addition, antibodies have a hinge sequence that is typically situated between the Fab and Fc region (but a lower section of the hinge may include an amino-terminal portion of the Fc region). By way of background, an immunoglobulin hinge acts as a flexible spacer to allow the Fab portion to move freely in space. In contrast to the constant regions, hinges are structurally diverse, varying in both sequence and length between immunoglobulin classes and even among subclasses. For example, a human IgG1 hinge region is freely flexible, which allows the Fab fragments to rotate about their axes of symmetry and move within a sphere centered at the first of two inter-heavy chain disulfide bridges. By comparison, a human IgG2 hinge is relatively short and contains a rigid poly-proline double helix stabilized by four inter-heavy chain disulfide bridges, which restricts the flexibility. A human IgG3 hinge differs from the other subclasses by its unique extended hinge region (about four times as long as the IgG1 hinge), containing 62 amino acids (including 21 prolines and 11 cysteines), forming an inflexible poly-proline double helix and providing greater flexibility because the Fab fragments are relatively far away from the Fc fragment. A human IgG4 hinge is shorter than IgG1 but has the same length as IgG2, and its flexibility is intermediate between that of IgG1 and IgG2.

[0092] According to crystallographic studies, an IgG hinge domain can be functionally and structurally subdivided into three regions: the upper, the core or middle, and the lower hinge regions (Shin et al., *Immunological Reviews* 130:87 (1992)). Exemplary upper hinge regions include EPKSCDKTHT (SEQ ID NO:227) as found in IgG1, ERKCCVE (SEQ ID NO:211) as found in IgG2, ELKTPLGDTT HT (SEQ ID NO:245) or EPKSCDTPPP (SEQ ID NO:246) as found in IgG3, and ESKYGPP (SEQ ID NO:247) as found in IgG4. Exemplary middle or core hinge regions include CPPCP (SEQ ID NO:228) as found in IgG1 and IgG2, CPRCP (SEQ ID NO:248) as found in IgG3, and CPSCP (SEQ ID NO:249) as found in IgG4. While IgG1, IgG2, and IgG4 antibodies each appear to have a single upper and middle hinge, IgG3 has four in tandem - one being ELKTPLGDTTHTCPRCP (SEQ ID NO:250) and three being EPKSCDTPPP CPRCP (SEQ ID NO:251).

[0093] IgA and IgD antibodies appear to lack an IgG-like core region, and IgD appears to have two upper hinge regions in tandem (*see* SEQ ID NOS:222 and 252). Exemplary wild type upper hinge regions found in IgA1 and IgA2 antibodies are set forth in SEQ ID NOS:215 and 216.

[0094] IgE and IgM antibodies, in contrast, lack a typical hinge region and instead have a CH2 domain with hinge-like properties. Exemplary wild-type CH2 upper hinge-like sequences of IgE and IgM are set forth in SEQ ID NO:253 (VCSRDFTPPTVKILQSSSDGGGHFPPTIQLLCLVSGYTPGTINITWLEDG QVMVDVLSTASTTQEGELASTQSELTLSQKHWSLSDRTYTCQVYQGHTE DSTKKCA) and SEQ ID NO:254

(VIAELPPKVSFVPPRDGFFGNPRKSLIC QATGFSPRQIQVSWLREGKQVGSQVTTDQVQAEAKESGPTTYKVTSTLTI KESDWLGQSMFTCRVDHRLTFQQNASSMCVP), respectively.

[0095] As used herein, a "hinge region" or a "hinge" refers to (a) an immunoglobulin hinge region (made up of, for example, upper and core regions) or a functional variant thereof, including wild type and altered immunoglobulin hinges, (b) a lectin interdomain region or a functional variant thereof, (c) a cluster of differentiation (CD) molecule stalk region or a functional variant thereof, or (d) a portion of a cell surface receptor (interdomain region) that connects immunoglobulin V-like or immunoglobulin C-like domains.

[0096] As used herein, a "wild type immunoglobulin hinge region" refers to a naturally occurring upper and middle hinge amino acid sequences interposed between and connecting the CH1 and CH2 domains (for IgG, IgA, and IgD) or interposed between and connecting the CH1 and CH3 domains (for IgE and IgM) found in the heavy chain of an antibody. In certain embodiments, a wild type immunoglobulin hinge region sequence is human, and may comprise a human IgG hinge region. Exemplary human wild type immunoglobulin hinge regions are set forth in SEQ ID NOS:215 (IgA1 hinge), 216 (IgA2 hinge), 217 (IgD hinge), 667 (IgG1 hinge), 219 (IgG2 hinge), 220 (IgG3 hinge) and 221 (IgG4 hinge).

[0097] An "altered wild type immunoglobulin hinge region" or "altered immunoglobulin hinge region" refers to (a) a wild type immunoglobulin hinge region with up to 30% amino acid changes (e.g., up to 25%, 20%, 15%, 10%, or 5% amino acid substitutions or deletions), or (b) a portion of a wild type immunoglobulin hinge region that has a length of about 5 amino acids (e.g., about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids) up to about 120 amino acids (for instance, having a length of about 10 to about 40 amino acids or about 15 to about 30 amino acids or about 15 to about 20 amino acids or about 20 to about 25 amino acids), has up to about 30% amino acid changes (e.g., up to about 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, or 1% amino acid substitutions or deletions or a combination thereof), and has an IgG core hinge region as set forth in SEQ ID NOS:228, 248, or 249.

[0098] A "peptide linker" refers to an amino acid sequence that connects a heavy chain variable region to a light chain variable region and provides a spacer function compatible with interaction of the two sub-binding domains so that the resulting polypeptide retains a specific binding affinity to the same target molecule as an antibody that comprises the same light and heavy chain variable regions. In certain embodiments, a linker is comprised of five to about 35 amino acids, for instance, about 15 to about 25 amino acids.

[0099] "Junction amino acids" or "junction amino acid residues" refer to one or more (e.g., about 2-10) amino acid residues between two adjacent regions or domains of a single chain polypeptide, such as between a hinge and an adjacent Fc region portion or between a hinge and an adjacent binding domain or between a peptide linker that links two immunoglobulin variable domains and an adjacent immunoglobulin variable domain. Junction amino acids may result from the construct design of a single chain polypeptide (e.g., amino acid residues resulting from the use of a restriction enzyme site during the construction of a nucleic acid molecule encoding a single chain polypeptide).

[0100] A "linker between CH3 and CH1 or CL" refers to one or more (e.g., about 2-12) amino acid residues between the C-terminus of a CH3 domain (e.g., a wild type CH3 or a mutated CH3) and the N-terminus of a CH1 domain or CL domain (e.g., Ck).

[0101] A "wild type immunoglobulin region" or "wild type immunoglobulin domain" refers to a naturally occurring immunoglobulin region or domain (e.g., a naturally occurring VL, VH, hinge, CL, CH1, CH2, CH3, or CH4) from various immunoglobulin classes or subclasses (including, for example, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, and IgM) and from various species (including, for example, human, sheep, mouse, rat, and other mammals). Exemplary wild type human CH1 regions are set forth in SEQ ID NOS:114, 186-192 and 194, wild type human Ck region in SEQ ID NO:112, wild type human CA regions in SEQ ID NO:113 and 224-226, wild type human CH2 domains in SEQ ID NOS:115, 195-201 and 203, wild type human CH3 domains in SEQ ID NOS:116, 204-210 and 212, and wild type human CH4 domains in SEQ ID NO:213 and 214.

[0102] An "altered immunoglobulin region," "altered immunoglobulin domain," "mutated immunoglobulin domain," or the like, refers to an immunoglobulin region with a sequence identity to a wild type immunoglobulin region or domain (e.g., a wild type VL, VH, hinge, CL, CH1, CH2, CH3, or CH4) of at least 75% (e.g., 80%, 82%, 84%, 86%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%). For example, an "altered immunoglobulin CH1 region" or "altered CH1 region" refers to a CH1 region with a sequence identity to a wild type immunoglobulin CH1 region (e.g., a human CH1) of at least 75% (e.g., 80%, 82%, 84%, 86%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%). Similarly, an "altered immunoglobulin CH2 domain" or "altered CH2 domain" refers to a CH2 domain with a sequence identity to a wild type immunoglobulin CH2 region (e.g., a human CH2) of at least 75% (e.g., 80%, 82%, 84%, 86%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or

99.5%).

[0103] "Sequence identity," as used herein, refers to the percentage of amino acid residues in one sequence that are identical with the amino acid residues in another reference polypeptide sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. The percentage sequence identity values are generated by the NCBI BLAST2.0 software as defined by Altschul et al. (1997) "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs," *Nucleic Acids Res.* 25:3389-3402, with the parameters set to default values.

[0104] In certain embodiments, an altered immunoglobulin domain only contains conservative amino acid substitutions of a wild type immunoglobulin domain. In certain other embodiments, an altered immunoglobulin domain only contains non-conservative amino acid substitutions of a wild type immunoglobulin domain. In yet other embodiments, an altered immunoglobulin domain contains both conservative and non-conservative amino acid substitutions.

[0105] A "conservative substitution" is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are well known in the art (see, e.g., WO 97/09433, page 10, published March 13, 1997; Lehninger, *Biochemistry*, Second Edition; Worth Publishers, Inc. NY:NY (1975), pp.71-77; Lewin, *Genes IV*, Oxford University Press, NY and Cell Press, Cambridge, MA (1990), p. 8). In certain embodiments, a conservative substitution includes a leucine to serine substitution.

[0106] As used herein, the term "derivative" refers to a modification of one or more amino acid residues of a peptide by chemical or biological means, either with or without an enzyme, e.g., by glycosylation, alkylation, acylation, ester formation, or amide formation. Generally, a "derivative" differs from an "analogue" in that a parent polypeptide may be the starting material to generate a "derivative," whereas the parent polypeptide may not necessarily be used as the starting material to generate an "analogue." A derivative may have different chemical, biological or physical properties of the parent polypeptide. For example, a derivative may be more hydrophilic or it may have altered reactivity (e.g., a CDR having an amino acid change that alters its affinity for a target) as compared to the parent polypeptide.

[0107] As used herein, unless otherwise provided, a position of an amino acid residue in a variable region of an immunoglobulin molecule is numbered according to the Kabat numbering convention (Kabat, *Sequence of Proteins of Immunological Interest*, 5th ed. Bethesda, MD: Public Health Service, National Institutes of Health (1991)), and a position of an amino acid residue in a constant region of an immunoglobulin molecule is numbered according to EU nomenclature (Ward et al., 1995 *Therap. Immunol.* 2:77-94).

[0108] A "receptor" is a protein molecule present in the plasma membrane or in the cytoplasm of a cell to which a signal molecule (*i.e.*, a ligand, such as a hormone, a neurotransmitter, a toxin, a cytokine) may attach. The binding of the signal molecule to the receptor results in a conformational change of the receptor, which ordinarily initiates a cellular response. However, some ligands merely block receptors without inducing any response (e.g., antagonists). Some receptor proteins are peripheral membrane proteins. Many hormone and neurotransmitter receptors are transmembrane proteins that are embedded in the phospholipid bilayer of cell membranes, and another major class of receptors are intracellular proteins such as those for steroid and intracrine peptide hormone receptors.

[0109] "B-cell associated disorder or disease" or "a disease or disorder associated with aberrant B-cell activity" refers to a disease or disorder associated with (e.g., causing or resulting from) aberrant B-cell activity or activity that deviates from the normal, proper, or expected course. For example, a B-cell associated disorder or disease may include inappropriate proliferation of B-cells that have damaged or defective DNA or other cellular components. Aberrant B-cell activity may include cell proliferation characterized by inappropriately high levels of B-cell division, inappropriately low levels of B-cell apoptosis, or both. Such diseases may have, for example, single or multiple local abnormal proliferations of B-cells, groups of B-cells or tissue(s), whether cancerous or non-cancerous, benign or malignant. A B-cell associated disorder or disease may also include aberrant antibody production, such as production of autoantibodies, or overproduction of antibodies more desirable when produced at normal levels. It is also contemplated herein that aberrant B-cell activity may occur in certain subpopulations of B-cells and not in other subpopulations, or may include inappropriate stimulation of T-cells, such as by inappropriate antigen presentation to T-cells or by other B-cell pathways. Examples of B-cell associated disorders or diseases include a B-cell malignancy or B-cell cancer (*e.g.*, B-cell lymphoma, B-cell leukemia or B-cell myeloma), a disease characterized by autoantibody production (*e.g.*, autoimmune diseases) or inflammation or a disease characterized by inappropriate T-cell stimulation caused by inappropriate B-cell antigen presentation to T-cells or caused by other pathways involving B-cells.

[0110] "Treatment," "treating" or "ameliorating" refers to either a therapeutic treatment or prophylactic/preventative treatment. A

treatment is therapeutic if at least one symptom of disease in an individual receiving treatment improves or a treatment may delay worsening of a progressive disease in an individual, or prevent onset of additional associated diseases.

[0111] A "therapeutically effective amount (or dose)" or "effective amount (or dose)" of a specific binding molecule or compound refers to that amount of the compound sufficient to result in amelioration of one or more symptoms of the disease being treated in a statistically significant manner. When referring to an individual active ingredient, administered alone, a therapeutically effective dose refers to that ingredient alone. When referring to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered serially or simultaneously (in the same formulation or concurrently in separate formulations).

[0112] The term "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce allergic or other serious adverse reactions when administered using routes well known in the art.

[0113] A "patient in need" refers to a patient at risk of, or suffering from, a disease, disorder or condition that is amenable to treatment or amelioration with a polypeptide heterodimer or a composition thereof provided herein.

[0114] The term "immunoglobulin-derived fusion protein," as used herein, refers to a fusion protein that comprises at least one immunoglobulin region, such as a VL, VH, CL, CH1, CH2, CH3, and CH4 domain. The immunoglobulin region may be a wild type immunoglobulin region or an altered immunoglobulin region. Exemplary immunoglobulin-derived fusion proteins include single chain variable antibody fragment (scFv) (see, e.g., Huston et al., Proc. Natl. Acad. Sci. USA 85: 5879-83, 1988), SMIP™ proteins (see, U.S. Patent Publication Nos. 2003/0133939, 2003/0118592, and 2005/0136049), PIMS proteins (see, PCT Application Publication No. WO 2009/023386), and multi-functional binding proteins (such as SCORPION™ and Xceptor proteins) (see, PCT Application Publication No. WO 2007/146968, U.S. Patent Application Publication No. 2006/0051844, and U.S. Patent No. 7,166,707).

[0115] Additional definitions are provided throughout the present disclosure.

Polypeptide Heterodimers

[0116] In one aspect, the present disclosure provides a polypeptide heterodimer formed by the association of two different single chain polypeptides. The first single chain polypeptide (SCP-I) comprises, consists essentially of, or consists of from one to four binding domains that specifically bind from one to four targets, a hinge (H-I), an immunoglobulin heterodimerization domain (HD-I), and an Fc region portion (FRP-I), whereas the second single chain polypeptide (SCP-II) comprises, consists essentially of, or consists of from zero to four binding domains that specifically bind from zero to four targets, a hinge (H-II), an immunoglobulin heterodimerization domain (HD-II), and an Fc region portion (FRP-II), provided that the polypeptide heterodimer comprises at least two binding domains that specifically bind to one or more targets, for instance, at least two different targets. The H-I and H-II may have the same sequence, but may be different. The HD-I may comprise an immunoglobulin CH1 region, and the HD-II may comprise an immunoglobulin CL region. Alternatively, the HD-I may comprise an immunoglobulin CL region, and the HD-II may comprise an immunoglobulin CH1 region. The FRP-I and FRP-II may have the same sequence, but may be different. The individual components of the polypeptide heterodimers of the present disclosure are described in detail herein.

Binding Domains

[0117] As indicated above, the polypeptide heterodimer of the present disclosure comprises two single chain polypeptides: One single chain polypeptide comprises from one to four binding domains that specifically bind from one to four targets, and the other single chain polypeptide of the polypeptide heterodimer comprises from zero to four binding domains that bind from zero to four targets. The total number of binding domains of the polypeptide heterodimer ranges from about two to eight, and the total number of different targets that the binding domains bind ranges from about one to eight, for instance, from two to eight, two to four, two to three or two targets.

[0118] If a single chain polypeptide of a polypeptide heterodimer comprises a single binding domain, the binding domain may be located either amino or carboxyl terminal to the Fc region portion of the single chain polypeptide. For example, a single chain polypeptide comprising two binding domains may have one binding domain located amino terminal and the other carboxyl terminal to the Fc region portion of the single chain polypeptide, or both binding domains may be amino terminal or both carboxyl terminal to the Fc region portion. In another example, a single chain polypeptide may comprise three binding domains wherein (a) two

binding domains are amino terminal on different single chain proteins and the third binding domain is carboxyl terminal to the Fc region portion on either SCP-I or SCP-II, (b) two binding domains are carboxyl terminal on different single chain proteins and the third binding domain is amino terminal to the Fc region portion on either SCP-I or SCP-II. In still a further example, a polypeptide heterodimer may comprise four binding domains, wherein two binding domains are located amino terminal to the Fc region portion on different chains and the other two binding domains are located carboxyl terminal to the Fc region portion on different chains. Alternatively, in any of these embodiments, two binding domains may be linked to each other in tandem and located on either SCP-I or SCP-II or both, depending on the number of binding domains present - the tandem stacking is used when five to eight binding domains combined are present in SCP-I and SCP-II.

[0119] Binding of a target by a binding domain modulates the interaction between the target (*e.g.*, a receptor or a ligand) and another molecule. In certain embodiments, the binding of a target (*e.g.*, a receptor) by a binding domain stimulates certain functions of the target (*e.g.*, signal transduction) or brings different targets closer together for a biological effect (*e.g.*, directing T cells to a tumor which in turn activates the T cells). In certain other embodiments, the binding of a target by a binding domain blocks the interaction between the target and another molecule and thus interferes, reduces or eliminates certain functions of the target.

[0120] A target molecule, which is specifically bound by a binding domain contained in a polypeptide heterodimer of the present disclosure, may be found on or in association with a cell of interest ("target cell"). Exemplary target cells include cancer cells, cells associated with an autoimmune disease or disorder or with an inflammatory disease or disorder, B-cells and T-cells. A target molecule may also not be associated with a cell. Exemplary target molecules not associated with a cell include soluble proteins, secreted proteins, deposited proteins, and extracellular structural (matrix) proteins.

[0121] In certain embodiments, binding domains of polypeptide heterodimers of the present disclosure specifically bind a target selected from T-cell targets, tumor antigens, B-cell targets, pro-inflammatory cytokines or chemokines, pro-oncogenic cytokines or growth factors, angiogenic agents, Fc receptors, transferrin receptor, receptor tyrosine kinases (RTKs), TNFSFRs, or any combination thereof. For instance, polypeptide heterodimers of the present disclosure specifically bind a T-cell target and a tumor target.

[0122] In certain embodiments, a binding domain of a polypeptide heterodimer of the present disclosure specifically binds a T-cell target, such as a TCR complex or a component thereof (*e.g.*, TCR α , TCR β , CD3 γ , CD3 δ , and CD3 ϵ), CD28, PD-1, HVEM, BTLA, CD80, CD86, GITR, and TGFBR1.

[0123] In certain embodiments, a binding domain of polypeptide heterodimer of the present disclosure specifically binds a TCR complex or a component thereof. For example, in certain embodiments, a binding domain specifically binds to an individual human CD3 chain (*e.g.*, human CD3 γ chain, human CD3 δ chain, and human CD3 ϵ chain) or a combination of two or more of the individual human CD3 chains (*e.g.*, a complex of human CD3 γ and human CD3 ϵ or a complex of human CD3 δ and human CD3 ϵ). In certain embodiments, a binding domain specifically binds to a human CD3 ϵ chain. In certain other embodiments, a binding domain specifically binds to one or more of human TCR α , human TCR β , or a heterodimer formed from human TCR α and human TCR β . In certain other embodiments, a binding domain of the present disclosure binds to a complex formed from one or more human CD3 chains with one or more human TCR chains, such as a complex formed from a human CD3 γ chain, a human CD3 δ chain, or a human CD3 ϵ chain with a human TCR α chain or a human TCR β chain. In any of these embodiments, a polypeptide heterodimer of the present disclosure may also bind a tumor target.

[0124] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure specifically bind a tumor target, including RON, c-Met, CEACAM-6, PSMA, EpCAM, CEA, PCTA-1, STEAP-1, PSCA, ALCAM (CD166), EphA2, CD151, CA-125, MUC-1, MAGE-1, TROP2, IGF1R, CD44v6, CD151, TGFBR2, GHRHR, GHR, IL-6R, gp130, TNFR2, OSMR β , Patched-1, Frizzled, Robo1, LT β T, CD80, CD81, CD86, CCR5, HER-3, HER-4, EGFR, CEA, MUC2, MUC3, MUC4, MUC5_{AC}, MUC5_b, MUC7, β hCG, Lewis-Y, CD33, CD30, ganglioside GD3, 9-O-Acetyl-GD3, GM2, Globo H, fucosyl GM1, Poly SA, GD2, Carboanhydrase IX (MN/CA IX), CD44v6, Sonic Hedgehog (Shh), Wue-1, Plasma Cell Antigen, (membrane-bound) IgE, Melanoma Chondroitin Sulfate Proteoglycan (MCSP), CCR8, TNF-alpha precursor, STEAP-2, mesothelin, A33 Antigen, Prostate Stem Cell Antigen (PSCA), Ly-6; desmoglein 4, E-cadherin neoepitope, Fetal Acetylcholine Receptor, CD25, CA19-9 marker, CA-125 marker and Muellerian Inhibitory Substance (MIS) Receptor type II, sTn (sialylated Tn antigen; TAG-72), FAP (fibroblast activation antigen), endosialin, EGFRvIII, LG, SAS, CD63, B7-H3, or any combination thereof.

[0125] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure specifically bind a B-cell target, such as CD 19, CD20, CD21, CD22, CD30, CD33, CD37, CD38, CD70, CD79b, HLA-DR, or any combination thereof.

[0126] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure specifically bind a pro-inflammatory cytokine or chemokine, such as TNF α , IL-6, hyperIL-6, IL-2, IL-1, IL-8, IP-10, IFN γ , IFN α , RANKL, FASL, EGF β , IL7, IL10, IL17A/F, TWEAK, CSF2, IGF1, IGF2 or BLyS/APRIL, or any combination thereof.

[0127] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure specifically bind a pro-oncogenic cytokine or growth factor, such as HGF, MSP, EGF (including epiregulin, herregulin, β -regulin, neuregulin), HIF-1 α , VEGFA, VEGFB, VEGFC, VEGFD, TNF α , IL-6, hyperIL-6, IL-8, Wnt, sHH, TGF β , PDGF, or any combination thereof.

[0128] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure specifically bind an angiogenic agent, such as PDGFR, VEGFR1-4, NRP1, Angiopoietin 2, c-Met or any combination thereof.

[0129] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure specifically bind an Fc receptor, such as CD64, CD32A, CD32B, CD16, FcRn, or any combination thereof.

[0130] In certain embodiments, a binding domain of a polypeptide heterodimer of the present disclosure specifically binds a transferrin receptor, such as CD71.

[0131] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure specifically binds a receptor tyrosine kinase, such as EGFR, EGFRvIII, ErbB2, ErbB3, ErbB4, IGF1R, EphA2, c-Met, RON, or any combination thereof.

[0132] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure specifically binds a TNFSFR, such as TNFR1, TNFR2, TWEAKR, TACI, BAFF-R, BCMA, FAS, OX40, GITR, 4-1-BB, LT β AR, HVEM, RANK, or any combination thereof.

[0133] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure specifically bind hyperIL-6, IL-10, LIGHT, CD40, PDL1, PDL2, or any combination thereof.

[0134] In certain embodiments, one or more binding domains of a polypeptide heterodimer of the present disclosure are an agonist of one of the following molecules: IL-10, HLA-G, HGF, IL-35, PD-1, BTLA, TNFR1, TNFR2, DR4, DR5, TWEAKR, FAS, or any combination thereof.

[0135] A binding domain may be any peptide that specifically binds a target of interest. Sources of binding domains include antibody variable regions from various species (which can be formatted as antibodies, sFvs, scFvs, Fabs, or soluble VH domain or domain antibodies), including human, rodent, avian, and ovine. Additional sources of binding domains include variable regions of antibodies from other species, such as camelid (from camels, dromedaries, or llamas; Ghahroudi et al. (1997) FEBS Letters 414(3):521-526; Vincke et al. (2009) Journal of Biological Chemistry (2009) 284:3273-3284; Hamers-Casterman et al. (1993) Nature, 363:446 and Nguyen et al. (1998) J. Mol. Biol., 275:413), nurse sharks (Roux et al. (1998) Proc. Nat'l. Acad. Sci. (USA) 95:11804), spotted ratfish (Nguyen et al. (2002) Immunogenetics, 54:39), or lamprey (Herrin et al., (2008) Proc. Nat'l. Acad. Sci. (USA) 105:2040-2045 and Alder et al. (2008) Nature Immunology 9:319-327). These antibodies can apparently form antigen-binding regions using only heavy chain variable region, *i.e.*, these functional antibodies are homodimers of heavy chains only (referred to as "heavy chain antibodies") (Jespersen et al. (2004) Nature Biotechnology 22:1161-1165; Cortez-Retamozo et al. (2004) Cancer Research 64:2853-2857; Baral et al. (2006) Nature Medicine 12:580-584, and Barthelemy et al. (2008) Journal of Biological Chemistry 283:3639-3654).

[0136] Exemplary anti-CD3 antibodies from which the binding domain of this disclosure may be derived include Cris-7 monoclonal antibody (Reinherz, E. L. et al. (eds.), Leukocyte typing II., Springer Verlag, New York, (1986)), BC3 monoclonal antibody (Anasetti et al. (1990) J. Exp. Med. 172:1691), OKT3 (Ortho multicenter Transplant Study Group (1985) N. Engl. J. Med. 313:337) and derivatives thereof such as OKT3 ala-ala (Herold et al. (2003) J. Clin. Invest. 11:409), visilizumab (Carpenter et al. (2002) Blood 99:2712), and 145-2C11 monoclonal antibody (Hirsch et al. (1988) J. Immunol. 140: 3766). An exemplary anti-TCR antibody is H57 monoclonal antibody (Lavassani et al. (2007) Scandinavian Journal of Immunology 65:39-47).

[0137] An alternative source of binding domains of this disclosure includes sequences that encode random peptide libraries or sequences that encode an engineered diversity of amino acids in loop regions of alternative non-antibody scaffolds, such as fibrinogen domains (*see, e.g.*, Weisel et al. (1985) Science 230:1388), Kunitz domains (*see, e.g.*, US Patent No. 6,423,498), ankyrin repeat proteins (Binz et al. (2003) Journal of Molecular Biology 332:489-503 and Binz et al. (2004) Nature Biotechnology 22(5):575-582), fibronectin binding domains (Richards et al. (2003) Journal of Molecular Biology 326:1475-1488; Parker et al.

(2005) Protein Engineering Design and Selection 18(9):435-444 and Hackel et al. (2008) Journal of Molecular Biology 381:1238-1252), cysteine-knot miniproteins (Vita et al. (1995) Proc. Nat'l. Acad. Sci. (USA) 92:6404-6408; Martin et al. (2002) Nature Biotechnology 21:71-76 and Huang et al. (2005) Structure 13:755-768), tetratricopeptide repeat domains (Main et al. (2003) Structure 11:497-508 and Cortajarena et al. (2008) ACS Chemical Biology 3:161-166), leucine-rich repeat domains (Stump et al. (2003) Journal of Molecular Biology 332:471-487), lipocalin domains (see, e.g., WO 2006/095164, Beste et al. (1999) Proc. Nat'l. Acad. Sci. (USA) 96:1898-1903 and Schönfeld et al. (2009) Proc. Nat'l. Acad. Sci. (USA) 106:8198-8203), V-like domains (see, e.g., US Patent Application Publication No. 2007/0065431), C-type lectin domains (Zelensky and Gready (2005) FEBS J. 272:6179; Beavil et al. (1992) Proc. Nat'l. Acad. Sci. (USA) 89:753-757 and Sato et al. (2003) Proc. Nat'l. Acad. Sci. (USA) 100:7779-7784), mAb² or FCABTM (see, e.g., PCT Patent Application Publication Nos. WO 2007/098934; WO 2006/072620), or the like (Nord et al. (1995) Protein Engineering 8(6):601-608; Nord et al. (1997) Nature Biotechnology 15:772-777; Nord et al. (2001) European Journal of Biochemistry 268(15):4269-4277 and Binz et al. (2005) Nature Biotechnology 23:1257-1268).

[0138] Binding domains of this disclosure can be generated as described herein or by a variety of methods known in the art (see, e.g., U.S. Patent Nos. 6,291,161 and 6,291,158). For example, binding domains of this disclosure may be identified by screening a Fab phage library for Fab fragments that specifically bind to a target of interest (see Hoet et al. (2005) Nature Biotechnol. 23:344). Additionally, traditional strategies for hybridoma development using a target of interest as an immunogen in convenient systems (e.g., mice, HUMAB MOUSE®, TC MOUSETM, KM-MOUSE®, llamas, chicken, rats, hamsters, rabbits, etc.) can be used to develop binding domains of this disclosure.

[0139] In certain embodiments, a polypeptide heterodimer comprises a CD86 binding domain, such as a CTLA4 ectodomain, a CD28 ectodomain, or an immunoglobulin variable region binding domain (such as a scFv) specific for CD86 (e.g., from monoclonal antibodies 3D1 or FUN1). In some embodiments, less than an entire ectodomain is used. For example, domains within the CTLA4 ectodomain that bind CD86 and prevent binding of CD86 to CD28 can be used. The CD86 binding domain can block binding of CD86 to CD28 and thereby downregulate T-cell activation.

[0140] In certain embodiments, a polypeptide heterodimer comprises an IL-10 agonist, such as IL-10, monoIL-10, or a functional region thereof. "MonoIL-10" refers to an IL-10 molecule having a short linker (GGGSGG, SEQ ID NO:760) that separates the two subdomains of the molecule (amino and carboxyl end domains) so that these subdomains can form an intramolecular dimer.

[0141] In certain embodiments, a polypeptide heterodimer comprises an HLA-G agonist, such as an HLA-G5, an HLA-G1, an HLA-G mutein, or a functional region thereof; an ectodomain of an HLA-G5, an HLA-G1 or an HLA-G mutein; or an immunoglobulin variable region binding domain (such as an scFv) specific for ILT2, ILT4 or KIR2DL4.

[0142] In certain embodiments, a polypeptide heterodimer comprises an HGF agonist, such as an HGF or a sub-domain thereof.

[0143] In certain embodiments, a polypeptide heterodimer comprises an IL35 agonist, such as an immunoglobulin variable region binding domain (such as an scFv) specific for IL35R or IL35, or a functional region thereof.

[0144] In certain embodiments, a polypeptide heterodimer comprises a LIGHT antagonist, such as an immunoglobulin variable region binding domain (such as an scFv) specific for LIGHT, or a HVEM ectodomain or a functional region thereof.

[0145] In certain embodiments, a polypeptide heterodimer comprises a PD-1 agonist, such as an immunoglobulin variable region binding domain (such as an scFv) specific for PD-1, or a PD-1 ligand (e.g. PD-L1 or PD-L2) or a functional region thereof.

[0146] In certain embodiments, a polypeptide heterodimer comprises a BTLA agonist, such as an immunoglobulin-like variable region binding domain (such as an scFv) specific for BTLA, or a HVEM ectodomain or a functional region thereof.

[0147] In certain embodiments, a polypeptide heterodimer comprises a GITRL antagonist, such as an immunoglobulin-like variable region binding domain (such as an scFv) specific for GITRL, or a GITR ectodomain, soluble GITR, or a functional region thereof.

[0148] In certain embodiments, a polypeptide heterodimer comprises a CD40 antagonist, such as an immunoglobulin-like variable region binding domain (such as an scFv) specific for CD40.

[0149] In some embodiments, a binding domain is a single chain Fv fragment (scFv) that comprises VH and VL regions specific for a target of interest. In certain embodiments, the V_H and V_L domains are human. Exemplary VH regions include the VH region of 2E12 (anti-CD28) scFv as set forth in SEQ ID NO:106, the VH region of P2C2 (anti-CD79b) scFv as set forth in SEQ ID

NO:184, the VH region of 5D5 (anti-c-Met) scFv as set forth in SEQ ID NO:258, the VH region of A2 (anti-hyperIL-6) scFv as set forth in SEQ ID NO:80, the VH region of 3D1 (anti-CD86) scFv as set forth in SEQ ID NO:92, the VH region of MET021 (anti-c-Met) scFv as set forth in SEQ ID NO:100, the VH region of G19-4 (anti-CD3) scFv as set forth in SEQ ID NO:103, the VH region of HD37 (anti-CD 19) scFv as set forth in SEQ ID NO:117, the VH region of M0042 (anti-HLA-DR) scFv as set forth in SEQ ID NO:121, the VH region of BMA031 (anti-TCR) scFv as set forth in SEQ ID NO:828, the VH region of OKT3-M (anti-CD3) scFv as set forth in SEQ ID NO:831, and the VH region of HuM291 (anti-CD3) scFv as set forth in SEQ ID NO:835. The nucleotide sequences encoding the VH regions of the A2 (anti-hyperIL-6) and 3D1 (anti-CD86) scFv's are set forth in SEQ ID NOS:79 and 91, respectively.

[0150] Exemplary VL domains are the VL region of 2E12 (anti-CD28) scFv as set forth in SEQ ID NO:107, the VL region of P2C2 (anti-CD79b) scFv as set forth in SEQ ID NO:182, the VL region of 5D5 (anti-c-Met) scFv as set forth in SEQ ID NO:259, the VL region of A2 (anti-hyper IL-6) scFv as set forth in SEQ ID NO:84, the VL region of 3D1 (anti-CD86) scFv as set forth in SEQ ID NO:96, the VL region of MET021 (anti-c-Met) scFv as set forth in SEQ ID NO:101, the VL region of G19-4 (anti-CD3) scFv as set forth in SEQ ID NO:104, the VL region of HD37 (anti-CD19) scFv as set forth in SEQ ID NO:119, the VL region of M0042 (anti-HLA-DR) scFv as set forth in SEQ ID NO:122, the VL region of BMA031 (anti-TCR) scFv as set forth in SEQ ID NO:829, the VL region of OKT3-M (anti-CD3) scFv as set forth in SEQ ID NO:833, and the VL region of HuM291 (anti-CD3) scFv as set forth in SEQ ID NO:836. The nucleotide sequences encoding the VL regions of the A2 (anti-hyperIL-6) and 3D1 (anti-CD86) scFv's are set forth in SEQ ID NOS:83 and 95, respectively.

[0151] In some embodiments, a binding domain is a single chain Fv fragment (scFv) that comprises V_H and V_L domains specific for a TCR complex or a component thereof. In certain embodiments, the V_H and V_L domains are human or humanized V_H and V_L domains. Exemplary V_H domains include BC3 (anti-CD3) V_H, OKT3 (anti-CD3) V_H, H57 (anti-TCR) V_H, and 2C11 (anti-CD3) V_H domains as set forth in SEQ ID NOS:301, 303, 313, and 317, respectively. Further exemplary V_H domains include Cris-7 (anti-CD3) V_H domains, such as those set forth in SEQ ID NOS:327 and 331-333. Exemplary V_L domains are BC3 (anti-CD3) V_L, OKT3 (anti-CD3) V_L, H57 (anti-TCR) V_L, and 2C11 (anti-CD3) V_L domains as set forth in SEQ ID NOS:302, 304, 315 and 318, respectively. Further exemplary V_L domains include Cris-7 (anti-CD3) V_L domains, such as those set forth in SEQ ID NOS:328, 329 and 330.

[0152] In certain embodiments, a binding domain comprises or is a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% identical to an amino acid sequence of a light chain variable region (V_L) or to a heavy chain variable region (V_H), or both, wherein each CDR comprises zero changes or at most one, two, or three changes, from a monoclonal antibody or fragment or derivative thereof that specifically binds to a target of interest (e.g., c-Met, RON, CD28, CD79b, CD3ε, TCRα, TCRβ, hyper IL-6, CD86, CD19, and HLA-DR) and such mutant or derivative still binds its target.

[0153] In certain embodiments, a binding domain VH or VL region of the present disclosure can be derived from or based on a VH or VL of a known monoclonal antibody and contains one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10) insertions, one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10) deletions, one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10) amino acid substitutions (e.g., conservative amino acid substitutions or non-conservative amino acid substitutions), or a combination of the above-noted changes, when compared with the VH or VL of a known monoclonal antibody. The insertion(s), deletion(s) or substitution(s) may be anywhere in the VH region, including at the amino- or carboxy-terminus or both ends of this region, provided that each CDR comprises zero changes or at most one, two, or three changes and provided that a binding domain containing the modified VH or VL region can still specifically bind its target with an affinity about the same as the wild type binding domain.

[0154] The VH and VL domains may be arranged in either orientation (*i.e.*, from amino-terminus to carboxyl terminus, VH-VL or VL-VH) and may be joined by an amino acid sequence (e.g., having a length of about five to about 35 amino acids) capable of providing a spacer function such that the two sub-binding domains can interact to form a functional binding domain. In certain embodiments, an amino acid sequence that joins the VH and VL domains (also referred to herein as a "linker") includes those belonging to the (Gly_nSer) family, such as (Gly₃Ser)_n(Gly₄Ser)₁, (Gly₃Ser)₁(Gly₄Ser)_n, (Gly₃Ser)_n(Gly₄Ser)_n, or (Gly₄Ser)_n, wherein n is an integer of 1 to 5. In certain embodiments, the linker is GGGGSGGGGS GGGGS (SEQ ID NO:183) or GGGGSGGGGS GGGGSGGGGS (SEQ ID NO:108). An additional exemplary linker is GGGGSGGGGS GGGGAS (SEQ ID NO:739). In certain embodiments, these (Gly_nSer)-based linkers are used to link the VH and VL domains in a binding domain, but are not used to link a binding domain to an immunoglobulin heterodimerization domain or to an Fc region portion.

[0155] Exemplary binding domains specific for CD28 include a 2E12 scFv as set forth in SEQ ID NO:109, binding domains specific for CD79b include a P2C2 scFv as set forth in SEQ ID NO:185; binding domains specific for c-Met include a 5D5 scFv as

set forth in SEQ ID NO:257; binding domains specific for RON include a 4C04 scFv as set forth in SEQ ID NO:261 and a 11H09 scFv as set forth in SEQ ID NO:265; binding domains specific for hyperIL-6 include an A2 scFv as set forth in SEQ ID NO:86; binding domains specific for CD86 include a 3D1 scFv as set forth in SEQ ID NO:98; binding domains specific for HLA-DR include an M0042 scFv as set forth in SEQ ID NO:120; binding domains specific for CD3 include a G19-4 scFv as set forth in SEQ ID NO:102, an OKT3-M scFv as set forth in SEQ ID NO:834, and a HuM291 scFv as set forth in SEQ ID NO:837; binding domain specific for CD19 include a H37 scFv as set forth in SEQ ID NO:105; and binding domains specific for c-Met include an MET021 scFv as set forth in SEQ ID NO:120 (with the light chain CDR1, CDR2, CDR3 and heavy chain CDR1, CDR2 and CDR3 as set forth in SEQ ID NOS:296-298 and 464-466, respectively). The nucleotide sequences encoding the A2 (anti-hyperIL6) and 3D1 (anti-CD86) scFv's are set forth in SEQ ID NOS:85 and 97, respectively. Exemplary binding domains that bind a TCR complex or a component thereof include a BMA031 scFv as set forth in SEQ ID NO:830 and other scFv's as set forth in SEQ ID NOS:310, 311, 312, 319, and 334-340.

[0156] Additional exemplary binding domains include a PDL2 ectodomain as set forth in SEQ ID NO:88 and monoIL-10 as set forth in SEQ ID NO:90. The nucleotide sequences encoding the PDL2 ectodomain and monoIL-10 are set forth in SEQ ID NOS:87 and 89, respectively.

[0157] The light chain amino acid sequence of the 4C04 (anti-RON) scFv is set forth in SEQ ID NO:602, and its CDR1, CDR2, and CDR3 are set forth in SEQ ID NOS:604-606, respectively. The heavy chain amino acid sequence of the 4C04 (anti-RON) scFv is set forth in SEQ ID NO:603, and its CDR1, CDR2, and CDR3 are set forth in SEQ ID NOS:607-609, respectively.

[0158] The light chain amino acid sequence of the 11H09 (anti-RON) scFv is set forth in SEQ ID NO:610, and its CDR1, CDR2, and CDR3 are set forth in SEQ ID NOS:612-614, respectively. The heavy chain amino acid sequence of the 11H09 (anti-RON) scFv is set forth in SEQ ID NO:611, and its CDR1, CDR2, and CDR3 are set forth in SEQ ID NOS:615-617, respectively.

[0159] A binding domain may be located either at amino terminal or carboxyl terminal to the Fc region portion of a single chain polypeptide of the present disclosure. In certain embodiments, the binding domain is located at the amino terminus of a single chain polypeptide. In certain other embodiments, the binding domain is located at the carboxyl terminus of a single chain polypeptide. In certain other embodiments, a binding domain is located at both the amino and carboxyl terminus of a single chain polypeptide.

Heterodimerization Domains

[0160] As indicated above, a polypeptide heterodimer of the present disclosure comprises an immunoglobulin heterodimerization domain in each polypeptide chain. The immunoglobulin heterodimerization domains in the two single chain polypeptides of a polypeptide heterodimer are different from each other and thus may be differentially modified to facilitate heterodimerization of both chains and to minimize homodimerization of either chain. As shown in the examples, immunoglobulin heterodimerization domains provided herein allow for efficient heterodimerization between different polypeptides and facilitate purification of the resulting polypeptide heterodimers.

[0161] As provided herein, immunoglobulin heterodimerization domains useful for promoting heterodimerization of two different single chain polypeptides (e.g., one short and one long) according to the present disclosure include immunoglobulin CH1 and CL domains, for instance, human CH1 and CL domains. In certain embodiments, an immunoglobulin heterodimerization domain is a wild type CH1 region, such as a wild type IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM CH1 region. In further embodiments, an immunoglobulin heterodimerization domain is a wild type human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM CH1 region as set forth in SEQ ID NOS:114, 186-192 and 194, respectively. In certain embodiments, an immunoglobulin heterodimerization domain is a wild type human IgG1 CH1 region as set forth in SEQ ID NO:114.

[0162] In further embodiments, an immunoglobulin heterodimerization domain is an altered immunoglobulin CH1 region, such as an altered IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM CH1 region. In certain embodiments, an immunoglobulin heterodimerization domain is an altered human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM CH1 region. In still further embodiments, a cysteine residue of a wild type CH1 region (e.g., a human CH1) involved in forming a disulfide bond with a wild type immunoglobulin CL domain (e.g., a human CL) is deleted or substituted in the altered immunoglobulin CH1 region such that a disulfide bond is not formed between the altered CH1 region and the wild type CL domain.

[0163] In certain embodiments, an immunoglobulin heterodimerization domain is a wild type CL domain, such as a wild type Cκ domain or a wild type Cλ domain. In particular embodiments, an immunoglobulin heterodimerization domain is a wild type human

C κ or human C λ domain as set forth in SEQ ID NOS:112 and 113, respectively. In further embodiments, an immunoglobulin heterodimerization domain is an altered immunoglobulin CL domain, such as an altered C κ or C λ domain, for instance, an altered human C κ or human C λ domain.

[0164] In certain embodiments, a cysteine residue of a wild type CL domain (*e.g.*, a human CL) involved in forming a disulfide bond with a wild type immunoglobulin CH1 region (*e.g.*, a human CH1) is deleted or substituted in the altered immunoglobulin CL domain. Such altered CL domains may further comprise an amino acid deletion at their amino termini. An exemplary C κ domain is set forth in SEQ ID NO:141, in which the first arginine and the last cysteine of the wild type human C κ domain are both deleted. In certain embodiments, only the last cysteine of the wild type human C κ domain is deleted in the altered C κ domain because the first arginine deleted from the wild type human C κ domain may be provided by a linker that has an arginine at its carboxyl terminus and links the amino terminus of the altered C κ domain with another domain (*e.g.*, an Fc region portion). An exemplary C λ domain is set forth in SEQ ID NO:140, in which the first arginine of a wild type human C λ domain is deleted and the cysteine involved in forming a disulfide bond with a cysteine in a CH1 region is substituted by a serine.

[0165] In further embodiments, an immunoglobulin heterodimerization domain is an altered C κ domain that contains one or more amino acid substitutions, as compared to a wild type C κ domain, at positions that may be involved in forming the interchain-hydrogen bond network at a C κ -C κ interface. For example, in certain embodiments, an immunoglobulin heterodimerization domain is an altered human C κ domain having one or more amino acids at positions N29, N30, Q52, V55, T56, S68 or T70 that are substituted with a different amino acid. The numbering of the amino acids is based on their positions in the altered human C κ sequence as set forth in SEQ ID NO:141. In certain embodiments, an immunoglobulin heterodimerization domain is an altered human C κ domain having one, two, three or four amino acid substitutions at positions N29, N30, V55, or T70. The amino acid used as a substitute at the above-noted positions may be an alanine, or an amino acid residue with a bulk side chain moiety such as arginine, tryptophan, tyrosine, glutamate, glutamine, or lysine. Additional amino acid residues that may be used to substitute amino acid residues of the wild type human C κ sequence at the above noted positions (*e.g.*, N30) include aspartate, methionine, serine and phenylalanine. Exemplary altered human C κ domains are set forth in SEQ ID NOS: 142-178. Altered human C κ domains are those that facilitate heterodimerization with a CH1 region, but minimize homodimerization with another C κ domain. Representative altered human C κ domains are set forth in SEQ ID NOS:160 (N29W V55A T70A), 161 (N29Y V55A T70A), 202 (T70E N29A N30A V55A), 167 (N30R V55A T70A), 168 (N30K V55A T70A), 170 (N30E V55A T70A), 172 (V55R N29A N30A), 175 (N29W N30Y V55A T70E), 176 (N29Y N30Y V55A T70E), 177 (N30E V55A T70E), 178 (N30Y V55A T70E), 838 (N30D V55A T70E), 839 (N30M V55A T70E), 840 (N30S V55A T70E), and 841 (N30F V55A T70E).

[0166] In certain embodiments, in addition to or alternative to the mutations in C κ domains described herein, both the immunoglobulin heterodimerization domains (*i.e.*, immunoglobulin CH1 and CL domains) of a polypeptide heterodimer have mutations so that the resulting immunoglobulin heterodimerization domains form salt bridges (*i.e.*, ionic interactions) between the amino acid residues at the mutated sites. For example, the immunoglobulin heterodimerization domains of a polypeptide heterodimer may be a mutated CH1 domain in combination with a mutated C κ domain. In the mutated CH1 domain, valine at position 68 (V68) of the wild type human CH1 domain is substituted by an amino acid residue having a negative charge (*e.g.*, aspartate or glutamate), whereas leucine at position 29 (L29) of a mutated human C κ domain in which the first arginine and the last cysteine have been deleted is substituted by an amino acid residue having a positive charge (*e.g.*, lysine, arginine or histidine). The charge-charge interaction between the amino acid residue having a negative charge of the resulting mutated CH1 domain and the amino acid residue having a positive charge of the resulting mutated C κ domain forms a salt bridge, which stabilizes the heterodimeric interface between the mutated CH1 and C κ domains. Alternatively, V68 of the wild type CH1 may be substituted by an amino acid residue having a positive charge, whereas L29 of a mutated human C κ domain in which the first arginine and the last cysteine have been deleted may be substituted by an amino acid residue having a negative charge. Exemplary mutated CH1 sequences in which V68 is substituted by an amino acid with either a negative or positive charge are set forth in SEQ ID NOS:844 and 845. Exemplary mutated C κ sequences in which L29 is substituted by an amino acid with either a negative or positive charge are set forth in SEQ ID NOS:842 and 843.

[0167] Positions other than V68 of human CH1 domain and L29 of human C κ domain may be substituted with amino acids having opposite charges to produce ionic interactions between the amino acids in addition or alternative to the mutations in V68 of CH1 domain and L29 of C κ domain. Such positions can be identified by any suitable method, including random mutagenesis, analysis of the crystal structure of the CH1-C κ pair to identify amino acid residues at the CH1-C κ interface, and further identifying suitable positions among the amino acid residues at the CH1-C κ interface using a set of criteria (*e.g.*, propensity to engage in ionic interactions, proximity to a potential partner residue, *etc.*).

[0168] In certain embodiments, polypeptide heterodimers of the present disclosure contain only one pair of immunoglobulin heterodimerization domains. For example, a first chain of a polypeptide heterodimer may comprise a CH1 region as an immunoglobulin heterodimerization domain, while a second chain may comprise a CL domain (*e.g.*, a C κ or C λ) as an

immunoglobulin heterodimerization domain. Alternatively, a first chain may comprise a CL region (e.g., a C κ or C λ) as an immunoglobulin heterodimerization domain, while a second chain may comprise a CH1 region as an immunoglobulin heterodimerization domain. As set forth herein, the immunoglobulin heterodimerization domains of the first and second chains are capable of associating to form a polypeptide heterodimer of this disclosure.

[0169] In certain other embodiments, polypeptide heterodimers of the present disclosure may have two pairs of immunoglobulin heterodimerization domains. For example, a first chain of a polypeptide heterodimer may comprise two CH1 regions, while a second chain may have two CL domains that associate with the two CH1 regions in the first chain. Alternatively, a first chain may comprise two CL domains, while a second chain may have two CH1 regions that associate with the two CL domains in the first chain. In certain embodiments, a first chain polypeptide comprises a CH1 region and a CL domain, while a second chain polypeptide comprises a CL domain and a CH1 region that associate with the CH1 region and the CL domain, respectively, of the first chain polypeptide.

[0170] In the embodiments where a polypeptide heterodimer comprises only one heterodimerization pair (i.e., one immunoglobulin heterodimerization domain in each chain), the immunoglobulin heterodimerization domain of each chain may be located amino terminal to the Fc region portion of that chain. Alternatively, the immunoglobulin heterodimerization domain in each chain may be located carboxyl terminal to the Fc region portion of that chain.

[0171] In the embodiments where a polypeptide heterodimer comprises two heterodimerization pairs (i.e., two immunoglobulin heterodimerization domains in each chain), both immunoglobulin heterodimerization domains in each chain may be located amino terminal to the Fc region portion of that chain. Alternatively, both immunoglobulin heterodimerization domains in each chain may be located carboxyl terminal to the Fc region portion of that chain. In further embodiments, one immunoglobulin heterodimerization domain in each chain may be located amino terminal to the Fc region portion of that chain, while the other immunoglobulin heterodimerization domain of each chain may be located carboxyl terminal to the Fc region portion of that chain. In other words, in those embodiments, the Fc region portion is interposed between the two immunoglobulin heterodimerization domains of each chain.

Fc region portion

[0172] As indicated herein, polypeptide heterodimers of the present disclosure comprise an Fc region constant domain portion (also referred to as an Fc region portion) in each polypeptide chain. The inclusion of an Fc region portion slows clearance of the heterodimers from circulation after administration to a subject. By mutations or other alterations, the Fc region portion further enables relatively easy modulation of heterodimer polypeptide effector functions (e.g., ADCC, ADCP, CDC, complement fixation and binding to Fc receptors), which can either be increased or decreased depending on the disease being treated, as known in the art and described herein. In certain embodiments, an Fc region portion of polypeptide heterodimers of the present disclosure will be capable of mediating one or more of these effector functions.

[0173] An Fc region portion present in single chain polypeptides that form part of the polypeptide heterodimers of the present disclosure may comprise a CH2 domain, a CH3 domain, a CH4 domain or any combination thereof. For example, an Fc region portion may comprise a CH2 domain, a CH3 domain, both CH2 and CH3 domains, both CH3 and CH4 domains, two CH3 domains, a CH4 domain, or two CH4 domains.

[0174] A CH2 domain that may form an Fc region portion of a single chain polypeptide of a heterodimer of the present disclosure may be a wild type immunoglobulin CH2 domain or an altered immunoglobulin CH2 domain thereof from certain immunoglobulin classes or subclasses (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, or IgD) and from various species (including human, mouse, rat, and other mammals).

[0175] In certain embodiments, a CH2 domain is a wild type human immunoglobulin CH2 domain, such as wild type CH2 domains of human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, or IgD, as set forth in SEQ ID NOS:115, 199-201 and 195-197, respectively. In certain embodiments, the CH2 domain is a wild type human IgG1 CH2 domain as set forth in SEQ ID NO:115.

[0176] In certain embodiments, a CH2 domain is an altered immunoglobulin CH2 region (e.g., an altered human IgG1 CH2 domain) that comprises an amino acid substitution at the asparagine of position 297 (e.g., asparagine to alanine). Such an amino acid substitution reduces or eliminates glycosylation at this site and abrogates efficient Fc binding to Fc γ R and C1q. The sequence of an altered human IgG1 CH2 domain with an Asn to Ala substitution at position 297 is set forth in SEQ ID NO:324.

[0177] In certain embodiments, a CH2 domain is an altered immunoglobulin CH2 region (*e.g.*, an altered human IgG1 CH2 domain) that comprises at least one substitution or deletion at positions 234 to 238. For example, an immunoglobulin CH2 region can comprise a substitution at position 234, 235, 236, 237 or 238, positions 234 and 235, positions 234 and 236, positions 234 and 237, positions 234 and 238, positions 234-236, positions 234, 235 and 237, positions 234, 236 and 238, positions 234, 235, 237, and 238, positions 236-238, or any other combination of two, three, four, or five amino acids at positions 234-238. In addition or alternatively, an altered CH2 region may comprise one or more (*e.g.*, two, three, four or five) amino acid deletions at positions 234-238, for instance, at one of position 236 or position 237 while the other position is substituted. The above-noted mutation(s) decrease or eliminate the antibody-dependent cell-mediated cytotoxicity (ADCC) activity or Fc receptor-binding capability of a polypeptide heterodimer that comprises the altered CH2 domain. In certain embodiments, the amino acid residues at one or more of positions 234-238 has been replaced with one or more alanine residues. In further embodiments, only one of the amino acid residues at positions 234-238 have been deleted while one or more of the remaining amino acids at positions 234-238 can be substituted with another amino acid (*e.g.*, alanine or serine).

[0178] In certain other embodiments, a CH2 domain is an altered immunoglobulin CH2 region (*e.g.*, an altered human IgG1 CH2 domain) that comprises one or more amino acid substitutions at positions 253, 310, 318, 320, 322, and 331. For example, an immunoglobulin CH2 region can comprise a substitution at position 253, 310, 318, 320, 322, or 331, positions 318 and 320, positions 318 and 322, positions 318, 320 and 322, or any other combination of two, three, four, five or six amino acids at positions 253, 310, 318, 320, 322, and 331. The above-noted mutation(s) decrease or eliminate the complement-dependent cytotoxicity (CDC) of a polypeptide heterodimer that comprises the altered CH2 domain.

[0179] In certain other embodiments, in addition to the amino acid substitution at position 297, an altered CH2 region (*e.g.*, an altered human IgG1 CH2 domain) can further comprise one or more (*e.g.*, two, three, four, or five) additional substitutions at positions 234-238. For example, an immunoglobulin CH2 region can comprise a substitution at positions 234 and 297, positions 234, 235, and 297, positions 234, 236 and 297, positions 234-236 and 297, positions 234, 235, 237 and 297, positions 234, 236, 238 and 297, positions 234, 235, 237, 238 and 297, positions 236-238 and 297, or any combination of two, three, four, or five amino acids at positions 234-238 in addition to position 297. In addition or alternatively, an altered CH2 region may comprise one or more (*e.g.*, two, three, four or five) amino acid deletions at positions 234-238, such as at position 236 or position 237. The additional mutation(s) decreases or eliminates the antibody-dependent cell-mediated cytotoxicity (ADCC) activity or Fc receptor-binding capability of a polypeptide heterodimer that comprises the altered CH2 domain. In certain embodiments, the amino acid residues at one or more of positions 234-238 have been replaced with one or more alanine residues. In further embodiments, only one of the amino acid residues at positions 234-238 has been deleted while one or more of the remaining amino acids at positions 234-238 can be substituted with another amino acid (*e.g.*, alanine or serine).

[0180] In certain embodiments, in addition to one or more (*e.g.*, 2, 3, 4, or 5) amino acid substitutions at positions 234-238, a mutated CH2 region (*e.g.*, an altered human IgG1 CH2 domain) in a fusion protein of the present disclosure may contain one or more (*e.g.*, 2, 3, 4, 5, or 6) additional amino acid substitutions (*e.g.*, substituted with alanine) at one or more positions involved in complement fixation (*e.g.*, at positions I253, H310, E318, K320, K322, or P331). Examples of mutated immunoglobulin CH2 regions include human IgG1, IgG2, IgG4 and mouse IgG2a CH2 regions with alanine substitutions at positions 234, 235, 237 (if present), 318, 320 and 322. An exemplary mutated immunoglobulin CH2 region is mouse IGHG2c CH2 region with alanine substitutions at L234, L235, G237, E318, K320, and K322 (SEQ ID NO:314).

[0181] In still further embodiments, in addition to the amino acid substitution at position 297 and the additional deletion(s) or substitution(s) at positions 234-238, an altered CH2 region (*e.g.*, an altered human IgG1 CH2 domain) can further comprise one or more (*e.g.*, two, three, four, five, or six) additional substitutions at positions 253, 310, 318, 320, 322, and 331. For example, an immunoglobulin CH2 region can comprise a (1) substitution at position 297, (2) one or more substitutions or deletions or a combination thereof at positions 234-238, and one or more (*e.g.*, 2, 3, 4, 5, or 6) amino acid substitutions at positions I253, H310, E318, K320, K322, and P331, such as one, two, three substitutions at positions E318, K320 and K322. The amino acids at the above-noted positions may be substituted by alanine or serine.

[0182] In certain embodiments, an immunoglobulin CH2 region polypeptide comprises: (i) an amino acid substitution at the asparagines of position 297 and one amino acid substitution at position 234, 235, 236 or 237; (ii) an amino acid substitution at the asparagine of position 297 and amino acid substitutions at two of positions 234-237; (iii) an amino acid substitution at the asparagine of position 297 and amino acid substitutions at three of positions 234-237; (iv) an amino acid substitution at the asparagine of position 297, amino acid substitutions at positions 234, 235 and 237, and an amino acid deletion at position 236; (v) amino acid substitutions at three of positions 234-237 and amino acid substitutions at positions 318, 320 and 322; or (vi) amino acid substitutions at three of positions 234-237, an amino acid deletion at position 236, and amino acid substitutions at positions 318, 320 and 322.

[0183] Exemplary altered immunoglobulin CH2 regions with amino acid substitutions at the asparagine of position 297 include: human IgG1 CH2 region with alanine substitutions at L234, L235, G237 and N297 and a deletion at G236 (SEQ ID NO:325), human IgG2 CH2 region with alanine substitutions at V234, G236, and N297 (SEQ ID NO:326), human IgG4 CH2 region with alanine substitutions at F234, L235, G237 and N297 and a deletion of G236 (SEQ ID NO:322), human IgG4 CH2 region with alanine substitutions at F234 and N297 (SEQ ID NO:343), human IgG4 CH2 region with alanine substitutions at L235 and N297 (SEQ ID NO:344), human IgG4 CH2 region with alanine substitutions at G236 and N297 (SEQ ID NO:345), and human IgG4 CH2 region with alanine substitutions at G237 and N297 (SEQ ID NO:346).

[0184] In certain embodiments, in addition to the amino acid substitutions described above, an altered CH2 region (*e.g.*, an altered human IgG1 CH2 domain) may contain one or more additional amino acid substitutions at one or more positions other than the above-noted positions. Such amino acid substitutions may be conservative or non-conservative amino acid substitutions. For example, in certain embodiments, P233 may be changed to E233 in an altered IgG2 CH2 region (*see, e.g.*, SEQ ID NO:326). In addition or alternatively, in certain embodiments, the altered CH2 region may contain one or more amino acid insertions, deletions, or both. The insertion(s), deletion(s) or substitution(s) may anywhere in an immunoglobulin CH2 region, such as at the N- or C-terminus of a wild type immunoglobulin CH2 region resulting from linking the CH2 region with another region (*e.g.*, a binding domain or an immunoglobulin heterodimerization domain) via a hinge.

[0185] In certain embodiments, an altered CH2 region in a polypeptide heterodimer of the present disclosure comprises or is a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a wild type immunoglobulin CH2 region, such as the CH2 region of wild type human IgG1, IgG2, or IgG4, or mouse IgG2a (*e.g.*, IGHG2c).

[0186] An altered immunoglobulin CH2 region in a polypeptide heterodimer of the present disclosure may be derived from a CH2 region of various immunoglobulin isotypes, such as IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, and IgD, from various species (including human, mouse, rat, and other mammals). In certain embodiments, an altered immunoglobulin CH2 region in a fusion protein of the present disclosure may be derived from a CH2 region of human IgG1, IgG2 or IgG4, or mouse IgG2a (*e.g.*, IGHG2c), whose sequences are set forth in SEQ ID NOS:115, 199, 201 and 320.

[0187] In certain embodiments, an altered CH2 domain is a human IgG1 CH2 domain with alanine substitutions at positions 235, 318, 320, and 322 (*i.e.*, a human IgG1 CH2 domain with L235A, E318A, K320A and K322A substitutions) (SEQ ID NO:595), and optionally an N297 mutation (*e.g.*, to alanine). In certain other embodiments, an altered CH2 domain is a human IgG1 CH2 domain with alanine substitutions at positions 234, 235, 237, 318, 320 and 322 (*i.e.*, a human IgG1 CH2 domain with L234A, L235A, G237A, E318A, K320A and K322A substitutions) (SEQ ID NO:596), and optionally an N297 mutation (*e.g.*, to alanine).

[0188] In certain embodiments, an altered CH2 domain is an altered human IgG1 CH2 domain with mutations known in the art that enhance immunological activities such as ADCC, ADCP, CDC, complement fixation, Fc receptor binding, or any combination thereof.

[0189] The CH3 domain that may form an Fc region portion of a single chain polypeptide of a heterodimer of the present disclosure may be a wild type immunoglobulin CH3 domain or an altered immunoglobulin CH3 domain thereof from certain immunoglobulin classes or subclasses (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, IgM) of various species (including human, mouse, rat, and other mammals). In certain embodiments, a CH3 domain is a wild type human immunoglobulin CH3 domain, such as wild type CH3 domains of human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM as set forth in SEQ ID NOS:116, 208-210, 204-207, and 212, respectively. In certain embodiments, the CH3 domain is a wild type human IgG1 CH3 domain as set forth in SEQ ID NO:116. In certain embodiments, a CH3 domain is an altered human immunoglobulin CH3 domain, such as an altered CH3 domain based on or derived from a wild-type CH3 domain of human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM antibodies. For example, an altered CH3 domain may be a human IgG1 CH3 domain with one or two mutations at positions H433 and N434 (positions are numbered according to EU numbering). The mutations in such positions may be involved in complement fixation. In certain other embodiments, an altered CH3 domain may be a human IgG1 CH3 domain but with one or two amino acid substitutions at position F405 or Y407. The amino acids at such positions are involved in interacting with another CH3 domain. In certain embodiments, an altered CH3 domain may be an altered human IgG1 CH3 domain with its last lysine deleted. The sequence of this altered CH3 domain is set forth in SEQ ID NO:761.

[0190] In certain embodiments, a polypeptide heterodimer comprises a CH3 pair that comprises so called "knobs-into-holes" mutations (*see*, Marvin and Zhu, *Acta Pharmacologica Sinica* 26:649-58, 2005; Ridgway et al., *Protein Engineering* 9:617-21, 1996). More specifically, mutations may be introduced into each of the two CH3 domains so that the steric complementarity required for CH3/CH3 association obligates these two CH3 domains to pair with each other. For example, a CH3 domain in one

single chain polypeptide of a polypeptide heterodimer may contain a T366W mutation (a "knob" mutation, which substitutes a small amino acid with a larger one), and a CH3 domain in the other single chain polypeptide of the polypeptide heterodimer may contain a Y407A mutation (a "hole" mutation, which substitutes a large amino acid with a smaller one). Other exemplary knobs-into-holes mutations include (1) a T366Y mutation in one CH3 domain and a Y407T in the other CH3 domain, and (2) a T366W mutation in one CH3 domain and T366S, L368A and Y407V mutations in the other CH3 domain.

[0191] The CH4 domain that may form an Fc region portion of a single chain polypeptide of a heterodimer of the present disclosure may be a wild type immunoglobulin CH4 domain or an altered immunoglobulin CH4 domain thereof from IgE or IgM molecules. In certain embodiments, the CH4 domain is a wild type human immunoglobulin CH4 domain, such as wild type CH4 domains of human IgE and IgM molecules as set forth in SEQ ID NOS:213 and 214, respectively. In certain embodiments, a CH4 domain is an altered human immunoglobulin CH4 domain, such as an altered CH4 domain based on or derived from a CH4 domain of human IgE or IgM molecules, which have mutations that increase or decrease an immunological activity known to be associated with an IgE or IgM Fc region.

[0192] In certain embodiments, an Fc region constant domain portion in heterodimers of the present disclosure comprises a combination of CH2, CH3 or CH4 domains (*i.e.*, more than one constant sub-domain selected from CH2, CH3 and CH4). For example, the Fc region portion may comprise CH2 and CH3 domains or CH3 and CH4 domains. In certain other embodiments, the Fc region portion may comprise two CH3 domains and no CH2 or CH4 domains (*i.e.*, only two or more CH3). The multiple constant sub-domains that form an Fc region portion may be based on or derived from the same immunoglobulin molecule, or the same class or subclass immunoglobulin molecules. In certain embodiments, the Fc region portion is an IgG CH2CH3 (*e.g.*, IgG1 CH2CH3, IgG2 CH2CH3, and IgG4 CH2CH3) and may be a human (*e.g.*, human IgG1, IgG2, and IgG4) CH2CH3. For example, in certain embodiments, the Fc region portion comprises (1) wild type human IgG1 CH2 and CH3 domains, (2) human IgG1 CH2 with N297A substitution (*i.e.*, CH2(N297A)) and wild type human IgG1 CH3, or (3) human IgG1 CH2(N297A) and an altered human IgG1 CH3 with the last lysine deleted.

[0193] Alternatively, the multiple constant sub-domains may be based on or derived from different immunoglobulin molecules, or different classes or subclasses immunoglobulin molecules. For example, in certain embodiments, an Fc region portion comprises both human IgM CH3 domain and human IgG1 CH3 domain. The multiple constant sub-domains that form an Fc region portion may be directly linked together or may be linked to each other via one or more (*e.g.*, about 2-10) amino acids.

[0194] Exemplary Fc region portions are set forth in SEQ ID NOS:305-309, 321, 323, 341, 342, and 762.

[0195] In certain embodiments, the Fc region portions of both single chain polypeptides of a polypeptide heterodimer are identical to each other. In certain other embodiments, the Fc region portion of one single chain polypeptide of a polypeptide heterodimer is different from the Fc region portion of the other single chain polypeptide of the heterodimer. For example, one Fc region portion may contain a CH3 domain with a "knob" mutation, whereas the other Fc region portion may contain a CH3 domain with a "hole" mutation.

Hinge

[0196] A hinge region contained in a single chain polypeptide of a polypeptide heterodimer according to the present disclosure may be located (a) immediately amino terminal to an Fc region portion (*e.g.*, depending on the isotype, amino terminal to a CH2 domain wherein the Fc region portion is a CH2CH3, or amino terminal to a CH3 domain wherein the Fc region portion is a CH3CH4), (b) interposed between and connecting a binding domain (*e.g.*, scFv) and an immunoglobulin heterodimerization domain, (c) interposed between and connecting an immunoglobulin heterodimerization domain and an Fc region portion (*e.g.*, wherein the Fc region portion is a CH2CH3 or a CH3CH4, depending on the isotype or isotypes), (d) interposed between and connecting an Fc region portion and a binding domain, (e) at the amino terminus of the single chain polypeptide, or (f) at the carboxyl terminus of the single chain polypeptide. The single chain polypeptide comprising a hinge region as described herein will be capable of associating with a different single chain fusion polypeptide to form a polypeptide heterodimer provided herein, and the polypeptide heterodimer formed will contain a binding domain that retains its target specificity or its specific target binding affinity.

[0197] In certain embodiments, a hinge present in a single chain polypeptide that forms a polypeptide heterodimer with another single chain polypeptide may be an immunoglobulin hinge region, such as a wild type immunoglobulin hinge region or an altered immunoglobulin hinge region thereof.

[0198] In certain embodiments, a hinge is a wild type human immunoglobulin hinge region (e.g., human immunoglobulin hinge regions as set forth in SEQ ID NOS:215-221). In certain other embodiments, one or more amino acid residues may be added at the amino- or carboxy- terminus of a wild type immunoglobulin hinge region as part of a fusion protein construct design. For example, additional junction amino acid residues at the hinge amino-terminus can be "RT," "RSS," "TG," or "T", or at the hinge carboxy-terminus can be "SG", or a hinge deletion can be combined with an addition, such as Δ P with "SG" added at the carboxyl terminus.

[0199] In certain embodiments, a hinge is an altered immunoglobulin hinge in which one or more cysteine residues in a wild type immunoglobulin hinge region is substituted with one or more other amino acid residues (e.g., serine or alanine). For example, a hinge may be an altered immunoglobulin hinge based on or derived from a wild type human IgG1 hinge as set forth in SEQ ID NO:667, which from amino terminus to carboxyl terminus comprises the upper hinge region (EPKSCDKTHT, SEQ ID NO:227) and the core hinge region (CPPCP, SEQ ID NO:228). Exemplary altered immunoglobulin hinges include an immunoglobulin human IgG1 hinge region having one, two or three cysteine residues found in a wild type human IgG1 hinge substituted by one, two or three different amino acid residues (e.g., serine or alanine). An altered immunoglobulin hinge may additionally have a proline substituted with another amino acid (e.g., serine or alanine). For example, the above-described altered human IgG1 hinge may additionally have a proline located carboxyl terminal to the three cysteines of wild type human IgG1 hinge region substituted by another amino acid residue (e.g., serine, alanine). In one embodiment, the prolines of the core hinge region are not substituted. Exemplary altered immunoglobulin hinges are set forth in SEQ ID NOS: 229-240, 255, 664-677, and 748-759. An example of an altered IgG1 hinge is an altered human IgG1 hinge in which the first cysteine is substituted by serine. The sequence of this altered IgG1 hinge is set forth in SEQ ID NO:664, and is referred to as the "human IgG1 SCC-P hinge" or "SCC-P hinge." In certain embodiments, one or more amino acid residues (e.g., "RT," "RSS," or "T") may be added at the amino-or carboxy-terminus of a mutated immunoglobulin hinge region as part of a fusion protein construct design.

[0200] In certain embodiments, a hinge polypeptide comprises or is a sequence that is at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a wild type immunoglobulin hinge region, such as a wild type human IgG1 hinge, a wild type human IgG2 hinge, or a wild type human IgG4 hinge.

[0201] In further embodiments, a hinge present in a single chain polypeptide that forms a polypeptide heterodimer with another single chain polypeptide may be a hinge that is not based on or derived from an immunoglobulin hinge (i.e., not a wild type immunoglobulin hinge or an altered immunoglobulin hinge). These types of non-immunoglobulin based hinges may be used on or near the carboxyl end (e.g., located carboxyl terminal to Fc region portions) of the single chain polypeptides that form the polypeptide heterodimers. Examples for such hinges include peptides of about five to about 150 amino acids of the interdomain or stalk region of type II C-lectins or CD molecules, for instance, peptides of about eight to 25 amino acids and peptides of about seven to 18 amino acids, and derivatives thereof.

[0202] The "interdomain or stalk region" of a type II C-lectin or CD molecule refers to the portion of the extracellular domain of the type II C-lectin or CD molecule that is located between the C-type lectin-like domain (CTLCD; e.g., similar to CTLCD of natural killer cell receptors) and the transmembrane domain. For example, in the human CD94 molecule (GenBank Accession No. AAC50291.1, PRI November 30, 1995), the extracellular domain corresponds to amino acid residues 34-179, whereas the CTLCD corresponds to amino acid residues 61-176. Accordingly, the interdomain or stalk region of the human CD94 molecule includes amino acid residues 34-60, which is found between the membrane and the CTLCD (see Boyington *et al.*, Immunity 10:75, 1999; for descriptions of other stalk regions, see also Beavil *et al.*, Proc. Nat'l. Acad. Sci. USA 89:753, 1992; and Figdor *et al.*, Nature Rev. Immunol. 2:77, 2002). These type II C-lectin or CD molecules may also have from six to 10 junction amino acids between the stalk region and the transmembrane region or the CTLCD. In another example, the 233 amino acid human NKG2A protein (GenBank Accession No. P26715.1, PRI June 15, 2010) has a transmembrane domain ranging from amino acids 71-93 and an extracellular domain ranging from amino acids 94-233. The CTLCD is comprised of amino acids 119-231, and the stalk region comprises amino acids 99-116, which is flanked by junctions of five and two amino acids. Other type II C-lectin or CD molecules, as well as their extracellular ligand-bind domains, interdomain or stalk regions, and CTLCDs are known in the art (see, e.g., GenBank Accession Nos. NP_001993.2; AAH07037.1, PRI July 15, 2006; NP_001773.1, PRI June 20, 2010; AAL65234.1, PRI January 17, 2002, and CAA04925.1, PRI November 14, 2006, for the sequences of human CD23, CD69, CD72, NKG2A and NKG2D and their descriptions, respectively).

[0203] A "derivative" of an interdomain or stalk region, or fragment thereof, of a type II C-lectin or CD molecule includes an about an eight to about 150 amino acid sequence in which one, two, or three amino acids of the stalk region of a wild type type II C-lectin or CD molecule have a deletion, insertion, substitution, or any combination thereof, for instance, the one or more changes are substitutions or the one or more mutations include only one deletion. In further embodiments, a derivative of an interdomain

or stalk region is more resistant to proteolytic cleavage as compared to the wild-type interdomain or stalk region sequence, such as those derived from about eight to about 20 amino acids of NKG2A, NKG2D, CD23, CD64, CD72, or CD94.

[0204] In certain embodiments, interdomain or stalk region hinges have seven to 18 amino acids and can form an α -helical coiled coil structure. In certain embodiments, interdomain or stalk region hinges contain 0, 1, 2, 3, or 4 cysteines. Exemplary interdomain or stalk region hinges are peptide fragments of the interdomain or stalk regions, such as ten to 150 amino acid fragments from the stalk regions of CD69, CD72, CD94, NKG2A and NKG2D, as set forth in SEQ ID NOS:241-244, 716 and 601. Additional exemplary stalk region or interdomain hinges include those as set forth in SEQ ID NOS:78, 734-737, 742-747, and 766-790.

[0205] Alternative hinges that can be used in single chain polypeptides of polypeptide heterodimers are from portions of cell surface receptors (interdomain regions) that connect immunoglobulin V-like or immunoglobulin C-like domains. Regions between Ig V-like domains where the cell surface receptor contains multiple Ig V-like domains in tandem and between Ig C-like domains where the cell surface receptor contains multiple tandem Ig C-like regions are also contemplated as hinges useful in single chain polypeptides of polypeptide heterodimers. In certain embodiments, hinge sequences comprised of cell surface receptor interdomain regions may further contain a naturally occurring or added motif, such as an IgG core hinge sequence that confers one or more disulfide bonds to stabilize the polypeptide heterodimer formation. Examples of hinges include interdomain regions between the Ig V-like and Ig C-like regions of CD2, CD4, CD22, CD33, CD48, CD58, CD66, CD80, CD86, CD150, CD166, and CD244.

[0206] In certain embodiments, hinge sequences have about 5 to 150 amino acids, 5 to 10 amino acids, 10 to 20 amino acids, 20 to 30 amino acids, 30 to 40 amino acids, 40 to 50 amino acids, 50 to 60 amino acids, 5 to 60 amino acids, 5 to 40 amino acids, 8 to 20 amino acids, or 10 to 15 amino acids. The hinge may be primarily flexible, but may also provide more rigid characteristics or may contain primarily α -helical structure with minimal β -sheet structure. The lengths or the sequences of the hinges may affect the binding affinities of the binding domains to which the hinges are directly or indirectly (via another region or domain, such as an immunoglobulin heterodimerization domain) connected as well as one or more activities of the Fc region portions to which the hinges are directly or indirectly connected (see, Examples 9 and 10).

[0207] In certain embodiments, hinge sequences are stable in plasma and serum and are resistant to proteolytic cleavage. The first lysine in the IgG1 upper hinge region may be mutated to minimize proteolytic cleavage, for instance, the lysine may be substituted with methionine, threonine, alanine or glycine, or is deleted (see, e.g., SEQ ID NOS:379-434, which may include junction amino acids at the amino terminus such as RT).

[0208] In some embodiments, hinge sequences may contain a naturally occurring or added motif such as an immunoglobulin hinge core structure CPPCP (SEQ ID NO:228) that confers the capacity to form a disulfide bond or multiple disulfide bonds to stabilize the carboxy-terminus of a molecule. In other embodiments, hinge sequences may contain one or more glycosylation sites.

[0209] Exemplary hinges, including altered immunoglobulin hinges, are set forth in SEQ ID NOS:379-434, 618-749, and 763-791.

[0210] In certain embodiments, a single chain polypeptide of a polypeptide heterodimer according to the present disclosure comprises more than one hinge. For example, a single chain polypeptide having two binding domains, one of which at the amino terminus and the other at the carboxyl terminus, may have two hinges. One hinge may be directly or indirectly (e.g., via an immunoglobulin heterodimerization domain) connected to the binding domain at or near the amino terminus, and the other hinge may be connected (e.g., directly connected) to the other binding domain at or near the carboxyl terminus. In certain embodiments, even if a single chain polypeptide has only one binding domain, it may have more than one hinge, for example, at its amino or carboxyl terminus. Such a hinge may interact with a corresponding hinge in the other chain of the heterodimer, such as forming one or more interchain disulfide bonds, to facilitate or enhance the heterodimerization of the two chains. A hinge (H-I) of a SCP-I of a polypeptide heterodimer "corresponds to" a hinge (H-II) of a SCP-II of the heterodimer when H-I and H-II are located on the same end of the Fc region portion of their respective single chain polypeptide. For example, a polypeptide heterodimer may comprise the following two single chain polypeptides: A first chain polypeptide from amino to carboxyl terminus comprises a first binding domain, CH1, hinge, CH2, and CH3, and a second chain polypeptide from amino to carboxyl terminus comprises a CK, first hinge, CH2, CH3, second hinge, and a second binding domain. The hinge in the first chain would be regarded as "corresponding" to the first hinge of the second chain because both are amino terminal to the Fc region portions to which they are connected.

[0211] In certain embodiments where a single chain polypeptide of a polypeptide heterodimer comprises a binding domain at or near its carboxyl terminus, a hinge may be present to link the binding domain with another portion of the single chain polypeptide

(e.g., an Fc region portion or an immunoglobulin heterodimerization domain). In one embodiment, such a hinge is a non-immunoglobulin hinge (i.e., a hinge not based on or derived from a wild type immunoglobulin hinge) and may be a stalk region of a type II C-lectin or CD molecule, an interdomain region that connect IgV-like or IgC-like domains of a cell surface receptor, or a derivative or functional variant thereof. Exemplary carboxyl terminal hinges, sometimes referred to as "back-end" hinges, includes those set forth in SEQ ID NOS:78, 734-737, 742-747, and 766-790.

[0212] In certain embodiments, a hinge of one single chain polypeptide of a polypeptide heterodimer is identical to a corresponding hinge of the other single chain polypeptide of the heterodimer. In certain other embodiments, a hinge of one chain is different from that of the other chain (in their length or sequence). The different hinges in the different chains allow different manipulation of the binding affinities of the binding domains to which the hinges are connected, so that the heterodimer is able to preferentially bind to the target of one binding domain over the target of the other binding domain. For example, in certain embodiments, a polypeptide heterodimer has a CD3 or TCR binding domain in one chain and a tumor antigen binding domain in another chain. Having two different hinges in the two chains may allow the heterodimer to bind to the tumor antigen first, and then to a CD3 or TCR molecule second. Thus, the heterodimer may recruit CD3⁺ T cells to tumor cells carrying the tumor antigen, which in turn may damage or destroy the tumor cells.

Other components or modifications

[0213] In certain embodiments, a single chain polypeptide that forms a heterodimer with another single chain polypeptide may contain one or more additional domains or regions. Such additional regions may be a leader sequence (also referred to as "signal peptide") at the amino-terminus for secretion of an expressed single chain polypeptide. Exemplary leader peptides of this disclosure include natural leader sequences or others, such as those as set forth in SEQ ID NOS:110 and 111.

[0214] Additional regions may also be sequences at the carboxy-terminus for identifying or purifying single chain polypeptides (e.g., epitope tags for detection or purification, such as a histidine tag, biotin, a FLAG® epitope, or any combination thereof).

[0215] Further optional regions may be additional amino acid residues (referred to as "junction amino acids" or "junction amino acid residues") having a length of 1 to about 10 amino acids (e.g., about 2 to 5 amino acids), which may be resulted from use of specific expression systems or construct design for the single chain polypeptides of the present disclosure. Such additional amino acid residues (for instance, one, two, three, four or five additional amino acids) may be present at the amino or carboxyl terminus or between various regions or domains of a single chain polypeptide, such as between a binding domain and an immunoglobulin heterodimerization domain, between an immunoglobulin heterodimerization domain and a hinge, between a hinge and an Fc region portion, between domains of an Fc region portion (e.g., between CH2 and CH3 domains or between two CH3 domains), between a binding domain and a hinge, between an Fc region portion and an immunoglobulin heterodimerization domain, or between a variable domain and a linker. Exemplary junction amino acids amino-terminal to a hinge include RDQ (SEQ ID NO:598), RT, SS, SASS (SEQ ID NO:599) and SSS (SEQ ID NO:600). Exemplary junction amino acids carboxy-terminal to a hinge include amino acids SG. Additional exemplary junction amino acids include SR.

[0216] In certain embodiments, junction amino acids are present between an Fc region portion that comprises CH2 and CH3 domains and an immunoglobulin heterodimerization domain (CH1 or CL). These junction amino acids are also referred to as a "linker between CH3 and CH1 or CL" if they are present between the C-terminus of CH3 and the N-terminus of CH1 or CL. Such a linker may be about 2-12 amino acids in length. In certain embodiments, the Fc region portion comprises human IgG1 CH2 and CH3 domains in which the C-terminal lysine residue of human IgG1 CH3 is deleted. Exemplary linkers between CH3 and CH1 include those set forth in SEQ ID NO:847-849. Exemplary linkers between CH3 and Ck include those set forth in SEQ ID NOS:850-852 (in which the carboxyl terminal arginine in the linkers may alternatively be regarded as the first arginine of Ck). In certain embodiments, the presence of such linkers or linker pairs (e.g., SEQ ID NO:847 as a CH3-CH1 linker in one single chain polypeptide of a heterodimer and SEQ ID NO:850 as a CH3-Ck linker in the other single chain polypeptide of the heterodimer; SEQ ID NO:848 as a CH3-CH1 linker and SEQ ID NO:851 as a CH3-Ck linker; and SEQ ID NO:849 as a CH3-CH1 linker and SEQ ID NO:852 as a CH3-Ck linker) improves the production of heterodimer compared the presence of a reference linker as set forth in SEQ ID NO:846 (in which the last lysine of CH3 is included as part of the linker) in both single chain polypeptides of a heterodimer.

[0217] In certain embodiments, an immunoglobulin Fc region (e.g., CH2, CH3, and/or CH4 regions) of a polypeptide heterodimer of the present disclosure may have an altered glycosylation pattern relative to an immunoglobulin reference sequence. For example, any of a variety of genetic techniques may be employed to alter one or more particular amino acid residues that form a glycosylation site (see Co et al. (1993) Mol. Immunol. 30:1361; Jacquemon et al. (2006) J. Thromb. Haemost. 4:1047; Schuster et

al. (2005) Cancer Res. 65:7934; Warnock et al. (2005) Biotechnol. Bioeng. 92:831), such as N297 of the CH2 domain (EU numbering). Alternatively, the host cells producing polypeptide heterodimers of this disclosure may be engineered to produce an altered glycosylation pattern. One method known in the art, for example, provides altered glycosylation in the form of bisected, non-fucosylated variants that increase ADCC. The variants result from expression in a host cell containing an oligosaccharide-modifying enzyme. Alternatively, the POTEILLIGENT® technology of BioWa/Kyowa Hakko is contemplated to reduce the fucose content of glycosylated molecules according to this disclosure. In one known method, a CHO host cell for recombinant immunoglobulin production is provided that modifies the glycosylation pattern of the immunoglobulin Fc region, through production of GDP-fucose.

[0218] Alternatively, chemical techniques are used to alter the glycosylation pattern of polypeptide heterodimers of this disclosure. For example, a variety of glycosidase and/or mannosidase inhibitors provide one or more of desired effects of increasing ADCC activity, increasing Fc receptor binding, and altering glycosylation pattern. In certain embodiments, cells expressing polypeptide heterodimers of the instant disclosure are grown in a culture medium comprising a carbohydrate modifier at a concentration that increases the ADCC of immunoglycoprotein molecules produced by said host cell, wherein said carbohydrate modifier is at a concentration of less than 800 μ M. In one embodiment, the cells expressing these polypeptide heterodimers are grown in a culture medium comprising castanospermine or kifunensine, for instance, castanospermine at a concentration of 100-800 μ M, such as 100 μ M, 200 μ M, 300 μ M, 400 μ M, 500 μ M, 600 μ M, 700 μ M, or 800 μ M. Methods for altering glycosylation with a carbohydrate modifier such as castanospermine are provided in U.S. Patent No. 7,846,434 or PCT Publication No. WO 2008/052030.

Structural Arrangements and Exemplary Heterodimers

[0219] To form a polypeptide heterodimer according to the present invention, two single chain polypeptides are designed so that the immunoglobulin heterodimerization domain of the first single chain polypeptide is properly aligned and interacts with the immunoglobulin heterodimerization domain of the second single chain polypeptide. In certain embodiments, the heterodimer may comprise a second immunoglobulin heterodimerization domain pair to facilitate or enhance the heterodimerization of the two chains. In certain embodiments, in addition to the interaction between the two immunoglobulin heterodimerization domains, an Fc region portion (*e.g.*, a CH3 domain) in the first chain may interact with an Fc region in the second chain to enhance heterodimerization (*e.g.*, via interaction between two wild type CH3 domains or between a CH3 domain pair with "knobs-into-holes" mutations). Moreover, in certain embodiments, the hinge in the first chain (*e.g.*, an altered human IgG1 hinge with two cysteine residues as set forth in SEQ ID NO:664) may interact with the hinge in the second chain (*e.g.*, the same altered human IgG1 hinge as set forth in SEQ ID NO:664) to form, for example, disulfide bonds, which may further strengthen the interaction between the first and second single chain polypeptides to form a polypeptide heterodimer of the present disclosure. Furthermore, in certain embodiments, the first and second chain may comprise a second hinge pair (*e.g.*, at the carboxyl termini of the two chains) to further enhance the interactions between the two chains.

[0220] In certain embodiments, a polypeptide heterodimer of the present disclosure comprises two binding domains (BD1 and BD2), wherein the binding domains bind to two different target molecules. In certain embodiments, the two binding domains (BD1 and BD2) are both on the SCP-I with the immunoglobulin heterodimerization domain (HD-I) and the Fc region portion (FRP-1) disposed between BD1 and BD2. In certain other embodiments, the first binding domain (BD1) is on the SCP-I and the second binding domain (BD2) is on the SCP-II. In certain embodiments, both BD1 and BD2 are amino terminal to the Fc region portion of the SCP-I and SCP-II, respectively. In certain other embodiments, BD1 is amino terminal to the Fc region portion of the SCP-I and BD2 is carboxyl terminal to the Fc region portion of the SCP-II. In certain other embodiments, BD1 is carboxyl terminal to the Fc region portion of the SCP-I and BD2 is amino terminal to the Fc region portion of the SCP-II. In certain other embodiments, both BD1 and BD2 are carboxyl terminal to the Fc region portion of the SCP-I and SCP-II, respectively.

[0221] In certain embodiments, a polypeptide heterodimer comprises three binding domains (BD1, BD2 and BD3), wherein the binding domains bind to two or three different target molecules. For example, BD1, BD2, and BD3 each bind a different target, or BD1 and BD2 bind a first target while BD3 binds a second target, or BD1 and BD3 bind a first target while BD2 binds a second target, or BD2 and BD3 bind a first target while BD1 binds a second target. In certain embodiments, the immunoglobulin heterodimerization domain and the Fc region portion are disposed between BD1 and BD2 on SCP-I, and BD3 is amino terminal to the Fc region portion of the SCP-II. In further embodiments, the immunoglobulin heterodimerization domain and the Fc region portion are disposed between BD1 and BD2 on SCP-II, and BD3 is carboxyl terminal to the Fc region portion of the SCP-I.

[0222] In certain embodiments, a polypeptide heterodimer comprises four binding domains (BD1, BD2, BD3 and BD4), wherein the binding domains bind to two to four different target molecules. In certain embodiments, the immunoglobulin heterodimerization

domain and Fc region portion of the SCP-I are disposed between BD1 and BD2, and the immunoglobulin heterodimerization domain and Fc region portion of SCP-II are disposed between BD3 and BD4.

[0223] In certain embodiments, a polypeptide heterodimer comprises five binding domains (BD1, BD2, BD3, BD4 and BD5), wherein the binding domains bind to two to four different target molecules. In certain embodiments, SCP-I comprises three binding domains (BD1, BD2 and BD3), and SCP-II comprises two binding domains (BD4 and BD5). In further embodiments, BD1 and BD2 may be, for example, linked in tandem to each other (either directly or via a peptide linker of about two to eight amino acids) at the amino (or carboxyl) terminus of SCP-I with BD3 located at the carboxyl (or amino) terminus of SCP-I or SCP-II, wherein BD4 and BD5 are on SCP-II if BD3 is on SCP-I, or BD4 or BD5 are on SCP-I if BD3 is on SCP-II.

[0224] In still further embodiments, the polypeptide heterodimer comprises six binding domains (BD1-BD6). In certain embodiments, SCP-I and SCP-II each comprise three binding domains (e.g., BD1-BD3 on SCP-I, and BD4-BD6 on SCP-II). In such embodiments, for example, BD1 and BD2 may be linked in tandem and located at the SCP-I amino (or carboxyl) terminus, and BD3 may be located at the SCP-I carboxyl (or amino) terminus. Similarly, BD4 and BD5 may be linked in tandem and located at the SCP-II amino (or carboxyl) terminus, and BD6 may be located at the SCP-II carboxyl (or amino) terminus. In certain other embodiments, the first single chain polypeptide (SCP-I) comprises four binding domains (BD1-BD4) and the second single chain polypeptide (SCP-II) comprises two binding domains (BD5 and BD6). In such embodiments, BD1 and BD2 may be linked in tandem and located at or near amino terminus of SCP-I, BD3 and BD4 may be linked in tandem and located at or near carboxyl terminus of SCP-I, and BD5 and BD6 may be located at or near the amino and carboxyl termini of SCP-II, respectively.

[0225] In certain embodiments, the polypeptide heterodimer comprises seven binding domains (BD1-BD7). In such embodiments, SCP-I may comprise four binding domains (BD1-BD4), and SCP-II may comprise the other three binding domains (BD5-BD7). For example, BD1 and BD2 may be linked in tandem and located at or near the amino terminus of SCP-I, and BD3 and BD4 may be linked in tandem and located at or near the carboxyl terminus of SCP-I. BD5 and BD6 may be linked in tandem and located at or near the amino (or carboxyl) terminus of SCP-II, and BD7 may be located at or near the carboxyl (or amino) terminus of SCP-II.

[0226] In certain embodiments, the polypeptide heterodimer comprises eight binding domains (BD1-BD8). In such embodiments, the first and second single chain polypeptides may each comprise four binding domains. In each chain, two binding domains may be located at or near the amino terminus, and the other two binding domains located at or near the carboxyl terminus.

[0227] To simplify the description of how various components can be arranged to make first and second single chain polypeptides that form polypeptide heterodimers of the present disclosure, arrangements in exemplary embodiments (1) to (50) are provided below in which only two binding domains are included in each heterodimer.

[0228] In embodiment (1), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino terminus to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge, and an Fc region portion; and a second single chain polypeptide comprising a second binding domain, a CL region (e.g., Cκ, Cλ), a hinge, and an Fc region portion.

[0229] In embodiment (2), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino terminus to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, and a CH1 region; and a second single chain polypeptide comprising a second binding domain, a hinge, an Fc region portion, and a CL region.

[0230] In embodiment (3), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino terminus to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge, an Fc region portion, and a second CH1 region; and a second single chain polypeptide comprising a second binding domain, a CL region, a hinge, an Fc region portion, and a second CL region.

[0231] In embodiment (4), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino terminus to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a second CH1 region, a hinge, and an Fc region portion; and a second single chain polypeptide comprising a second binding domain, a CL region, a second CL region, a hinge and an Fc region portion.

[0232] In embodiment (5), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino terminus to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, a CH1 region, and a second CH1 region; and a second single chain polypeptide comprising a second binding domain, a hinge, an Fc region portion, a CL region and a second CL region.

[0256] In embodiment (29), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino terminus to carboxyl terminus, a first single chain polypeptide comprising a CH1 region, a CL region, a hinge, an Fc region portion, a second hinge, and a first binding domain; and a second single chain polypeptide comprising a CL region, a CH1 region, a hinge, an Fc region portion, a second hinge, and a second binding domain.

[0257] In embodiment (30), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino terminus to carboxyl terminus, a first single chain polypeptide comprising a CL region, a CH1 region, a hinge, an Fc region portion, a second hinge, and a first binding domain; and a second single chain polypeptide comprising a CH1 region, a CL region, a hinge, an Fc region portion, a second hinge, and a second binding domain.

[0258] In embodiment (31), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino terminus to carboxyl terminus, a first single chain polypeptide comprising a hinge, an Fc region portion, a CH1 region, a CL region, a second hinge, and a first binding domain; and a second single chain polypeptide comprising a hinge, an Fc region portion, a CL region, a CH1 region, a second hinge, and a second binding domain.

[0259] In embodiment (32), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino terminus to carboxyl terminus, a first single chain polypeptide comprising a hinge, an Fc region portion, a CL region, a CH1 region, a second hinge, and a first binding domain; and a second single chain polypeptide comprising a hinge, an Fc region portion, a CH1 region, a CL region, a second hinge, and a second binding domain.

[0260] In embodiment (33), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge, an Fc region portion, a second hinge, and a second binding domain; and a second single chain polypeptide comprising a CL region, a hinge, and an Fc region.

[0261] In embodiment (34), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CL region, a hinge, an Fc region portion, a second hinge, and a second binding domain; and a second single chain polypeptide comprising a CH1 region, a hinge and an Fc region portion.

[0262] In embodiment (35), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge and an Fc region portion; and a second single chain polypeptide comprising a CL region, a hinge, an Fc region portion, a second hinge and a second binding domain.

[0263] In embodiment (36), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a CH1 region, a hinge, an Fc region portion, a second hinge and a first binding domain; and a second single chain polypeptide comprising a second binding domain, a CL region, a hinge and an Fc region portion.

[0264] In embodiment (37), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge, an Fc region portion, and a second hinge; and a second single chain polypeptide comprising a second binding domain, a CL region, a hinge, an Fc region portion, and a second hinge.

[0265] In embodiment (38), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, a CH1 region, a second hinge, and a second binding domain; and the second single chain polypeptide comprising a hinge, an Fc region portion, and a CL region.

[0266] In embodiment (39), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a hinge, an Fc region portion, and a CH1 region; and a second single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, a CL region, a second hinge, and a second binding domain.

[0267] In embodiment (40), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to

carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, and a CH1 region; and a second single chain polypeptide comprising a hinge, an Fc region portion, a CL region, a second hinge and a second binding domain.

[0268] In embodiment (41), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a hinge, an Fc region portion, a CH1 region, a second hinge and a first binding domain; and the second single chain polypeptide comprising a second binding domain, a hinge, an Fc region portion, and a CL region.

[0269] In embodiment (42), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, a CH1 region, and a second hinge; and a second single chain polypeptide comprising a second binding domain, a hinge, an Fc region portion, a CL region and a second hinge.

[0270] In embodiment (43), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge an Fc region portion, a CL region, a second hinge and a second binding domain; and the second single chain polypeptide comprising a CL region, a hinge, an Fc region portion and a CH1 region.

[0271] In embodiment (44), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a CH1 region, a hinge, an Fc region portion, and a CL region; and a second single chain polypeptide comprising a first binding domain, a CL region, a hinge, an Fc region, a CH1 region, a second hinge and a second binding domain.

[0272] In embodiment (45), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge, an Fc region portion, and a CL region; and a second single chain polypeptide comprising a CL region, a hinge, an Fc region portion, a CH1 region, a second hinge, and a second binding domain.

[0273] In embodiment (46), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a CH1 region, a hinge, an Fc region portion, a CL, a second hinge and a first binding domain; and a second single chain polypeptide comprising a second binding domain, a CL region, a hinge, an Fc region portion, and a CH1 region.

[0274] In embodiment (47), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge, an Fc region portion, a second CH1 region, a second hinge, and a second binding domain; and a second single chain polypeptide comprising a CL region, a hinge, an Fc region portion, and a second CL region.

[0275] In embodiment (48), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a CH1 region, a hinge, an Fc region portion, and a second CH1 region; and a second single chain polypeptide comprising a first binding domain, a CL region, a hinge, an Fc region portion, a second CL region, a second hinge, and a second binding domain.

[0276] In embodiment (49), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge, an Fc region portion, and a second CH1 region; and a second single chain polypeptide comprising a CL region, a hinge, an Fc region portion, a second CL region, a second hinge and a second binding domain.

[0277] In embodiment (50), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a CH1 region, a hinge, an Fc region portion, a CH1 region, a second hinge, and a first binding domain; and a second single chain polypeptide comprising a second binding domain, a CL region, a hinge, an Fc region portion, and a second CL region.

[0278] Exemplary embodiments (51) to (60) are also provided below in which three or four binding domains are included in each heterodimer. Additional binding domains may be included to make polypeptide heterodimers that comprise five to eight binding domains according to the present disclosure in view of the general description provided herein.

[0279] In embodiment (51), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge, an Fc region portion, a second hinge and a second binding domain; and a second single chain polypeptide comprising a third binding domain, a CL region, a hinge and an Fc region portion.

[0280] In embodiment (52), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CH1 region, a hinge, an Fc region portion, a second hinge, and a second binding domain; and a second single chain polypeptide comprising a CL region, a hinge, an Fc region portion, a second hinge and a third binding domain.

[0281] In embodiment (53), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CL region, a hinge, an Fc region portion, a second hinge and a second binding domain; and the second single chain polypeptide comprising a third binding domain, a CH1 region, a hinge and an Fc region portion.

[0282] In embodiment (54), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a CL region, a hinge, an Fc region portion, a second hinge and a second binding domain; and a second single chain polypeptide comprising a CH1 region, a hinge, an Fc region portion, a second hinge and a third binding domain.

[0283] In embodiment (55), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, a CH1 region, a second hinge and a second binding domain; and the second single chain polypeptide comprising a third binding domain, a hinge, an Fc region portion and a CL region.

[0284] In embodiment (56), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, a CH1 region, a second hinge, and a second binding domain; and a second single chain polypeptide comprising a hinge, an Fc region portion, a CL region, a second hinge, and a third binding domain.

[0285] In embodiment (57), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, a CL region, a second hinge, and a second binding domain; and a second single chain polypeptide comprising a third binding domain, a hinge, an Fc region portion and a CH1 region.

[0286] In embodiment (58), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, a CL region, a second hinge, and a second binding domain; and a second single chain polypeptide comprising a hinge, an Fc region portion, a CH1 region, a second hinge, and a third binding domain.

[0287] In embodiment (59), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus: a first binding domain, a CH1 region, a hinge, an Fc region portion, a second hinge, and a second binding domain; and a second single chain polypeptide comprising a third binding domain, a CL region, a hinge, an Fc region portion, a second hinge and a fourth binding domain.

[0288] In embodiment (60), a polypeptide heterodimer comprises the following two single chain polypeptides: from amino to carboxyl terminus, a first single chain polypeptide comprising a first binding domain, a hinge, an Fc region portion, a CH1 region, a second hinge and a second binding domain; and a second single chain polypeptide comprising a third binding domain, a hinge, an Fc region portion, a CL region, a second hinge and a fourth binding domain.

[0289] In embodiments (1) to (32), a polypeptide heterodimer of the present disclosure comprises the following two single chain polypeptides: a first single chain polypeptide comprising a first binding domain (BD1) that specifically binds to a T cell target (*e.g.*, a TCR complex or a component thereof, including TCR α , TCR β , CD3 γ , CD3 δ , and CD3 ϵ), a hinge that is an SCC-P IgG1 hinge, an Fc region portion that is a wild type or altered human IgG1 CH2CH3, and a CL region that is wild type or an altered human Ck region with N30Y V55A T70E (YAE) substitutions; and a second single chain polypeptide comprising binding domain (BD2) that specifically binds to a B-cell target (*e.g.*, CD19, CD79b, HLA-DR, CD37, CD20) or a tumor or cancer antigen (*e.g.*, RON, c-Met, EpCAM, CEACAM-6, PSMA), a hinge that is also an SCC-P IgG1 hinge, an Fc region portion that is a wild type or altered human

IgG1 CH2CH3, and a CH1 region that is human CH1 region.

[0290] In further embodiments, a polypeptide heterodimer of embodiments (1) to (32) may further comprise a third binding domain (BD3) that is identical to BD1 or BD2, and is linked to a single chain polypeptide via a second hinge (e.g., linker H75 or H68 as set forth in SEQ ID NOS:742 and 78, respectively). In still further embodiments, a polypeptide heterodimer of embodiments (1) to (32) may further comprise third and fourth binding domains (BD3) and (BD4) that each are identical or different to BD1 or BD2 and linked to the single chain polypeptide(s) via a second hinge (e.g., linker H75 or H68 as set forth in SEQ ID NOS:742 and 78).

[0291] In certain embodiments, the polypeptide heterodimers of the present disclosure can be engineered to have binding domains with different affinities to target specific cell types. For example, it may be desirable for a polypeptide heterodimer with a binding domain for a TCR complex or a component thereof and another binding domain for a tumor antigen (or a B-cell target) to preferentially bind tumor cells having the tumor antigen (or B-cells carrying the B-cell target) with a higher affinity so that the polypeptide heterodimer will bind the tumor cells (or the B-cells) first and then recruit T cells via its TCR/CD3 binding domain to the tumor site or cells. Differential binding affinities may be achieved by, for example, choosing a binding domain for one target with a higher binding affinity than the other binding domain has for its target or by including multiple binding domains for one target on a polypeptide heterodimer and a single binding domain or fewer binding domains for the second or other targets. In addition, using different hinges (e.g., using hinges of different lengths) may affect binding of one domain more than another or using different hinges for different binding domains in order to alter the binding activity of the binding domains.

[0292] In certain embodiments, multiple binding domains may need to be located at an appropriate distance from each other so that their interactions with their targets will produce a desirable effect. For example, in certain embodiments, a polypeptide heterodimer comprising a binding domain for a TCR complex or a component thereof in a single chain polypeptide and another binding domain for a tumor antigen or a B-cell target in a second single chain polypeptide may have both binding domains at the amino or carboxyl termini of their corresponding chains so that they are in physical proximity to each other in the polypeptide heterodimer.

[0293] Exemplary heterodimers may be formed from single chain polypeptide pairs described herein. If sequence identification numbers noted herein contain signal peptide sequences (e.g., the first 20 amino acids), such signal peptide sequences are not part of the mature single chain polypeptides that form the exemplary polypeptide heterodimers and thus should be considered excluded.

[0294] Exemplary single chain polypeptides are set forth in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29-32, 53-72, 74, 810-826, 859-864, and 874-882.

[0295] Exemplary heterodimers may be formed from the following single chain polypeptide pairs: SEQ ID NOS:2 and 4, SEQ ID NOS:6 and 8, SEQ ID NOS:10 and 12, SEQ ID NOS:14 and 16, SEQ ID NOS:18 and 20, SEQ ID NOS:20 and 22, SEQ ID NOS:20 and 24, SEQ ID NOS:30 and 32, SEQ ID NOS:29 and 31, SEQ ID NOS:29 and 32, SEQ ID NOS:30 and 72, SEQ ID NOS:53 and 72, SEQ ID NOS:54 and 72, SEQ ID NOS:55 and 72, SEQ ID NOS:70 and 72, SEQ ID NOS:71 and 72, SEQ ID NOS:63 and 56, SEQ ID NOS:64 and 57, SEQ ID NOS:65 and 60, SEQ ID NOS:66 and 58, SEQ ID NOS:67 and 59, SEQ ID NOS:68 and 61, SEQ ID NOS:69 and 62, SEQ ID NOS:54 and 811, SEQ ID NOS:54 and 812, SEQ ID NOS:54 and 813, SEQ ID NOS:814 and 818, SEQ ID NOS:815 and 818, SEQ ID NOS:816 and 818, SEQ ID NOS:817 and 818, SEQ ID NOS:814 and 820, SEQ ID NOS:814 and 821, SEQ ID NOS:54 and 819, SEQ ID NOS:814 and 826, SEQ ID NOS:814 and 822, SEQ ID NOS:814 and 823, SEQ ID NOS:814 and 824, SEQ ID NOS:859 and 862, SEQ ID NOS:860 and 863, SEQ ID NOS:861 and 864, SEQ ID NOS:874 and 825, SEQ ID NOS:875 and 879, SEQ ID NOS:876 and 880, SEQ ID NOS:877 and 881, or SEQ ID NOS:878 and 882.

Nucleic Acids, Vectors, Host Cells, and Methods for Making Heterodimers

[0296] In a related aspect, the present disclosure also provides isolated nucleic acid (used interchangeably with "polynucleotide") molecules that encode single chain polypeptides provided herein. Exemplary nucleic acid molecules (either with or without a nucleotide sequence encoding a signal peptide sequence) are set forth in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25-28, 33-52 and 792-808.

[0297] The present disclosure also provides vectors that comprise nucleic acid sequence encoding single chain polypeptides provided herein. As used herein, "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. Exemplary vectors include plasmids, yeast artificial chromosomes, and viral genomes. Certain vectors can

autonomously replicate in a host cell, while other vectors can be integrated into the genome of a host cell and thereby are replicated with the host genome.

[0298] In certain embodiments, the vectors may be recombinant expression vectors. "Recombinant expression vectors" or "expression vectors" refer to vectors that contain nucleic acid sequences that are operatively linked to an expression control sequence (e.g., a promoter) and are thus capable of directing the expression of those sequences.

[0299] Promoter sequences useful in expression vectors provided herein can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. In certain embodiments, the promoters are inducible promoters.

[0300] In certain embodiments, a vector is an expression vector that comprises a nucleic acid sequence encoding a first single chain polypeptide of a polypeptide heterodimer provided herein. In certain other embodiments, a vector is an expression vector that comprises a nucleic acid sequence encoding a second single chain polypeptide of a polypeptide heterodimer provided herein.

[0301] In certain embodiments, a vector is an expression vector that comprises nucleic acid sequences encoding both first and second single chain polypeptides of a polypeptide heterodimer. The promoter for the nucleic acid sequence encoding the first single chain polypeptide may be the same as the promoter for the nucleic acid encoding the second single chain polypeptide. Alternatively, the promoter for the nucleic acid sequence encoding the first single chain polypeptide may be different from the promoter for the nucleic acid encoding the second single chain polypeptide so that the expression level of the first and second single chain polypeptides may be differentially modulated to maximum heterodimerization of the first and second single chain polypeptides. In certain embodiments, one or both the promoters for the nucleic acid encoding the first and second single chain polypeptides are inducible promoters.

[0302] The present disclosure also provides a host cell transformed or transfected with, or otherwise containing, any of the nucleic acids or vectors provided herein. Exemplary host cells include VERO cells, HeLa cells, Chinese hamster ovary (CHO) cell lines (including modified CHO cells capable of modifying the glycosylation pattern of expressed multivalent binding molecules, see US Patent Application Publication No. 2003/0115614), COS cells (such as COS-7), W138, BHK, HepG2, 3T3, RIN, MDCK, A549, PC 12, K562, HEK293 cells, HepG2 cells, N cells, 3T3 cells, *Spodoptera frugiperda* cells (e.g., Sf9 cells), *Saccharomyces cerevisiae* cells, *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or members of the *Streptomyces* family.

[0303] In certain embodiments, a host cell comprises a first expression vector containing a nucleic acid encoding a first single chain polypeptide and a second expression vector containing a nucleic acid encoding a second single chain polypeptide.

[0304] In certain other embodiments, a host cell comprises an expression vector containing a nucleic acid encoding both first and second single chain polypeptides.

[0305] The disclosure also includes a method of producing polypeptide heterodimers described herein. In certain embodiments, the method comprises culturing a host cell that comprises nucleic acids encoding both the first and second single chain polypeptides under conditions suitable to express the polypeptides, and optionally isolating or purifying the heterodimers formed from the first and second single chain polypeptides from the culture. The nucleic acid encoding the first single chain polypeptide and the nucleic acid encoding the second single chain polypeptide may be present in a single expression vector in the host cell or in two different expression vectors in the host cells. In the latter case, the ratio between the two expression vectors may be controlled to maximize heterodimerization of the first and second single chain polypeptides.

[0306] The present disclosure provides purified polypeptide heterodimers as described herein. The term "purified," as used herein, refers to a composition, isolatable from other components, wherein the polypeptide heterodimer is enriched to any degree relative to its naturally obtainable state. In certain embodiments, the present disclosure provides substantially purified polypeptide heterodimers as described herein. "Substantially purified" refers to a polypeptide heterodimer composition in which the polypeptide heterodimer forms the major component of the composition, such as constituting at least about 50%, such as at least about 60%, about 70%, about 80%, about 90%, about 95%, about 99%, of the polypeptides, by weight, in the composition.

[0307] Protein purification techniques are well known to those of skill in the art. These techniques involve, at one level, the crude fractionation of the polypeptide and non-polypeptide fractions. Further purification using chromatographic and electrophoretic techniques to achieve partial or complete purification (or purification to homogeneity) is frequently desired. Analytical methods particularly suited to the preparation of a pure fusion protein are ion-exchange chromatography, size exclusion chromatography;

polyacrylamide gel electrophoresis; and isoelectric focusing. Particularly efficient methods of purifying peptides are fast protein liquid chromatography and HPLC.

[0308] Various methods for quantifying the degree of purification are known to those of skill in the art in light of the present disclosure. These include, for example, assessing the amount of polypeptide heterodimers in a fraction by SDS/PAGE analysis and HPLC as illustrated in the examples provided herein.

[0309] The method for making polypeptide heterodimers provided herein is advantageous over a method for first expressing and purifying separately individual single chain polypeptides and then incubating purified individual single chain polypeptides together to form polypeptide heterodimers. For example, certain single chain polypeptides (*e.g.*, certain polypeptides containing only CH1 regions as their immunoglobulin heterodimerization domains) are unstable when expressed alone. In addition, separate expression and purification of individual single chain polypeptides followed by combining the purified individual single chain polypeptides involve more steps than coexpressing both single chain polypeptides followed by purifying resulting polypeptide heterodimers and generally less efficient.

Compositions and Methods for Using Heterodimers

[0310] In addition to polypeptide heterodimers, the present disclosure also provides pharmaceutical compositions and unit dose forms that comprise the polypeptide heterodimers as well as methods for using the polypeptide heterodimers, the pharmaceutical compositions and unit dose forms.

[0311] Compositions of polypeptide heterodimers of this disclosure generally comprise a polypeptide heterodimer provided herein in combination with a pharmaceutically acceptable excipient, including pharmaceutically acceptable carriers and diluents. Pharmaceutical acceptable excipients will be nontoxic to recipients at the dosages and concentrations employed. They are well known in the pharmaceutical art and described, for example, in Rowe et al., *Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety*, 5th Ed., 2006.

[0312] Pharmaceutically acceptable carriers for therapeutic use are also well known in the pharmaceutical art, and are described, for example, in Remington's *Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro (Ed.) 1985). Exemplary pharmaceutically acceptable carriers include sterile saline and phosphate buffered saline at physiological pH. Preservatives, stabilizers, dyes and the like may be provided in the pharmaceutical composition. In addition, antioxidants and suspending agents may also be used.

[0313] Pharmaceutical compositions may also contain diluents such as buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates (*e.g.*, glucose, sucrose, dextrins), chelating agents (*e.g.*, EDTA), glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary diluents. For instance, the product may be formulated as a lyophilizate using appropriate excipient solutions (*e.g.*, sucrose) as diluents.

[0314] The present disclosure also provides a method for treating a disease or disorder associated with, for example, excessive receptor-mediated signal transduction, comprising administering to a patient in need thereof an effective amount of a polypeptide heterodimer comprising a binding domain that specifically binds a receptor, such as a receptor tyrosine kinase, including EGFR, EGFRvIII, ErbB2, ErbB3, ErbB4, IGF1R, c-Met, RON, and EphA2.

[0315] Exemplary diseases or disorders associated with excess receptor-mediated signal transduction include cancer (*e.g.*, solid malignancy and hematologic malignancy), autoimmune or inflammatory diseases or conditions, sepsis resulting from bacterial infection, and viral infection.

[0316] In one aspect, the present disclosure provides a method for directing T cell activation, comprising administering to a patient in need thereof an effective amount of a polypeptide heterodimer that comprises a binding domain that specifically binds TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ or a combination thereof, and a second binding domain that specifically binds a different target, for instance, a tumor-specific antigen or other antigen of choice at a site or cell where T cell activation is desired.

[0317] In another aspect, the present disclosure provides a method for inhibiting growth, metastasis or metastatic growth of a malignancy (*e.g.*, a solid malignancy or a hematologic malignancy), comprising administering to a patient in need thereof an effective amount of a polypeptide heterodimer provided herein or a composition thereof.

[0318] A wide variety of cancers, including solid malignancy and hematologic malignancy, are amenable to the compositions and methods disclosed herein. Types of cancer that may be treated include, but are not limited to: adenocarcinoma of the breast, prostate, pancreas, colon and rectum; all forms of bronchogenic carcinoma of the lung (including squamous cell carcinoma, adenocarcinoma, small cell lung cancer and non-small cell lung cancer); myeloid; melanoma; hepatoma; neuroblastoma; papilloma; apudoma; choristoma; branchioma; malignant carcinoid syndrome; carcinoid heart disease; and carcinoma (*e.g.*, Walker, basal cell, basosquamous, Brown-Pearce, ductal, Ehrlich tumor, Krebs 2, merkel cell, mucinous, non-small cell lung, oat cell, papillary, scirrhous, bronchiolar, bronchogenic, squamous cell, and transitional cell). Additional types of cancers that may be treated include: histiocytic disorders; leukemia; histiocytosis malignant; Hodgkin's disease; immunoproliferative small; non-Hodgkin's lymphoma; plasmacytoma; reticuloendotheliosis; melanoma; chondroblastoma; chondroma; chondrosarcoma; fibroma; fibrosarcoma; giant cell tumors; histiocytoma; lipoma; liposarcoma; mesothelioma; myxoma; myxosarcoma; osteoma; osteosarcoma; chordoma; craniopharyngioma; dysgerminoma; hamartoma; mesenchymoma; mesonephroma; myosarcoma; ameloblastoma; cementoma; odontoma; teratoma; thymoma; trophoblastic tumor. Further, the following types of cancers are also contemplated as amenable to treatment: adenoma; cholangioma; cholesteatoma; cylindroma; cystadenocarcinoma; cystadenoma; granulosa cell tumor; gynandroblastoma; hepatoma; hidradenoma; islet cell tumor; Leydig cell tumor; papilloma; sertoli cell tumor; theca cell tumor; leiomyoma; leiomyosarcoma; myoblastoma; myomma; myosarcoma; rhabdomyoma; rhabdomyosarcoma; ependymoma; ganglioneuroma; glioma; medulloblastoma; meningioma; neurilemmoma; neuroblastoma; neuroepithelioma; neurofibroma; neuroma; paraganglioma; paraganglioma nonchromaffin; and glioblastoma multiforme. The types of cancers that may be treated also include, but are not limited to, angiokeratoma; angiolymphoid hyperplasia with eosinophilia; angioma sclerosing; angiomatosis; glomangioma; hemangioendothelioma; hemangioma; hemangiopericytoma; hemangiosarcoma; lymphangioma; lymphangiomyoma; lymphangiosarcoma; pinealoma; carcinosarcoma; chondrosarcoma; cystosarcoma phyllodes; fibrosarcoma; hemangiosarcoma; leiomyosarcoma; leukosarcoma; liposarcoma; lymphangiosarcoma; myosarcoma; myxosarcoma; ovarian carcinoma; rhabdomyosarcoma; sarcoma; neoplasms; neurofibromatosis; and cervical dysplasia.

[0319] Additional exemplary cancers that are also amenable to the compositions and methods disclosed herein are B-cell cancers, including B-cell lymphomas [such as various forms of Hodgkin's disease, non-Hodgkins lymphoma (NHL) or central nervous system lymphomas], leukemias [such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), Hairy cell leukemia and chronic myoblastic leukemia] and myelomas (such as multiple myeloma). Additional B cell cancers include small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, solitary plasmacytoma of bone, extraosseous plasmacytoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated (MALT) lymphoid tissue, nodal marginal zone B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, B-cell proliferations of uncertain malignant potential, lymphomatoid granulomatosis, and post-transplant lymphoproliferative disorder.

[0320] In certain embodiments, polypeptide heterodimers useful for inhibiting growth of a solid malignancy or metastasis or metastatic growth of a solid malignancy or a hematologic malignancy include those that specifically bind to a tumor or cancer antigen and a T cell target. Such heterodimers are typically designed to have a higher binding affinity to the tumor or cancer antigen (*e.g.*, at least about 5, 10, 15, 20, 25, 50, 75 or 100 folds higher) than to the T cell target so that they preferentially bind to the tumor or cancer antigen first and subsequently bind to the T cell target, which in turn recruit and activate T cells to damage or destroy the tumor or cancer cells carrying the tumor or cancer antigen on their surface. Exemplary tumor or cancer antigens and T cell targets include those provided above in the section describing binding domains of polypeptide heterodimers. For instance, a T cell target can be CD3 or PSMA.

[0321] In certain embodiments, polypeptide heterodimers useful for inhibiting growth, metastasis, or metastatic growth of a malignancy, or by directed T cell activation, comprise at least one binding domain that specifically binds an oncology target (including a tumor or cell antigen, such as RON, c-Met, CEACAM-6, or PSMA) and another binding domain that specifically binds a TCR complex or a component thereof (*e.g.*, TCR α , TCR, CD3 γ , CD3 δ , and CD3 ϵ).

[0322] In certain other embodiments, polypeptide heterodimers useful for inhibiting growth, metastasis, or metastatic growth of a malignancy comprise at least one binding domain that specifically binds CD28 and another binding domain that specifically binds CD79b. Such polypeptide heterodimers may further comprise a binding domain that comprises a PDL2 ectodomain, a binding domain that specifically binds hyperIL-6, or both binding domains.

[0323] In certain other embodiments, polypeptide heterodimers useful for inhibiting growth, metastasis, or metastatic growth of a malignancy comprise at least one binding domain that specifically binds RON and another binding domain that specifically binds c-Met.

[0324] In certain other embodiments, polypeptide heterodimers useful for inhibiting growth, metastasis, or metastatic growth of a malignancy comprise binding domains that specifically bind one or more of the following receptor tyrosine kinases: c-Met, RON, EGFR, EGFRvIII, Her2, ErbB3, ErbB4, and IGF1R, EphA2. In certain embodiments, the heterodimers may further comprise one or more binding domains that specifically bind to one or more of the following antiangiogenic agents: PDGFR, VEGFR1-4, and angiopoietin 2. In certain embodiments, the above heterodimers may further comprise one or more binding domains that specifically bind to one or more of the following Fc receptors to increase targeting of cytotoxic effector function: CD64, CD32A and CD16. In certain embodiments, the above heterodimers may further comprise a binding domain that specifically binds the transferrin receptor (CD71) to enable degradation of the receptors.

[0325] In certain other embodiments, polypeptide heterodimers useful for inhibiting growth, metastasis, or metastatic growth of a malignancy comprise binding domains that are agonists of two or more of the following TNFSFRs: TNFR1, TNFR2, DR4, DR5, TWEAKR, and FAS.

[0326] In certain other embodiments, polypeptide heterodimers useful for inhibiting growth, metastasis, or metastatic growth of a malignancy comprise binding domains that specifically bind two or more of the following pro-oncogenic cytokines or growth factors: HGF, MSP, EGF (including epiregulin, herregulin, β -regulin, neuregulin), HIF-1 α , VEGFA, VEGFB, VEGFC, VEGFD, TNF α , IL-6, hyperIL-6, IL-8, Wnt, SHH, TGF β , or PDGF.

[0327] In certain embodiments, polypeptide heterodimers useful for inhibiting growth of a solid malignancy or metastasis or metastatic growth of a solid malignancy include those that specifically bind to, for example, EGFR, ErbB3, ErbB4, c-Met, RON, EphA2, IGF1R, VEGFR1, VEGFR2, VEGFR3, CD44v6, CD151, EpCAM, CEACAM6, TGFBR2, , GHRHR, GHR, IL-6R, gp130, TNFR2, PD1, TWEAK-R, OSMR β , Patched-1, Frizzled, or Robol.

[0328] Polypeptide heterodimers useful for inhibiting metastasis or metastatic growth of a hematologic malignancy include those that specifically bind to, for example, EGFR, ErbB3, c-Met, RON, EphA2, IGF1R, TGFBR2, IL-6R, gp130, TNFR2, PD1, OSMR β , LT β R, CD19, CD80, CD81, or CD86.

[0329] In another aspect, the present disclosure provides a method for treating an autoimmune or inflammatory disease, disorder or condition, comprising administering to a patient in need thereof an effective amount of a polypeptide heterodimer provided herein or a composition thereof.

[0330] Exemplary autoimmune or inflammatory diseases, disorders or conditions that may be treated by the fusion proteins and compositions and unit dose forms thereof include, and are not limited to, inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), diabetes mellitus (e.g., type I diabetes), dermatomyositis, polymyositis, pernicious anaemia, primary biliary cirrhosis, acute disseminated encephalomyelitis (ADEM), Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome (APS), autoimmune hepatitis, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, lupus nephritis, neuropsychiatric lupus, multiple sclerosis (MS), myasthenia gravis, pemphigus vulgaris, asthma, psoriatic arthritis, rheumatoid arthritis, Sjögren's syndrome, temporal arteritis (also known as "giant cell arteritis"), autoimmune hemolytic anemia, Bullous pemphigoid, vasculitis, coeliac disease, chronic obstructive pulmonary disease, endometriosis, Hidradenitis suppurativa, interstitial cystitis, morphea, scleroderma, narcolepsy, neuromyotonia, vitiligo, and autoimmune inner ear disease.

[0331] Exemplary polypeptide heterodimers useful for treating an autoimmune or inflammatory disease, disorder or condition may comprises one or more binding domain that specifically binds CD28, and one, two, or three of the following additional binding domains: a binding domain that comprises PDL2 ectodomain, a binding domain that comprises monolL-10, and a binding domain that specifically binds CD86. For example, a polypeptide heterodimer may comprise a binding domain that specifically binds CD28 and one to three binding domains that specifically bind CD86.

[0332] Additional exemplary polypeptide heterodimers useful for treating an autoimmune or inflammatory disease, disorder or condition may comprise one or more binding domains that specifically bind CD28 and one or more binding domains that are an IL-10 agonist (e.g., monolL-10), an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist. Alternatively, polypeptide heterodimers may comprise two or more binding domains selected from an IL-10 agonist (e.g., monolL-10), an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist.

[0333] Additional exemplary polypeptide heterodimers useful for treating an autoimmune or inflammatory disease, disorder or

condition may comprise one or more binding domains that specifically bind CD32B and one or more binding domains that are an IL-10 agonist (e.g., monolL-10), an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist.

[0334] Additional exemplary polypeptide heterodimers useful for treating an autoimmune or inflammatory disease, disorder or condition may comprise binding domains that specifically bind one or more of the following TNFSFRs: TNFR1, TNFR2, HVEV, LT β R, TWEAKR, TACI, BAFF-R, BCMA, or FAS.

[0335] Additional exemplary polypeptide heterodimers useful for treating an autoimmune or inflammatory disease, disorder or condition may comprise binding domains that specifically bind two or more of the following pro-inflammatory cytokines/chemokines, such as TNF α , IL-6, IL-2, IL-1, IL-8, IP-10, IFN γ , IFN α , RANKL, FASL, TGF β , IL7, IL10, IL17A/F, TWEAK, CSF2, IGF1, IGF2 or BLyS/APRIL.

[0336] Polypeptide heterodimers useful for treating an autoimmune or inflammatory disease, disorder or condition include those that specifically bind to, for example, TGFBR2, IL-6R, gp130, TNFR1, TNFR2, PD1, HVEM, OX40, CD40, CD137, TWEAK-R, LT β R, LIFER β , OSMR β , CD3, TCR α , TCR β CD19, CD28, CD80, CD81, CD86, TLR7, TLR9, or any combination thereof.

[0337] In another aspect, the present disclosure provides a method for treating a B-cell associated disorder or disease that comprises administering to a patient in need thereof (e.g., a patient having or suspected of having a B-cell associated disorder or disease) an effective amount of a polypeptide heterodimer provided herein, such as those that specifically bind a B cell target.

[0338] Polypeptide heterodimers useful in treating a B-cell associated disorder or disease may comprise binding domains that specifically bind one or more B-cell targets, such as CD79b, CD19, HLA-DR, CD20, CD21, CD22, CD30, CD33, CD37, CD38, or CD70. The polypeptide heterodimers may further comprise a binding domain that specifically binds a T-cell target, such as a TCR complex or a component thereof, including TCR α , TCR β , CD3 γ , CD3 δ , or CD3 ϵ .

[0339] Polypeptide heterodimers useful in treating a B-cell associated disorder or disease may comprise a binding domain that specifically bind a B-cell target, such as CD79b, CD19, HLA-DR, CD20, CD21, CD22, CD30, CD33, CD37, CD38, and CD70, and a binding domain that specifically binds CD64, CD32A, or CD16 to increase targeting of cytotoxic effector function.

[0340] The polypeptide heterodimers or compositions thereof of the present disclosure may be administered orally, topically, transdermally, parenterally, by inhalation spray, vaginally, rectally, or by intracranial injection, or any combination thereof. In one embodiment, the polypeptide heterodimers or compositions thereof are administered parenterally. The term "parenteral," as used herein, includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or infusion techniques. Administration by intravenous, intradermal, intramuscular, intramammary, intraperitoneal, intrathecal, retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site is contemplated as well. For instance, the invention includes administering polypeptide heterodimers or compositions thereof by intravenous injection.

[0341] The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of subject being treated, the physical characteristics of the specific subject under consideration for treatment, concurrent medication, and other factors that those skilled in the medical arts will recognize. For example, an amount between 0.01 mg/kg and 1000 mg/kg (e.g., about 0.1 to 1 mg/kg, about 1 to 10 mg/kg, about 10-50 mg/kg, about 50-100 mg/kg, about 100-500 mg/kg, or about 500-1000 mg/kg) body weight (which can be administered as a single dose, daily, weekly, monthly, or at any appropriate interval) of active ingredient may be administered depending on the potency of a polypeptide heterodimer of this disclosure.

[0342] Also contemplated is the administration of polypeptide heterodimers or compositions thereof in combination with a second agent. A second agent may be one accepted in the art as a standard treatment for a particular disease state or disorder, such as in cancer, inflammation, autoimmunity, and infection. Exemplary second agents contemplated include polypeptide heterodimers that bind to targets different from those that primary polypeptide heterodimers bind, polyclonal antibodies, monoclonal antibodies, immunoglobulin-derived fusion proteins, chemotherapeutics, ionizing radiation, steroids, NSAIDs, anti-infective agents, or other active and ancillary agents, or any combination thereof.

[0343] In certain embodiments, a polypeptide heterodimer and a second agent act synergistically. In other words, these two compounds interact such that the combined effect of the compounds is greater than the sum of the individual effects of each compound when administered alone (see, e.g., Berenbaum, Pharmacol. Rev. 41:93, 1989).

[0344] In certain other embodiments, a polypeptide heterodimer and a second agent act additively. In other words, these two compounds interact such that the combined effect of the compounds is the same as the sum of the individual effects of each

compound when administered alone.

[0345] Second agents useful in combination with polypeptide heterodimers or compositions thereof provided herein may be steroids, NSAIDs, mTOR inhibitors (e.g., rapamycin (sirolimus), temsirolimus, deforolimus, everolimus, zotarolimus, curcumin, farnesylthiosalicylic acid), calcineurin inhibitors (e.g., cyclosporine, tacrolimus), antimetabolites (e.g., mycophenolic acid, mycophenolate mofetil), polyclonal antibodies (e.g., anti-thymocyte globulin), monoclonal antibodies (e.g., daclizumab, basiliximab), and CTLA4-Ig fusion proteins (e.g., abatacept or belatacept).

[0346] Second agents useful for inhibiting growth of a solid malignancy, inhibiting metastasis or metastatic growth of a solid malignancy, or treating or ameliorating a hematologic malignancy include chemotherapeutic agents, ionizing radiation, and other anti-cancer drugs. Examples of chemotherapeutic agents contemplated as further therapeutic agents include alkylating agents, such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, ifosfamide, melphalan, and chlorambucil); bifunctional chemotherapeutics (e.g., bendamustine); nitrosoureas (e.g., carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU)); ethyleneimines and methyl-melamines (e.g., triethylenemelamine (TEM), triethylene thiophosphoramide (thiotepa), and hexamethylmelamine (HMM, altretamine)); alkyl sulfonates (e.g., buslfan); and triazines (e.g., dacabazine (DTIC)); antimetabolites, such as folic acid analogues (e.g., methotrexate, trimetrexate, and pemetrexed (multi-targeted antifolate)); pyrimidine analogues (such as 5-fluorouracil (5-FU), fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, and 2,2'-difluorodeoxycytidine); and purine analogues (e.g., 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine phosphate, 2-chlorodeoxyadenosine (cladribine, 2-CdA)); Type I topoisomerase inhibitors such as camptothecin (CPT), topotecan, and irinotecan; natural products, such as epipodophylotoxins (e.g., etoposide and teniposide); and vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine); anti-tumor antibiotics such as actinomycin D, doxorubicin, and bleomycin; radiosensitizers such as 5-bromodeoxyuridine, 5-iododeoxyuridine, and bromodeoxycytidine; platinum coordination complexes such as cisplatin, carboplatin, and oxaliplatin; substituted ureas, such as hydroxyurea; and methylhydrazine derivatives such as N-methylhydrazine (MIH) and procabazine.

[0347] In certain embodiments, second agents useful for inhibiting growth metastasis or metastatic growth of a malignancy include polypeptide heterodimers according to the present disclosure that bind to cancer cell targets other than the target that the first polypeptide heterodimer binds. In certain other embodiments, second agents useful for such treatments include polyclonal antibodies, monoclonal antibodies, and immunoglobulin-derived fusion proteins that bind to cancer cell targets. Exemplary cancer cell targets are provided above in the context of describing targets of polypeptide heterodimers useful for the above-noted treatment.

[0348] Further therapeutic agents contemplated by this disclosure for treatment of autoimmune diseases are referred to as immunosuppressive agents, which act to suppress or mask the immune system of the individual being treated. Immunosuppressive agents include, for example, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) for the treatment of arthritis, or biologic response modifiers. Compositions in the DMARD description are also useful in the treatment of many other autoimmune diseases aside from rheumatoid arthritis.

[0349] Exemplary NSAIDs are chosen from the group consisting of ibuprofen, naproxen, naproxen sodium, Cox-2 inhibitors such as Vioxx and Celebrex, and sialylates. Exemplary analgesics are chosen from the group consisting of acetaminophen, oxycodone, tramadol or propoxyphene hydrochloride. Exemplary glucocorticoids are chosen from the group consisting of cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, or prednisone. Exemplary biological response modifiers include molecules directed against cell surface markers (e.g., CD4, CD5, etc.), cytokine inhibitors, such as the TNF antagonists (e.g. etanercept (Enbrel), adalimumab (Humira) and infliximab (Remicade)), chemokine inhibitors and adhesion molecule inhibitors. The biological response modifiers include monoclonal antibodies as well as recombinant forms of molecules. Exemplary DMARDs include azathioprine, cyclophosphamide, cyclosporine, methotrexate, penicillamine, leflunomide, sulfasalazine, hydroxychloroquine, Gold (oral (auranofin) and intramuscular) and minocycline.

[0350] Additional second agents useful for treating an autoimmune or inflammatory disease, disorder or condition may be a polyclonal or monoclonal antibody, an immunoglobulin-derived fusion protein (e.g., scFv, SMIP™, PIMS, SCORPION™ fusion proteins), or a polypeptide heterodimer according to the present disclosure that specifically bind a target associated with such a disease, disorder or condition. Examples of such targets are provided above in the context of targets of polypeptide heterodimers of the present disclosure useful in the above-noted treatment.

[0351] It is contemplated the binding molecule composition and the second active agent may be given simultaneously in the same formulation. Alternatively, the second agents may be administered in a separate formulation but concurrently (*i.e.*, given within less than one hour of each other).

[0352] In certain embodiments, the second active agent may be administered prior to administration of a polypeptide heterodimer or a composition thereof. Prior administration refers to administration of the second active agent at least one hour prior to treatment with the polypeptide heterodimer or the composition thereof. It is further contemplated that the active agent may be administered subsequent to administration of the binding molecule composition. Subsequent administration is meant to describe administration at least one hour after the administration of the polypeptide heterodimer or the composition thereof.

[0353] This disclosure contemplates a dosage unit comprising a pharmaceutical composition of this disclosure. Such dosage units include, for example, a single-dose or a multi-dose vial or syringe, including a two-compartment vial or syringe, one comprising the pharmaceutical composition of this disclosure in lyophilized form and the other a diluent for reconstitution. A multi-dose dosage unit can also be, *e.g.*, a bag or tube for connection to an intravenous infusion device.

[0354] This disclosure also contemplates a kit comprising a pharmaceutical composition of this disclosure in unit dose, or multi-dose, container, *e.g.*, a vial, and a set of instructions for administering the composition to patients suffering a disorder such as a disorder described above.

EXAMPLES

EXAMPLE 1

BIVALENT POLYPEPTIDE HETERODIMER WITH TWO PAIRS OF HETERODIMERIZATION DOMAINS

[0355] Polypeptide heterodimer X0172 was made by co-expressing single chain polypeptides X0130 (2E12 CH1 CH2 CH3 Ck) and X0168 (Ck CH2 CH3 CH1 H68 2E12). Single chain polypeptide X0130 comprises, from its amino to carboxyl terminus: 2E12 (anti-CD28) scFv, human IgG1 CH1, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and altered human Ck (without the first Arg or the last Cys). The nucleic acid and amino acid sequences of X130 are set forth in SEQ ID NOS:1 and 2, respectively. Single chain polypeptide X0168 comprises, from its amino to carboxyl terminus: altered human Ck (without the first Arg or the last Cys), human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, human IgG1 CH1, H68 linker, and 2E12 (anti-CD28) scFv. The nucleic acid and amino acid sequences of X0168 are set forth in SEQ ID NOS:3 and 4, respectively. The amino acid sequence of H68 linker is set forth in SEQ ID NO:78.

[0356] For comparison, polypeptide heterodimer X0124 was made by co-expressing single chain polypeptide X0112 (2E12 CH1 CH2 CH3) and X0113 (Ck CH2 CH3). Single chain polypeptide X0112 comprises, from its amino to carboxyl terminus: 2E12 (anti-CD28) scFv, human IgG1 CH1, human IgG1 SCC-P hinge, human IgG1 CH2, and human IgG1 CH3. The nucleic acid and amino acid sequences of X0112 are set forth in SEQ ID NOS:5 and 6, respectively. Single chain polypeptide X0113 comprises, from its amino to carboxyl terminus: altered human Ck (without the first Arg or the last Cys), human IgG1 SCC-P hinge, human IgG1 CH2, and human IgG1 CH3. The nucleic acid and amino acid sequence of X0113 are set forth in SEQ ID NOS:7 and 8, respectively.

Expression

[0357] The day before transfection, HEK293 cells were suspended at a cell concentration of 0.5×10^6 cells/ml in Freestyle 293 expression medium (Gibco). For a large transfection, 250 ml of cells were used, but for a small transfection, 60 ml of cells were used. On the transfection day, 320 μ l of 293fectin reagent (Invitrogen) was mixed with 8 ml of media. At the same time, 250 μ g of DNA for each of the two chains were also mixed with 8 ml of media and incubated for 5 minutes. After 15 minutes of incubation, the DNA-293fectin mixture was added to the 250ml of 293 cells and returned to the shaker at 37°C and shaken at a speed of 120 RPM. For the smaller transfection using 60 ml of cells, a fourth of the DNA, 293fectin and media were used.

Purification

[0358] Protein A affinity chromatography was used to purify the proteins. 2 mL of packed protein A agarose (Repligen) was added to a Biorad column (Econo-column chromatography column, size 2.5 x 10 cm), washed extensively with PBS (10x column

volume) and the supernatants were loaded, washed with PBS again and eluted with 3 column volumes of Pierce IgG elution buffer. Proteins were then dialyzed extensively against PBS. Proteins were then concentrated using Amicon centrifugal filter devices to a final volume of around 0.5 mL.

[0359] For second step purification, Protein L affinity chromatography or cation exchange chromatography were used. For Protein L purification, protein A purified Polypeptide heterodimer was passed over a Protein L agarose column that had been pre-equilibrated with PBS, washed with PBS (10x column volume) and then eluted with Pierce IgG elution buffer. Proteins were then dialyzed against PBS extensively and concentrated using Amicon centrifugal filter devices to a final volume of around 0.5 mL.

[0360] Samples (200-300 ug) of previously affinity purified (Protein A or Protein L) Polypeptide heterodimer constructs were dialyzed into 20 mM MES, pH 6.0 (Buffer A) and loaded onto a MonoS 5/50 GL cation exchange column (GE Healthcare) at a flow rate of 2 mL/min, using an AKTA Explorer FPLC. The column was allowed to equilibrate for 5 column volumes (CV) and then run in a gradient format to a mixture of 50%:50% buffer A:buffer B (buffer B being 20 mM MES, 1 M NaCl, pH 6.0) over 20 CV. A following mixture of 100% buffer B was run for 5 CV to clean the column, and the system was run for another 5 CV at 100% buffer A to re-equilibrate prior to the next injection. Peaks were collected and analyzed by SDS-PAGE and electrospray mass spectrometry.

SDS-PAGE Analysis

[0361] Proteins purified were analyzed on a 10 % SDS-PAGE gel using Invitrogen's X-cell Surelock gel box.

Synergy with Suboptimal Concentration of PMA

[0362] Peripheral blood mononuclear cells (PBMC) from in-house donors were isolated from heparinized whole blood via centrifugation over Lymphocyte Separation Media (MP Biomedicals, Aurora, OH) and washed two times with RPMI media (Gibco-Invitrogen, Carlsbad, CA). CD4⁺ T-cells were then enriched from the PBMC using negative selection with a MACS CD4⁺ T-cell Isolation Kit (Miltenyi Biotec, Auburn, CA). The enriched (>95%) CD4⁺ T-cells were then resuspended at a concentration of 1×10^6 cell/ml in complete RPMI/10% FCS. Test reagents were prepared at 40 ug/ml (yielding a final concentration of 10 ug/ml) in complete RPMI/10% FCS and added in 50 ul/well to flat-bottom 96-well plates (BD Falcon, San Jose, CA). PMA (Phorbol 12 myristate 13-acetate; A.G. Scientific, Inc., San Diego, CA) in complete RPMI/10% FCS was added in 50 ul/well at 4 ug/ml (final concentration of 1 ug/ml). Then T-cells in complete RPMI/10% FCS were added at a concentration of 5×10^4 cells/well in a 50 ul volume, and finally an appropriate amount of complete RPMI/10% FCS was added to each well (typically 50 ul) to bring the final volume to 200 ul/well. The cells were treated with the test samples +/- PMA and incubated for 72 hours at 37°C in 5% CO₂. One microliter of tritiated thymidine (Amersham Biosciences, Piscataway, NJ) in a 1:50 dilution of complete RPMI/10% FCS (50 ul/well) was added to the wells for the last 6 hours of culture. Plates were harvested onto a Unifilter-96, GF/C microplate (Perkin Elmer, Boston, MA) with a Packard Filtermate Harvester (Perkin Elmer, Boston, MA). Numbers are expressed as cpm and are the mean of replicate samples.

[0363] Figure 2 shows that Polypeptide heterodimer X0172 has a differential property compared to 2E12 SMP M0039 (SEQ ID NO:77). It did not synergize with PMA as well as the SMP. This bivalent polypeptide heterodimer has a property closer to the monovalent polypeptide heterodimer, X0124, rather than the bivalent SMP.

[0364] Figure 3 shows that bivalent polypeptide heterodimer X0172 bound to CD4⁺ cells better than 2E12 scFv (SEQ ID NO:109) and monovalent polypeptide heterodimer X0124.

EXAMPLE 2

BIVALENT, TRIVALENT, TETRAVALENT POLYPEPTIDE HETERODIMER USING SINGLE HETERODIMERIZATION DOMAIN PAIR

[0365] Bivalent polypeptide heterodimer X0251 was made by co-expressing single chain polypeptides X0244 (Ck(YAE)

CH2(N297A) CH3 H68 2E12) and X0245 (2E12 CH1 CH2(N297A) CH3). Single chain polypeptide X0244 comprises, from its amino to carboxyl terminus: human Ck(YAE) (*i.e.*, human Ck without the first Arg or last Cys but with N30Y, V55A, and T70E substitutions), human IgG1 SCC-P hinge, human IgG1 CH2 (N297A) (*i.e.*, human IgG1 CH2 with a N297A substitution), human IgG1 CH3, H68 linker, and 2E12 (anti-CD28) scFv. The nucleotide and amino acid sequences of X0244 are set forth in SEQ ID NOS:9 and 10, respectively. Single chain polypeptide X0245 comprises, from its amino to carboxyl terminus: 2E12 (anti-CD28) scFv, human IgG1 CH1, human IgG1 SCC-P hinge, human IgG1 CH2 (N297A), and human IgG1 CH3. The nucleotide and amino acid sequences of X0245 are set forth in SEQ ID NOS:11 and 12, respectively.

[0366] Trivalent, bispecific polypeptide heterodimer X0252 was made by co-expressing single chain polypeptides X0246 (P2C2 Ck(YAE) CH2(N297A) CH3) and X0247 (2E12 CH1 CH2(N297A) CH3 H68 2E12). Single chain polypeptide X0246 comprises, from its amino to carboxyl terminus: P2C2 (anti-CD79b) scFv, human Ck (YAE), human IgG1 SCC-P hinge, human IgG1 CH2 (N297A), and human IgG1 CH3. The nucleotide and amino acid sequences of X0246 are set forth in SEQ ID NOS:13 and 14, respectively. Single chain polypeptide X0247 comprises, from its amino to carboxyl terminus: 2E12 (anti-CD28) scFv, human IgG1 CH1, human IgG1 SCC-P hinge, human IgG1 CH2 (N297A), human IgG1 CH3, H68 linker, and 2E12 (anti-CD28) scFv. The nucleotide and amino acid sequences of X0247 are set forth in SEQ ID NOS:15 and 16, respectively.

[0367] Tetraivalent, trispecific polypeptide heterodimer X0253 was made by co-expressing single chain polypeptides X0248 (P2C2 Ck(YAE) CH2(N297A) CH3 H68 A2) and X0249 (PDL2 ECD CH1 CH2(N297A) CH3 H68 2E12). Single chain polypeptide X0248 comprises, from its amino to carboxyl terminus: P2C2 (anti-CD79b) scFv, human Ck (YAE), human IgG1 SCC-P hinge, human IgG1 CH2 (N297A), human IgG1 CH3, H68 linker, and A2 (anti-hyperIL-6) scFv. The nucleotide and amino acid sequences of X0248 are set forth in SEQ ID NOS:17 and 18, respectively. Single chain polypeptide X0249 comprises, from its amino to carboxyl terminus: PDL2 ECD (*i.e.*, PDL2 ectodomain), human IgG1 CH1, human IgG1 SCC-P hinge, human IgG1 CH2 (N297A), human IgG1 CH3, H68 linker, and 2E12 (anti-CD28) scFv. The nucleotide and amino acid sequences of X0249 are set forth in SEQ ID NOS:19 and 20, respectively.

[0368] Another tetraivalent, tetraspecific polypeptide heterodimer X0283, was made by co-expressing single chain polypeptides X0249 (PDL2 ECD CH1 CH2(N297A) CH3 H68 2E12) and X0281 (monolL-10 Ck(YAE) CH2(N297A) CH3 H68 3D1). Single chain polypeptide X0281 comprises, from its amino to carboxyl terminus: monolL-10, human Ck(YAE), human IgG1 SCC-P hinge, human IgG1 CH2 (N297A), human IgG1 CH3, H68 linker, and 3D1(anti-CD86) scFv. The nucleotide and amino acid sequences of X0281 are set forth in SEQ ID NOS:21 and 22.

[0369] As a control for polypeptide heterodimer X0283, tetraivalent heterodimer, polypeptide heterodimer X0284, was made by co-expressing single chain polypeptides X0249 (PDL2 ECD CH1 CH2(N297A) CH3 H68 2E12) and X0282 (monolL-10 Ck CH2(N297A) CH3 H68 3D1). Single chain polypeptide X0282 is identical to X0281 except that it does not contain N30Y V55A T70E substitutions in the human Ck sequence. Thus, single chain polypeptide X0282 comprises, from its amino to carboxyl terminus: monolL-10, altered human Ck (without the first Arg or the last Cys), human IgG1 SCC-P hinge, human IgG1 CH2 (N297A), human IgG1 CH3, H68 linker, and 3D1(anti-CD86) scFv. The nucleotide and amino acid sequences of X0282 are set forth in SEQ ID NOS:23 and 24, respectively.

[0370] The polypeptide heterodimer molecules were expressed and purified according to Example 1. Purified proteins were analyzed using SDS-PAGE electrophoresis under reduced and non-reduced conditions. Size exclusion chromatography was performed on an AKTA Explorer FPLC (Pharmacia Biotech) using a Superdex200 10/300 GL column. Some proteins were analyzed by electrospray mass spectrometry using an Agilent 6120 TOF ES/MS.

[0371] Surface plasmon resonance (SPR) measurements were performed on a Biacore T100 SPR using HBS-P+ (GE Healthcare) as a running buffer. Target was directly immobilized onto a CM5 chip using standard amine coupling chemistry (BIAcore® Amine Coupling Kit, GE Healthcare), with final immobilization levels between 800 and 1900 Ru (resonance units). Polypeptide heterodimer X0283 was injected at 25°C or 37°C for 150 seconds at a flow rate of 30 µl/min in a series of concentrations from 10 nM to 1 µM. Dissociation was monitored for 1200 seconds, and the surface was regenerated by injecting 50 mM NaOH for 60 seconds. Binding interactions with the surface were stable through at least 60 regeneration cycles. Data were analyzed using BiaEvaluation for the T100 software (version 2.0, GE Healthcare).

[0372] The SDS-PAGE electrophoresis and cation exchange chromatography analyses show that polypeptide heterodimers X0251, X0252 and X0253 were reasonably well expressed and purified (Figure 4). Mass spectrometry analysis of X0252 shows that the protein is mostly homogeneous with an undetectable amount of the homodimers (Figure 5). In addition, the SDS-PAGE electrophoresis and cation exchange chromatography analyses of polypeptide heterodimers X0283 and X0284 show that polypeptide heterodimer X0283 having the CH1/Ck(YAE) heterodimerization domains efficiently assembled into a heterodimer compared to control polypeptide heterodimer X0284 having the CH1/Ck heterodimerization domains, which formed homodimers

as well (Figure 6). The Biocore analysis further shows that the 3D1 (anti-CD86) binding domain at the carboxyl terminus of single chain polypeptide X0281 monovalently bound to CD86 (Figure 7).

EXAMPLE 3

POLYPEPTIDE HETERODIMERS WITH ANTI-RON AND ANTI-C-MET BINDING DOMAINS

[0373] A bivalent polypeptide heterodimer with anti-RON binding domains (ORN151) and two bispecific polypeptide heterodimers comprising anti-RON and anti-cMet binding domains (ORN152 and ORN153) were made.

[0374] Bivalent polypeptide heterodimer ORN151 comprises single chain polypeptides ORN145 (4C04 CH2 CH3 CH1) and ORN148 (11H09 CH2 CH3 Ck(YAE)). Single chain polypeptide ORN145 comprises from its amino to carboxyl terminus: 4C04 (anti-RON) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human IgG1 CH1. The nucleotide and amino acid sequences of ORN145 are set forth in SEQ ID NOS:26 and 30, respectively. Single chain polypeptide ORN148 comprises from its amino to carboxyl terminus: 11H09 (anti-RON) scFv, human IgG1 SCC-P hinge, human CH2, human CH3, and human Ck(YAE). The nucleotide and amino acid sequences of ORN148 are set forth in SEQ ID NOS:28 and 32, respectively.

[0375] Bispecific (c-Met, RON) polypeptide heterodimer ORN152 comprises single chain polypeptides ORN116 (MET021 CH2 CH3 CH1) and ORN146 (4C04 CH2 CH3 Ck(YAE)). Single chain polypeptide ORN116 comprises from its amino to carboxyl terminus: MET021 (anti-c-Met) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human IgG1 CH1. The nucleotide and amino acid sequences of ORN116 are set forth in SEQ ID NOS:25 and 29, respectively. Single chain polypeptide ORN146 comprises from its amino to carboxyl terminus: 4C04 (anti-RON) scFv, human IgG1 SCC-P hinge, human CH2, human CH3, and human Ck(YAE). The nucleotide and amino acid sequences of ORN146 are set forth in SEQ ID NOS:27 and 31, respectively.

[0376] Bispecific (c-Met, RON) polypeptide heterodimer ORN153 comprises single chain polypeptides ORN116 (MET021 CH2 CH3 CH1) and ORN148 (11H09 CH2 CH3 Ck(YAE)).

[0377] Polypeptide heterodimers ORN151, ORN152 and ORN153 were expressed according to Example 1. The following expression levels were obtained: 1.9 µg protein / mL of culture for ORN151, 3.1 µg / mL for ORN152, and 4.9 µg / mL for ORN153.

EXAMPLE 4

POLYPEPTIDE HETERODIMERS WITH ANTI-CD3 BINDING DOMAINS

[0378] Several bispecific polypeptide heterodimers with an anti-CD3 binding domain were made: polypeptide heterodimers S0268, S0269, and TSC020 to TSC030. Polypeptide heterodimer S0268 comprises single chain polypeptides ORN145 (4C04 CH2 CH3 CH1) and TSC019 (G19-4 CH2 CH3 Ck(YAE)). Single chain polypeptide TSC019 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, human IgG1 SCC-P hinge, human CH2, human CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC019 are set forth in SEQ ID NOS:52 and 72, respectively.

[0379] Bispecific (CD3, c-Met) Polypeptide heterodimer S0269 comprises single chain polypeptides ORN160 (5D5 CH2 CH3 CH1) and TSC019 (G19-4 CH2 CH3 Ck(YAE)). Single chain polypeptide ORN160 comprises from its amino to carboxyl terminus: 5D5 (anti-c-Met) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of ORN160 are set forth in SEQ ID NOS:33 and 53, respectively.

[0380] Bivalent (CD19) polypeptide heterodimer TSC020 comprises single chain polypeptides TSC001 (HD37 CH2 CH3 CH1) and TSC019 (G19-4 CH2 CH3 Ck(YAE)). Single chain polypeptide TSC001 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human IgG1 CH1. The nucleotide and amino acid sequences of TSC001 are set forth in SEQ ID NOS:34 and 54, respectively.

[0381] Bispecific (CD20, CD3) polypeptide heterodimer TSC021 comprises single chain polypeptides TSC002 (2H7 CH2 CH3 CH1) and TSC019 (G19-4 CH2 CH3 Ck(YAE)). Single chain polypeptide TSC002 comprises from its amino to carboxyl terminus: 2H7 (anti-CD20) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human IgG1 CH1. The nucleotide and amino acid sequences of TSC002 are set forth in SEQ ID NOS:35 and 55, respectively.

[0382] Bispecific (CD79b, CD3) polypeptide heterodimer TSC022 comprises single chain polypeptides TSC017 (P2C2 H2 CH3 CH1) and TSC019 (G19-4 CH2 CH3 Ck(YAE)). Single chain polypeptide TSC017 comprises from its amino to carboxyl terminus: P2C2 (anti-CD79b) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human IgG1 CH1. The nucleotide and amino acid sequences of TSC017 are set forth in SEQ ID NOS:50 and 70, respectively.

[0383] Bispecific (HLA-DR, CD3) polypeptide heterodimer TSC023 comprises single chain polypeptides TSC018 (M0042 CH2 CH3 CH1) and TSC019 (G19-4 CH2 CH3 Ck(YAE)). Single chain polypeptide TSC018 comprises from its amino to carboxyl terminus: M0042 (anti-HLA-DR) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC018 are set forth in SEQ ID NOS:51 and 71, respectively.

[0384] Bivalent polypeptide heterodimer TSC024 comprises single chain polypeptides TSC010 (HD37-"IgA1 hinge"-CH2 CH3 CH1) and TSC003 (G19-4-"IgA1 hinge"-CH2 CH3 Ck(YAE)). Single chain polypeptide TSC010 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, altered human IgA1 hinge (PSTPPTPSPSTPPTPSPSCPPCP, SEQ ID NO:752), human IgG1 CH2, human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC010 are set forth in SEQ ID NOS:43 and 63, respectively. Single chain polypeptide TSC003 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, altered human IgA1 hinge (SEQ ID NO:752), human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC003 are set forth in SEQ ID NOS:36 and 56, respectively.

[0385] Bivalent polypeptide heterodimer TSC025 comprises single chain polypeptides TSC011 (HD37-"IgA2 hinge"-CH2 CH3 CH1) and TSC004 (G19-4-"IgA2 hinge"-CH2 CH3 Ck(YAE)). Single chain polypeptide TSC011 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, altered human IgA2 hinge (PPPPPCPPCP, SEQ ID NO:748), human IgG1 CH2, human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC011 are set forth in SEQ ID NOS:44 and 64, respectively. Single chain polypeptide TSC004 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, altered human IgA2 hinge (SEQ ID NO:748), human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC004 are set forth in SEQ ID NOS:37 and 57, respectively.

[0386] Bivalent polypeptide heterodimer TSC026 comprises single chain polypeptides TSC012 (HD37-"IgG1 hinge"-CH2 CH3 CH1) and TSC007 (G19-4-"IgG1 hinge"-CH2 CH3 Ck(YAE)). Single chain polypeptide TSC012 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, altered human IgG1 hinge (EPKSSDKTHTSPSPCPPCP, SEQ ID NO:750), human IgG1 CH2, human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC012 are set forth in SEQ ID NOS:45 and 65, respectively. Single chain polypeptide TSC007 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, altered human IgG1 hinge (SEQ ID NO:750), human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC007 are set forth in SEQ ID NOS:40 and 60, respectively.

[0387] Bivalent polypeptide heterodimer TSC027 comprises single chain polypeptides TSC013 (HD37-"IgG3 hinge"-CH2 CH3 CH1) and TSC005 (G19-4-"IgG3 hinge"-CH2 CH3 Ck(YAE)). Single chain polypeptide TSC013 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, altered human IgG3 hinge (EPKSSDTPPPSPRSPCPPCP, SEQ ID NO:751), human IgG1 CH2, human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC013 are set forth in SEQ ID NOS:46 and 66, respectively. Single chain polypeptide TSC005 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, altered human IgG3 hinge (SEQ ID NO:751), human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC005 are set forth in SEQ ID NOS:38 and 58, respectively.

[0388] Bivalent polypeptide heterodimer TSC028 comprises single chain polypeptides TSC014 (HD37-"IgD hinge"-CH2 CH3 CH1) and TSC006 (G19-4-"IgD hinge"-CH2 CH3 Ck(YAE)). Single chain polypeptide TSC014 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, altered human IgD hinge (ESPKAQASSVPTAQPAEGSLAKATTAPATTRNTCPPCP, SEQ ID NO:754), human IgG1 CH2, human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC014 are set forth in SEQ ID NOS:47 and 67, respectively. Single chain polypeptide TSC006 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, altered human IgD hinge (SEQ ID NO:754), human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC006 are set forth in SEQ ID NOS:39 and 59, respectively.

[0389] Bivalent polypeptide heterodimer TSC029 comprises single chain polypeptides TSC015 (HD37-"IgE CH2 hinge"-CH2 CH3 CH1) and TSC008 (G19-4-"IgE CH2 hinge"-CH2 CH3 Ck(YAE)). Single chain polypeptide TSC015 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, altered human IgE CH2 hinge (SEQ ID NO:757), human IgG1 CH2, human IgG1 CH3,

and human IgG1 CH1. The nucleotide and amino acid sequences of TSC014 are set forth in SEQ ID NOS:48 and 68, respectively. Single chain polypeptide TSC008 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, altered human IgE CH2 hinge (SEQ ID NO:757), human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC008 are set forth in SEQ ID NOS:41 and 61, respectively.

[0390] Bivalent polypeptide heterodimer TSC030 comprises single chain polypeptides TSC016 (HD37-"IgM CH2 hinge"-CH2 CH3 CH1) and TSC009 (G19-4-"IgM CH2 hinge"-CH2 CH3 Ck(YAE)). Single chain polypeptide TSC016 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, altered human IgM CH2 hinge (SEQ ID NO:759), human IgG1 CH2, human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC015 are set forth in SEQ ID NOS:49 and 69, respectively. Single chain polypeptide TSC009 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, altered human IgM CH2 hinge (SEQ ID NO:759), human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC009 are set forth in SEQ ID NOS:42 and 62, respectively.

[0391] Bispecific polypeptide heterodimers S0268 (RON, CD3) and S0269 (CD3, c-Met) were expressed according to Example 1. The following expression levels were obtained: 2.2 µg protein / mL of culture for S0268 and 2.7 µg / mL for S0269.

EXAMPLE 5

CELL BINDING OF BISPECIFIC POLYPEPTIDE HETERODIMERS

[0392] To compare the effectiveness of bispecific polypeptide heterodimer molecules at targeting a tumor cell antigen and T-cells, the on-cell binding characteristics of an anti-RON (4C04 binding domain) x anti-CD3 (G19-4 binding domain) polypeptide heterodimer, S0268 (as described in Example 4), with a different bispecific scaffold (SCORPION™ protein) containing the same binding domains, S0266, were compared. Additionally, the on-cell binding characteristics of two bispecific polypeptide heterodimers, TSC020 and TSC021 (as described in Example 4), targeting different B-cell antigens (CD19 for TSC020 and CD20 for TSC021) as well as a T-cell antigen (CD3) were compared. The nucleotide and amino acid sequences of SCORPION protein S0266 are set forth in SEQ ID NOS:73 and 74, respectively. Nucleotide and amino acid sequences of the single chain polypeptides making up the bispecific polypeptide heterodimers S0268, TSC020, and TSC021 are set forth in SEQ ID NOS:26 and 52 (nucleotide), 30 and 72 (amino acid); 34 and 52 (nucleotide), 54 and 72 (amino acid); and 35 and 52 (nucleotide), 55 and 72 (amino acid), respectively (see also Example 4). Transient transfection in human 293 cells produced 6.9 µg protein / mL of culture for S0266; 2.3 µg / mL of culture for S0268; 3.0 µg / mL of culture for TSC020; and 3.2 µg / mL of culture for TSC021.

[0393] MDA-MB-453 (RON⁺) breast carcinoma cells, Rec1 (CD19⁺, CD20⁺) mantle cell lymphoma cells, and Jurkat (CD3⁺) T cell leukemia cells were obtained from ATCC (Manassas, VA), and cultured according to the provided protocol. T-cells were isolated from donor PBMCs using a Pan T-cell Isolation Kit II from Miltenyi Biotec (Bergisch Gladbach, Germany). Non T-cells were separated from PBMCs by being indirectly magnetically labeled with biotin-conjugated monoclonal antibodies and anti-biotin magnetic microbeads. These cells were then depleted by retaining them in a column surrounded by a magnetic field. The T-cells were not retained in the column and were collected in the flow through.

[0394] Binding was assessed by incubating 5×10^5 T cells or target (MDA-MB-453, Rec1, Jurkat) cells for 30 minutes at 4°C with serially diluted bispecific molecules S0266 (αRON × αCD3 SCORPION™ protein) or S0268 (αRON × αCD3 polypeptide heterodimer) (for MDA-MB-453 cells and isolated T cells); or TSC020 (αCD19 × αCD3) or TSC021 (αCD20 × αCD3) for Rec1 and Jurkat cells, in concentrations from 100 nM to 0.1 nM. The cells were washed three times and then incubated with goat anti-human IgG-FITC (1:200 dilution) for another 30 minutes at 4°C. The cells were then washed again three times, fixed in 1% paraformaldehyde and read on a FACS-Calibur instrument.

[0395] Analysis of the FSC high, SSC high subset in FlowJo v7.5 (Tree Star, Inc, Ashland, OR) showed dose-dependent binding of bispecific molecules S0266 and S0268 to both MDA-MB-453 and isolated T-cells (Figures 8A and 8B). Unexpectedly, the S0268 polypeptide heterodimer bound with similar affinity to the comparable SCORPION™ molecule (S0266) on both MDA-MB-453 cells and T-cells, although it lacked the potential for any avidity. Higher saturation on both target cell types was also observed with the polypeptide heterodimer, which would be the case if the polypeptide heterodimer was binding at a higher stoichiometry (1:1 binding of polypeptide heterodimer to surface antigen) than the equivalent SCORPION™ (potential 1:2 binding of the bivalent Scorpion to surface antigens). Comparison of the CD 19-targeting bispecific heterodimer (TSC020; HD37 and G19-4 binding domains) and the CD20-targeting bispecific heterodimer (TSC021; 2H7 and G19-4 binding domains) on Rec1 and Jurkat cells

revealed that the TSC020 heterodimer had higher affinity for the Rec1 cells than TSC021 heterodimer (Figure 9A). However, both TSC020 and TSC021 heterodimers showed similar binding to CD3⁺ Jurkat cells, which is expected since both heterodimers possess the same anti-CD3 binding domain (G19-4) (Figure 9B).

EXAMPLE 6

ADDITIONAL BIVALENT & TRIVALENT POLYPEPTIDE HETERODIMERS USING SINGLE HETERODIMERIZATION DOMAIN PAIR

[0396] Additional multispecific heterodimers were made: TSC046, TSC047, TSC048, TSC054, TSC055, TSC056, TSC057, TSC078, TSC079, TSC080, TSC099, TSC100, TSC101, and TSC102.

[0397] Bivalent polypeptide heterodimer TSC046 comprises single chain polypeptides TSC001 (HD37 CH2 CH3 CH1) and TSC039 (BMA031 CH2 CH3 Ck(YAE)). Single chain polypeptide TSC001 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC001 are set forth in SEQ ID NOS:34 and 54, respectively. Single chain polypeptide TSC039 comprises from its amino to carboxyl terminus: BMA031 (anti-TCR) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC039 are set forth in SEQ ID NOS:793 and 811, respectively.

[0398] Bivalent polypeptide heterodimer TSC047 comprises single chain polypeptides TSC001 (HD37 CH2 CH3 CH1) and TSC041 (CRIS7 CH2 CH3 Ck(YAE)). Single chain polypeptide TSC041 comprises from its amino to carboxyl terminus: CRIS7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC041 are set forth in SEQ ID NOS:794 and 812, respectively.

[0399] Bivalent polypeptide heterodimer TSC048 comprises single chain polypeptides TSC001 (HD37 CH2 CH3 CH1) and TSC043 (OKT3-M CH2 CH3 Ck(YAE)). Single chain polypeptide TSC043 comprises from its amino to carboxyl terminus: OKT3-M (Micromet variant anti-CD3, see also US 7,635,472) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC043 are set forth in SEQ ID NOS:795 and 813, respectively.

[0400] Bivalent polypeptide heterodimer TSC054 comprises single chain polypeptides TSC049 (HD37 CH2(ADCC/CDC null) CH3 CH1) and TSC053 (G19-4 CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC049 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null) (*i.e.*, human IgG1 CH2 with L234A, L235A, G237A, E318A, K320A, and K322A substitutions), human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC049 are set forth in SEQ ID NOS:796 and 814, respectively. Single chain polypeptide TSC053 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null) (*i.e.*, human IgG1 CH2 with L234A, L235A, G237A, E318A, K320A, and K322A substitutions), human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC053 are set forth in SEQ ID NOS:800 and 818, respectively.

[0401] Bivalent polypeptide heterodimer TSC055 comprises single chain polypeptides TSC050 (2H7 CH2(ADCC/CDC null) CH3 CH1) and TSC053 (G19-4 CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC050 comprises from its amino to carboxyl terminus: 2H7 (anti-CD20) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC050 are set forth in SEQ ID NOS:797 and 815, respectively.

[0402] Bivalent polypeptide heterodimer TSC056 comprises single chain polypeptides TSC051 (P2C2 CH2(ADCC/CDC null) CH3 CH1) and TSC053 (G19-4 CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC051 comprises from its amino to carboxyl terminus: P2C2 (anti-CD79) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC051 are set forth in SEQ ID NOS:798 and 816, respectively.

[0403] Bivalent polypeptide heterodimer TSC057 comprises single chain polypeptides TSC052 (5D5 CH2(ADCC/CDC null) CH3 CH1) and TSC053 (G19-4 CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC052 comprises from its amino to carboxyl terminus: 5D5 (anti-cMet) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC052 are set forth in SEQ ID NOS:799 and 817, respectively.

[0404] Bivalent polypeptide heterodimer TSC078 comprises single chain polypeptides TSC049 (HD37 CH2(ADCC/CDC null) CH3

CH1) and TSC076 (OKT3 CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC076 comprises from its amino to carboxyl terminus: OKT3 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC076 are set forth in SEQ ID NOS:802 and 820, respectively.

[0405] Bivalent polypeptide heterodimer TSC079 comprises single chain polypeptides TSC049 (HD37 CH2(ADCC/CDC null) CH3 CH1) and TSC077 (Nuvion CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC077 comprises from its amino to carboxyl terminus: Nuvion (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC077 are set forth in SEQ ID NOS:803 and 821, respectively.

[0406] Trivalent polypeptide heterodimer TSC080 comprises single chain polypeptides TSC001 (HD37 CH2 CH3 CH1) and TSC064 (G19-4 CH2 CH3 Ck(YAE) H75 Met021). Single chain polypeptide TSC064 comprises from its amino to carboxyl terminus: G19-4 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, human Ck(YAE), H75 linker, and Met021 (anti-c-Met) scFv (with the three serine residues at the C-terminus deleted). The nucleotide and amino acid sequences of TSC064 are set forth in SEQ ID NOS:801 and 819, respectively.

[0407] Bivalent polypeptide heterodimer TSC099 comprises single chain polypeptides TSC049 (HD37 CH2(ADCC/CDC null) CH3 CH1) and TSC097 (4C04 CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC097 comprises from its amino to carboxyl terminus: 4C04 (anti-RON) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC097 are set forth in SEQ ID NOS:808 and 826, respectively.

[0408] Bivalent polypeptide heterodimer TSC100 comprises single chain polypeptides TSC049 (HD37 CH2(ADCC/CDC null) CH3 CH1) and TSC093 (CRIS7 CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC093 comprises from its amino to carboxyl terminus: CRIS7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE). The nucleotide and amino acid sequences of TSC093 are set forth in SEQ ID NOS:804 and 822, respectively.

[0409] Bivalent polypeptide heterodimer TSC101 comprises single chain polypeptides TSC049 (HD37 CH2(ADCC/CDC null) CH3 CH1) and TSC094 (OKT3-M CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC094 comprises from its amino to carboxyl terminus: OKT3-M (Micromet variant anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, human Ck(YAE). The nucleotide and amino acid sequences of TSC094 are set forth in SEQ ID NOS:805 and 823, respectively.

[0410] Bivalent polypeptide heterodimer TSC102 comprises single chain polypeptides TSC049 (HD37 CH2(ADCC/CDC null) CH3 CH1) and TSC095 (BMA031 CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC095 comprises from its amino to carboxyl terminus: BMA031 (anti-TCR) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, human Ck(YAE). The nucleotide and amino acid sequences of TSC095 are set forth in SEQ ID NOS:806 and 824, respectively.

[0411] The polypeptide heterodimer molecules were expressed and purified according to Example 1.

EXAMPLE 7

TARGET-DEPENDENT T-CELL PROLIFERATION BY POLYPEPTIDE HETERODIMERS

[0412] To compare the effectiveness of different bispecific polypeptide heterodimer molecules at inducing target-dependent T-cell activation and proliferation, three different bispecific molecules (TSC054, TSC078, and TSC079 as described in Example 6) with a common anti-CD 19 binding domain (HD37) and three different anti-CD3 binding domains (G19-4 for TSC054, OKT3 for TSC078, HuM291 for TSC079) were compared. As a positive control, a Bispecific T-Cell Engaging molecule (BiTE) known as bsc19x3 was also prepared (see U.S. Patent 7,635,472). The nucleotide and amino acid sequences for bsc19x3 are set forth in SEQ ID NOS:809 and 827, respectively. Transient transfection in human 293 cells produced 2.33 ug/mL protein for TSC054, 0.67 ug/mL protein for TSC078, and 3.5 ug/mL for TSC079.

[0413] Daudi Burkitt's lymphoma cells (CD19⁺) and MDA-MB-453 (CD19⁻) breast carcinoma cells were obtained from ATCC (Manassas, VA) and cultured according to the provided protocol. Peripheral blood mononuclear cells (PBMC) were isolated from human blood using standard ficoll gradients. The isolated cells were washed in saline buffer. T cells were additionally isolated using a Pan T-cell Isolation Kit II from Miltenyi Biotec (Bergisch Gladbach, Germany) using the manufacturer's protocol (see also Example 5 for more information).

[0414] Proliferation was assessed by labeling isolated PBMC or T cell populations with carboxyfluorescein diacetate succinimidyl ester (CFSE). CFSE-labeled PBMC or T cells were plated in U-bottom 96-well plates at 150,000 or 100,000 cells/well, respectively, with various numbers of tumor cells, to achieve T cell to tumor cell ratios of 10:1 to 3:1. Concentrations of test molecules ranging from 8 nM to 0.08 pM were added to the cell mixtures in a total of 200 µl/well in RPMI 1640 media supplemented with 10% human or bovine serum, sodium pyruvate and non-essential amino acids. Plates were incubated at 37°C, 5% CO₂ in humidified incubators. After 3 days, cells were labeled with antibodies for flow cytometric analysis. Cells were labeled and washed in their original plates to minimize cell losses during transfers, and all labeling was done in saline buffer with 0.2% bovine serum albumin. First, cells were pre-incubated with 100 µg/ml human IgG at room temperature for 15 min. Subsequently, cells were incubated with a mixture (total volume 50 µl) of the following dye-labeled antibodies: CD5-PE, CD4-APC, CD8-Pacific Blue, CD25-PE-Cy7, as well as 7-Amino Actinomycin D (7AAD hereafter) for 40 min. Plates were washed twice, resuspended in 80 to 120 µl volumes and ran immediately in a BD LSRII flow cytometer to acquire 80% of the contents of each well. The sample files were analyzed using FlowJo software to calculate the percentages and numbers of cells that had undergone at least one cell division, according to their CFSE profile, by gating sequentially on activated, live CD4+ or CD8+ T cells (7AAD-, CD5+ CD25+ CD4+ or 7AAD- CD5+ CD25+ CD8+, respectively). Mean values and standard deviations were calculated using Microsoft Excel software. Graphs were plotted using Microsoft Excel or Graphpad Prism.

[0415] Analysis of live CD4+ and CD8+ populations from Daudi cells or MDA-MB-453 cells treated with whole PBMCs (Figures 10A-10D) revealed a significant increase in both the total number of cells and percent proliferating cells in the presence of Daudi cells displaying the target CD 19 antigen (Figures 10A, 10B), but a lack of significant proliferation in the presence of MDA-MB-453 cells that lacked the CD19 antigen (Figures 10C, 10D). Some proliferation was observed at a lower level with the MDA-MB-453 cells and whole PBMCs, since B-cells (CD19+) were present in the PBMCs, but overall proliferation was greatly reduced in comparison. This selectivity was observed with isolated T-cells as well. Proliferation was higher for CD8+ T-cells than CD4+ T-cells in the presence of Daudi cells or MDA-MB-453 cells treated with PBMCs (Figure 10A-10D), and the proliferation induced by TSC078 (HD37xOKT3) was generally higher at all concentrations than the response induced by TSC054 (HD37xG19-4) or TSC079 (HD37xHuM291)(Figures 10A-10D). Induced proliferation of CD4+ T-cells was lower in all cases for TSC054, TSC078, and TSC079 than the BiTE bsc19x3 (Figure 10A), although TSC078 and TSC079 showed superior induction of proliferation of CD8+ cells at lower concentrations (e.g. 5 pM) than the BiTE molecule (Figure 10B).

EXAMPLE 8

REDIRECTED T-CELL CYTOTOXICITY BY POLYPEPTIDE HETERODIMERS

[0416] To compare the effectiveness of different bispecific polypeptide heterodimer molecules at inducing target-dependent T-cell cytotoxicity, four different bispecific molecules were compared in a chromium (⁵¹Cr) release assay. Three different bispecific molecules (TSC054, TSC078, TSC079, as described in Example 6) with a common anti-CD19 binding domain (HD37) and three different anti-CD3 binding domains (G19-4 for TSC054, OKT3 for TSC078, HuM291 for TSC079) were tested alongside a fourth bispecific molecule (S0268, described in Example 4) with an anti-RON binding domain (4C04) and an anti-CD3 binding domain (G19-4). Transient transfection in human 293 cells produced about 2.33 µg/mL protein for TSC054, about 0.67 µg/mL protein for TSC078, and about 3.5 µg/mL protein for TSC079.

[0417] Daudi Burkitt's lymphoma cells (CD19+, RON-) and BxPC-3 cells (CD 19-, RON+) were obtained from ATCC (Manassas, VA) and cultured according to the provided protocol. Peripheral blood mononuclear cells (PBMC) were isolated from human blood using standard ficoll gradients. The isolated cells were washed in saline buffer. T cells were additionally isolated using a Pan T-cell Isolation Kit II from Miltenyi Biotec (Bergisch Gladbach, Germany) using the manufacturer's protocol (see also Example 5 for more information).

[0418] Cytotoxicity was assessed by a ⁵¹Cr release assay. Approximately 5×10⁶ Daudi or BxPC-3 cells were treated with 0.3 mCi of ⁵¹Cr and incubated for 75 minutes at 37°C. After 75 minutes, cells were washed 3 times with media (RPMI + 10% FBS) and resuspended in 11.5 mL of media. From this suspension, 50 µL was dispensed per well into 96 well U-bottom plates (approximately 20,000 cells/well). Concentrations of bispecific molecules ranging from 10 nM to 0.1 pM were added to the target (Daudi, BxPC-3) cells, bringing the total volume to 100 µL/well. Target cells were incubated at room temperature for 15 minutes. Then 100 µL of isolated T-cells (approximately 200,000) were added to bring the T-cell to target cell ratio to 10:1. 50 µL of 0.8% NP-40 was added to a control well containing target cells, left for 15 minutes, then 100 µL of media was added to provide a total

lysis control.

[0419] Plates were incubated for 4 hours, spun at 1500 rpm for 3 minutes, and 25 μ L of supernatant was transferred from each well to the corresponding well of a 96-well Luma sample plate. Sample plates were allowed to air dry in a chemical safety hood for 18 hours, and then radioactivity was read on a Topcount scintillation counter using a standard protocol.

[0420] Analysis of cytotoxicity data showed a lack of off-target cytotoxicity on the Daudi (RON-) cells from the anti-RON directed bispecific molecule S0268 (Figure 11A). Similarly, there was a lack of direct cytotoxicity observed from treating Daudi cells with TSC054 in the absence of T-cells (Figure 11A). However, strong T-cell directed cytotoxicity was observed with the Daudi cells in the presence of T-cells and an anti-CD19 directed bispecific molecule (TSC054), reaching maximal lysis at a concentration between 10 and 100 pM (Figure 11A). Similarly, using a second T-cell donor (Figure 11B), no off-target cytotoxicity of the BxPC-3 (CD19-) cells was observed from the CD19-directed bispecifics TSC054, TSC078, or TSC079, or the CD19-directed BiTE bsc19x3. The anti-RON directed S0268 bispecific molecule induced cytotoxicity in BxPC-3 (RON+) cells, reaching a maximum between 10 and 100 pM (Figure 11B).

EXAMPLE 9

MODULATION OF TARGET-DEPENDENT T-CELL PROLIFERATION BY POLYPEPTIDE HETERODIMERS WITH ALTERED HINGE SEQUENCES

[0421] To compare the effectiveness of different bispecific polypeptide heterodimer molecules with altered hinge sequences at inducing target-dependent T-cell activation and proliferation, six different bispecific heterodimers (TSC100, TSC127, TSC165, TSC166, TSC167 and TSC168 with a common anti-CD19 binding domain (HD37), a common anti-CD3 binding domain (Cris7) and five different hinge constructs (IgG1 SCC-P hinge for TSC100 and TSC127, IgA2 hinge without the first Val residue linked to a human IgG1 core hinge for TSC165, IgG1 SSS-P hinge linked to a human IgG1 core hinge for TSC166, a portion of mutated IgG3 hinge linked to a IgG1 core hinge for TSC167, and the IgM CH2 domain without the first Val linked to a IgG1 core hinge for TSC168) were compared.

[0422] More specifically, bispecific heterodimer TSC100 is as described in Example 6.

[0423] Bispecific heterodimer TSC127 comprises single chain polypeptides TSC125 (Cris7 CH2(ADCC/CDC null) CH3 CH1) and TSC096 (HD37 CH2(ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC125 comprises from its amino to carboxyl terminus: humanized Cris7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC125 are set forth in SEQ ID NOS:865 and 874, respectively. Single chain polypeptide TSC096 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human Ck (YAE). The nucleotide and amino acid sequences of TSC096 are set forth in SEQ ID NOS:807 and 825, respectively.

[0424] Bispecific heterodimer TSC 165 comprises single chain polypeptides TSC157 (Cris7 IgA2UH CH2 (ADCC/CDC null) CH3 CH1) and TSC161 (HD37 IgA2UH CH2 (ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC157 comprises from its amino to carboxyl terminus: humanized Cris7(anti-CD3) scFv, human IgA2 hinge without the first Val linked with a human IgG1core hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC157 are set forth in SEQ ID NOS:866 and 875, respectively. Single chain polypeptide TSC161 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgA2 hinge without the first Val linked with a human IgG1 core hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human Ck (YAE). The nucleotide and amino acid sequences of TSC161 are set forth in SEQ ID NOS:870 and 879, respectively. The amino acid sequence of the hinge used in TSC157 and TSC161 is set forth in SEQ ID NO:748.

[0425] Bispecific heterodimer TSC166 comprises single chain polypeptide TSC158 (Cris7 IgG1miniUH CH2 (ADCC/CDC null) CH3 CH1) and TSC162 (HD37 IgG1miniUH CH2 (ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC158 comprises from its amino to carboxyl terminus: humanized Cris7 (anti-CD3) scFv, human IgG1 SSC-P hinge linked with a human IgG1 core hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC158 are set forth in SEQ ID NOS:867 and 876, respectively. Single chain polypeptide TSC162 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgG1 SSC-P hinge linked with a human IgG1 core hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human Ck (YAE). The nucleotide and amino acid sequences of TSC162 are set forth in

SEQ ID NOS:871 and 880. The amino acid sequence of the hinge used in TSC158 and TSC162 is set forth in SEQ ID NO:750.

[0426] Bispecific heterodimer TSC167 comprises single chain polypeptide TSC159 (Cris7 IgG3UH CH2 (ADCC/CDC null) CH3 CH1) and TSC163 (HD37 IgG3UH CH2 (ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC159 comprises from its amino to carboxyl terminus: humanized Cris7 (anti-CD3) scFv, a portion of mutated human IgG3 hinge linked with a human IgG1 core hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC159 are set forth in SEQ ID NOS:868 and 877, respectively. Single chain polypeptide TSC163 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, a portion of mutated human IgG3 hinge linked with a human IgG1 core hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human Ck (YAE). The nucleotide and amino acid sequences of TSC163 are set forth in SEQ ID NOS:872 and 881. The amino acid sequence of the hinge used in TSC159 and TSC163 is set forth in SEQ ID NO:751.

[0427] Bispecific heterodimer TSC168 comprises single chain polypeptide TSC160 (Cris7 IgMCH2UH CH2 (ADCC/CDC null) CH3 CH1) and TSC164 (HD37 IgMCH2UH CH2 (ADCC/CDC null) CH3 Ck(YAE)). Single chain polypeptide TSC160 comprises from its amino to carboxyl terminus: humanized Cris7(anti-CD3) scFv, human IgM CH2 without the first Val linked with a human IgG1 core hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1. The nucleotide and amino acid sequences of TSC160 are set forth in SEQ ID NOS:869 and 878, respectively. Single chain polypeptide TSC163 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgM CH2 without the first Val linked with a human IgG1core hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, and human Ck (YAE). The nucleotide and amino acid sequences of TSC164 are set forth in SEQ ID NOS:873 and 882. The amino acid sequence of the hinge used in TSC160 and TSC164 is set forth in SEQ ID NO:759.

[0428] As a positive control, a Bispecific T-Cell Engaging molecule (BiTE) known as bsc19x3 was also prepared (see U.S. Patent 7,635,472). The nucleotide and amino acid sequences for bsc19x3 are set forth in SEQ ID NOS:809 and 827, respectively.

[0429] Transient transfection in human 293 cells produced 3.2 ug protein / mL of culture for TSC100, 6.1 ug protein / mL of culture for TSC127, 4.8 ug protein / mL of culture for TSC165, 6.2 ug protein / mL of culture for TSC166, 6.4 ug protein / mL of culture for TSC167, and 6.4 ug/mL protein for TSC168.

[0430] Daudi Burkitt's lymphoma cells (CD19⁺) and C4-2 (CD19⁻) prostate carcinoma cells were obtained from ATCC (Manassas, VA) and MD Anderson Cancer Center (Houston, TX) and cultured according to the provided protocol. T cells were isolated using a Pan T-cell Isolation Kit II from Miltenyi Biotec (Bergisch Gladbach, Germany) using the manufacturer's protocol (see also Example 5 for more information).

[0431] Proliferation was assessed by labeling isolated T cell populations with carboxyfluorescein diacetate succinimidyl ester (CFSE). CFSE-labeled T cells were plated in U-bottom 96-well plates at 100,000 cells/well, with 10,000 tumor cells/well, to achieve a T cell to tumor cell ratio of 10:1. Concentrations of test molecules ranging from 5 nM to 0.005 pM were added to the cell mixtures in a total of 200 ul/well in RPMI 1640 media supplemented with 10% human or bovine serum, sodium pyruvate and non-essential amino acids. Plates were incubated at 37°C, 5% CO₂ in humidified incubators. After 3 days, cells were labeled with antibodies for flow cytometric analysis. Cells were labeled and washed in their original plates to minimize cell losses during transfers, and all labeling was done in saline buffer with 0.2% bovine serum albumin. First, cells were pre-incubated with 100 ug/ml human IgG at room temperature for 15 min. Subsequently, cells were incubated with a mixture (total volume 50 ul) of the following dye-labeled antibodies: CD5-PE, CD4-APC, CD8-Pacific Blue, CD25-PE-Cy7, as well as 7-Amino Actinomycin D (7AAD hereafter) for 40 minutes. Plates were washed twice, resuspended in 80 to 120 ul volumes and ran immediately in a BD LSRII flow cytometer to acquire 80% of the contents of each well. The sample files were analyzed using FlowJo software to calculate the percentages and numbers of cells that had undergone at least one cell division, according to their CFSE profile, by gating sequentially on activated, live CD4⁺ or CD8⁺ T cells (7AAD⁻, CD5⁺ CD25⁺ CD4⁺ or 7AAD⁻ CD5⁺ CD25⁺ CD8⁺, respectively). Mean values and standard deviations were calculated using Microsoft Excel software. Graphs were plotted using Microsoft Excel or Graphpad Prism.

[0432] Analysis of live CD4⁺ and CD8⁺ populations from Daudi cells or C4-2 cells treated with isolated T-cells revealed a significant increase in both the total number of cells and percent proliferating cells in the presence of Daudi cells displaying the target CD 19 antigen, but a lack of significant proliferation in the presence of C4-2 cells that lacked the CD19 antigen (Figure 12). Proliferation of CD8⁺ cells was very similar for bispecific molecules with the default IgG1 hinge (TSC100) as well as those with longer hinges (TSC166, TSC167, TSC168). Slightly higher CD8⁺ proliferation at low concentrations was observed with the bispecific with the shorter IgA2 upper hinge (TSC165). Similar, but more marked differences were observed with proliferation of CD4⁺ cells, wherein the molecule containing the shorter IgA2 hinge (TSC165) showed higher proliferation at most concentrations

than the standard IgG1 hinge (TSC100), and molecules with longer hinges (TSC166, TSC167, TSC168) showed lower proliferation.

[0433] To confirm the differential activity of the IgA2 hinge, a second proliferation experiment was carried out with a titration to lower protein concentrations (Figure 13), comparing the bispecific featuring the IgA2 hinge (TSC165) to two different production lots of a bispecific featuring the default IgG1 hinge (TSC127) and the bsc19x3 BiTE molecule. Similar to the previous experiment, less variation was observed with proliferation of CD8+ cells, with TSC165 showing comparable or greater induction of proliferation to bsc19x3, which in turn showed slightly higher or comparable proliferation to TSC127. Again, similar to the previous experiment, these trends repeated in a magnified fashion with the CD4+ cell proliferation, with TSC165 and bsc19x3 showing comparable proliferation, which in turn was noticeably greater than that of TSC127.

EXAMPLE 10

MODULATION OF REDIRECTED T-CELL CYTOTOXICITY BY POLYPEPTIDE HETERODIMERS WITH ALTERED HINGE SEQUENCES

[0434] To compare the effectiveness of changing hinge composition in bispecific polypeptide heterodimer molecules on inducing target-dependent T-cell cytotoxicity, five different bispecific molecules were compared in a chromium (^{51}Cr) release assay. Five different bispecific molecules (TSC100, TSC165, TSC166, TSC167 and TSC168, as described in Example 9) with a common anti-CD 19 binding domain (HD37), a common anti-CD3 binding domain (Cris7) and five different hinge constructs (IgG1 SCC-P hinge for TSC100 and TSC127, IgA2 hinge without the first Val linked to a human IgG1 core hinge for TSC165, IgG1 SSS-P hinge linked to a human IgG1 core hinge for TSC166, a portion of mutated IgG3 hinge linked to a human IgG1 core hinge for TSC167, and the IgM CH2 domain without the first Val linked to a human IgG1 core hinge for TSC168) were compared.

[0435] Daudi Burkitt's lymphoma cells (CD19+, RON-) were obtained from ATCC (Manassas, VA) and cultured according to the provided protocol. T cells were isolated using a Pan T-cell Isolation Kit II from Miltenyi Biotec (Bergisch Gladbach, Germany) using the manufacturer's protocol (see also Example 5 for more information).

[0436] Cytotoxicity was assessed by a ^{51}Cr release assay. Approximately 5×10^6 Daudi cells were treated with 0.3 mCi of ^{51}Cr and incubated for 75 minutes at 37°C. After 75 minutes, cells were washed 3 times with media (RPMI + 10% FBS) and resuspended in 11.5 mL of media. From this suspension, 50 μL was dispensed per well into 96 well U-bottom plates (approximately 20,000 cells/well). Concentrations of bispecific molecules ranging from 10 nM to 0.1 pM were added to the target (Daudi) cells, bringing the total volume to 100 μL /well. Target cells were incubated at room temperature for 15 minutes. Then 100 μL of isolated T-cells (approximately 200,000) were added to bring the T-cell to target cell ratio to 10:1. 50 μL of 0.8% NP-40 was added to a control well containing target cells, left for 15 minutes, then 100 μL of media was added to provide a total lysis control.

[0437] Plates were incubated for 4 hours, spun at 1500 rpm for 3 minutes, and 25 μL of supernatant was transferred from each well to the corresponding well of a 96-well Luma sample plate. Sample plates were allowed to air dry in a chemical safety hood for 18 hours, and then radioactivity was read on a Topcount scintillation counter using a standard protocol.

[0438] Analysis of cytotoxicity data showed strong T-cell directed cytotoxicity with the Daudi cells in the presence of T-cells and the anti-CD 19 directed bispecific molecules (TSC100 - TSC168), reaching maximal lysis at a concentration between 5 and 50 pM (Figure 14). Similar to the trends observed in Example 9, the bispecific molecule with a shorter IgA2 upper hinge region (TSC165) showed comparable or greater cytotoxicity to the molecule with the standard IgG1 upper hinge region (TSC100), whereas the molecules with longer upper hinge regions (TSC166, TSC167, TSC168) were less potent at inducing cytotoxicity.

EXAMPLE 11

BISPECIFIC HETERODIMERS WITH CH3-CH1 AND CH3-CK LINKER VARIATIONS

[0439] The following bispecific heterodimers with CH3-CH1 and CH3-CK linker variations were made:

Bispecific heterodimer TSC151 comprises single chain polypeptides TSC145 and TSC148. Single chain polypeptide TSC145 comprises from its amino to carboxyl terminus: humanized Cris7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human CH2 (ADCC/CDC null), human CH3, and human IgG1 CH1. The human CH3 and human IgG1 CH1 are linked by a linker having the sequence GGGSS (SEQ ID NO:847). The nucleotide and amino acid sequences of TSC145 are set forth in SEQ ID NOS:853 and 859, respectively. Single chain polypeptide TSC148 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human CH2 (ADCC/CDC null), human CH3, and human Ck (YAE). The human CH3 and human Ck (YAE) are linked with a linker having the sequence GGGSR (SEQ ID NO:850) in which R may alternatively be regarded as the first arginine of human Ck (YAE). The nucleotide and amino acid sequences of TSC148 are set forth in SEQ ID NOS:856 and 862, respectively.

Bispecific heterodimer TSC152 comprises single chain polypeptides TSC146 and TSC149. Single chain polypeptide TSC146 comprises from its amino to carboxyl terminus: humanized Cris7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human CH2 (ADCC/CDC null), human CH3, and human IgG1 CH1. The human CH3 and human IgG1 CH1 are linked by a linker having the sequence SYSPNS (SEQ ID NO:848). The nucleotide and amino acid sequences of TSC146 are set forth in SEQ ID NOS:854 and 860, respectively. Single chain polypeptide TSC149 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human CH2 (ADCC/CDC null), human CH3, and human Ck (YAE). The human CH3 and human Ck (YAE) are linked with a linker having the sequence SYSPNSR (SEQ ID NO:851) in which R may alternatively be regarded as the first arginine of human Ck (YAE). The nucleotide and amino acid sequences of TSC149 are set forth in SEQ ID NOS:857 and 863, respectively.

Bispecific heterodimer TSC153 comprises single chain polypeptides TSC147 and TSC150. Single chain polypeptide TSC147 comprises from its amino to carboxyl terminus: humanized Cris7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human CH2 (ADCC/CDC null), human CH3, and human IgG1 CH1. The human CH3 and human IgG1 CH1 are linked by a linker having the sequence SSLNTPNS (SEQ ID NO:849). The nucleotide and amino acid sequences of TSC147 are set forth in SEQ ID NOS:855 and 861, respectively. Single chain polypeptide TSC150 comprises from its amino to carboxyl terminus: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human CH2 (ADCC/CDC null), human CH3, and human Ck (YAE). The human CH3 and human Ck (YAE) are linked with a linker having the sequence SSLNTPNSR (SEQ ID NO:852) in which R may alternatively be regarded as the first arginine of human Ck (YAE). The nucleotide and amino acid sequences of TSC150 are set forth in SEQ ID NOS:858 and 864, respectively.

[0440] The above bispecific heterodimers were expressed according to Example 1. The following expression levels were obtained: 9.2 µg protein / ml of culture for TSC151, 11.2 µg protein / ml of culture for TSC152, and 14.7 µg protein / ml of culture for TSC153. In comparison, about 6 µg protein / ml of culture was obtained for heterodimers with a CH3-CH1 and CH3-Ck linker having the amino acid sequence KSR (SEQ ID NO:846).

[0441] The various embodiments described above can be combined to provide further embodiments. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments.

[0442] These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

SEQUENCE LISTING

[0443]

<110> Emergent Product Development Seattle, LLC Blankenship, John W. Tan, Philip

<120> HETERODIMER BINDING PROTEINS AND USES THEREOF

<130> 910180.422PC

<140> PCT

<141> 2010-12-29

<150> US 61/290,840

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agtaactttc attactatgt tatggactac tggggtcaag gaacctcagt caccgtctcc 360
tctgggggtg gaggctctgg tggcggtgga tccggcggag gtgggtcggg tggcggcgga 420
tctgacattg tgcaccacca atctccagct tctttggctg tgcctctagg tcagagagcc 480
accatctcct gcagagccag tgaagtgtt gaattatg tcaaaagttt aatgcagtgg 540
taccacaga aaccaggaca gccacccaaa ctctcatct ctgctgctag caacgtagaa 600
tctgggttcc ctgcagagtt tagtggcagt ggtctggga cagactttag cctcaacatc 660
catcctgttg aggaggtga tattgcaatg tatttctgtc agcaaagtag gaaggttcca 720
tggacgttcg gtggaggcac caagctggaa atcaagtcct cagagcgcctc caccaagggc 780
ccatcggtct tccoctggc accctcctcc aagagcacct ctgggggac agcggccctg 840
ggctgcctgg tcaaggacta cttcccgag ccggtgacgg tgtogtggaa ctacggcgcc 900
ctgaccagcg gcgtgcacac cttcccgct gtctacagt cctcaggact ctactcctc 960
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gacaaaactc acacatgccc accgtgccca tccggagcac ctgaactcct ggggtggaccg 1140
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caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1740
aagagcctct ccctgtctcc gggtaaatct agaactgtgg ctgcaccatc tgtcttcac 1800
ttcccgccat ctgatgagca gttgaaatct ggaactgcct ctgttgtgtg cctgctgaat 1860

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aacttctatc ccagagagcc caaagtacag tggaaagtg ataacgcctt ccaatcgggt 1920
aactcccagg agagtgtcac agagcaggac agcaaggaca gcacctacag cctcagcagc 1980
acctgacgc tgagcaaac agactacgag aaacacaaag tctacgcctg cgaagtccac 2040
catcagggcc tgagctcgcc cgtcacaag agcttcaaca ggggagag 2088

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<210> 2

<211> 696

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequence of 2E12CH1CH2CH3Ck (X0130)

<400> 2

Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Ser Val Ala Pro Ser Gln
 1 5 10 15
 Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Gly Tyr
 20 25 30
 Gly Val Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45
 Gly Met Ile Trp Gly Asp Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys
 50 55 60
 Ser Arg Leu Ser Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
 65 70 75 80
 Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala
 85 90 95
 Arg Asp Gly Tyr Ser Asn Phe His Tyr Tyr Val Met Asp Tyr Trp Gly
 100 105 110
 Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Val
 130 135 140
 Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
 145 150 155 160
 Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr Val Thr Ser
 165 170 175
 Leu Met Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
 180 185 190
 Ile Ser Ala Ala Ser Asn Val Glu Ser Gly Val Pro Ala Arg Phe Ser
 195 200 205
 Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His Pro Val Glu
 210 215 220
 Glu Asp Asp Ile Ala Met Tyr Phe Cys Gln Gln Ser Arg Lys Val Pro
 225 230 235 240
 Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ser Ser Ser Ala
 245 250 255
 Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
 260 265 270
 Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
 275 280 285
 Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
 290 295 300
 Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
 305 310 315 320
 Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
 325 330 335
 Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
 340 345 350
 Val Arg Thr Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
 355 360 365
 Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 370 375 380
 Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 385 390 395 400
 Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 405 410 415
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 420 425 430
 Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
 435 440 445
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 450 455 460
 Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 465 470 475 480
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 485 490 495
 Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 500 505 510
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 515 520 525
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 530 535 540
 Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
 545 550 555 560
 Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 565 570 575
 His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr
 580 585 590
 Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
 595 600 605
 Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
 610 615 620
 Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
 625 630 635 640
 Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
 645 650 655
 Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
 660 665 670
 Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
 675 680 685
 Thr Lys Ser Phe Asn Arg Gly Glu
 690 695

<210> 3

<211> 2142

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of CKCH2CH3CH1-H68-2E12 (X0168)

<400> 3

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aaggtggata acgcccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacagagaa 240
cacaagtctc acgcctcgga agtcacccat cagggcctga gctcgcccg cacaagagac 300
ttcaacaggg gagagcgtac ggagcccaaa tcttctgaca aaactcacac atgcccaccg 360
tgcccatccg gagcacctga actcctgggt ggaccgtcag tcttctctt ccccccacaa 420
cccaaggaca cctcatgat ctcccggacc cctgaggtca catgctggt ggtggacgtg 480
agccacgaag accctgaggt caagttcaac tggtagctgg acggcgtgga ggtgcataat 540
gccaaagaaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 600
accgtcctgc accaggaactg cgtgaatggc aaggagtaca agtgcaaggt ctccaacaaa 660
gcccctccag ccccactcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 720
caggtgtaca cctgcctccc atcccgggat gagctgacca agaaccaggt cagcctgacc 780
tgctgtgtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 840
ccggagaaca actacaagac caogcctccc gtgctggact ccgacggctc cttcttctc 900
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcattgctc 960
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gtgatgcatt agggctctga caaccactac acgcagaaga gcctctccct gtctccgggt 1020
aaatcttaga cctccaccaa gggcccactc gtcttccccc tggcaccctc ctccaagagc 1080
acctctgggg gcacagcgcc cctgggctgc ctggccaagg actacttccc cgagccggtg 1140
acgggtgctg ggaactcagg cgcctgacc agcggcgtgc acacttccc ggctgtccta 1200
cagtcctcag gactctactc cctcagcagc gtggtgacgg tgccctccag cagcttgggc 1260
accagacact acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 1320
gttaactcat tattcaacca agaagttcaa attccttga ccgaaagtt cagcccgaat 1380
tctcaggtgc agctgaagga gtcaggacct ggcagcgtgg cgcctccaca gagcctgtcc 1440
atcacatgca ccgtctcagg gttctcatta accggtatg gtgtaaaact ggttcgccag 1500
cctccaggaa agggctcggg gtggctggga atgatatgg gtgatggaag cacagactat 1560
aattcagctc tcaaatccag actatcgatc accaaggaca actccaagag ccaagttttc 1620
ttaaaaatga acagtctgca aactgatgac acagccagat actactgtgc tcgggatggg 1680
tataagtaact ttctactacta tgttatggac tactggggtc aaggaacctc agtcaccgtc 1740
tcctctgggg gtggaggtct tgggtggcgt ggatccggcg gaggtgggtc ggttggcggc 1800
ggatctgaca ttgtgtcac ccaatctcca gcttcttgg ctgtgtctct aggtcagaga 1860
gccaccatct cctgcagagc cagtgaaggt gttgaatatt atgtcacaa tttaatgcag 1920
tggtaccaac agaaaccagg acagccaccc aaactcctca tctctgtgc tagcaacgta 1980
gaatctgggg tcctgccagg gtttagtggc agtgggtctg ggacagactt tagcctcaac 2040
atccatcctg tggaggagga tgatattgca atgtattct gtcagcaaa taggaaggtt 2100
ccatggacgt tcggtggagg caccagctg gaaatcaagt ga 2142
```

<210> 4

<211> 713

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of CKCH2CH3CH1-H68-2E12 (X0168)

<400> 4

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Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
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Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95
Val Thr Lys Ser Phe Asn Arg Gly Glu Arg Thr Glu Pro Lys Ser Ser
100 105 110
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu Leu
115 120 125
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
130 135 140
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
145 150 155 160
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
165 170 175
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
180 185 190
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
195 200 205
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
210 215 220
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
225 230 235 240
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
245 250 255
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
260 265 270
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Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
275
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
290
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
305
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
325
Leu Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe
340
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
355
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
370
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
385
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
405
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
420
Ser Asn Thr Lys Val Asp Lys Lys Val Asn Ser Leu Phe Asn Gln Glu
435
Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln
450
Leu Lys Glu Ser Gly Pro Gly Ser Val Ala Pro Ser Gln Ser Leu Ser
465
Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Gly Tyr Gly Val Asn
485
Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu Gly Met Ile
500
Trp Gly Asp Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys Ser Arg Leu
515
Ser Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
530
Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala Arg Asp Gly
545
Tyr Ser Asn Phe His Tyr Tyr Val Met Asp Tyr Trp Gly Gln Gly Thr
565
Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser
580
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln
595
Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser
610
Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr Val Thr Ser Leu Met Gln
625
Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Ser Ala
645
Ala Ser Asn Val Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly
660
Ser Gly Thr Asp Phe Ser Leu Asn Ile His Pro Val Glu Glu Asp Asp
675
Ile Ala Met Tyr Phe Cys Gln Gln Ser Arg Lys Val Pro Trp Thr Phe
690
Gly Gly Gly Thr Lys Leu Glu Ile Lys
705
710

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<210> 5

<211> 1770

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of 2E12CH1CH2CH3 (X0112)

<400> 5

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ccaggaaagg gtctggagtg gctgggaatg atatgggggtg atggaagcac agactataat 180
tcagctctca aatccagact atcgatcacc aaggacaact ccaagagcca agttttctta 240
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agtaactttc attactatgt tatggactac tgggggtcaag gaacctcagt caccgtctcc 360
tctgggggtg gaggtctctg tggcggtgga tcggcgaggag gtgggtcggg tggcggcgga 420
tctgacattg tgctcaacca atctccagct tctttggctg tgtctctagg tcagagagcc 480
accatctcct gcagagccag tgaagtgtt gaataattat tcacaagttt aatgcagtg 540
taccaacaga aaccaggaca gccacccaaa ctctcatct ctgctgctag caacgtagaa 600
tctgggggtc ctgccagggt tagtggcagt gggctctggga cagactttag cctcaacatc 660
catcctgtgg agggagatga tattgcaatg tatttctgtc agcaaagtag gaaggttcca 720
tggacgttcg ttggaggcac caagctggaa atcaagtcct cgagcgccct caccaagggc 780
ccatcggtct tcccctggc accctcctcc aagagcacct ctggggggac agcggccctg 840
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gacaaaaact acacatgccc accgtgccca tcgggagcac ctgaactcct ggggtgaccg 1140
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gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgct tcccgtgctg 1620
gactccgacg gctcctctct cctctacagc aagctcacog tggacaagag caggtggcag 1680
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgag 1740
aagagcctct ccctgtctcc gggtaaatga 1770

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<210> 6

<211> 589

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of 2E12CH1CH2CH3 (X0112)

<400> 6

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Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Ser Val Ala Pro Ser Gln
 1          5          10          15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Gly Tyr
 20          25          30
Gly Val Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35          40          45
Gly Met Ile Trp Gly Asp Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys
 50          55          60
Ser Arg Leu Ser Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
 65          70          75          80
Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala
 85          90          95
Arg Asp Gly Tyr Ser Asn Phe His Tyr Tyr Val Met Asp Tyr Trp Gly
100          105          110
Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115          120          125
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
130          135          140
Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
145          150          155          160
Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr Val Thr Ser
165          170          175
Leu Met Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu

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180      185      190
Ile Ser Ala Ala Ser Asn Val Glu Ser Gly Val Pro Ala Arg Phe Ser
195      200      205
Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His Pro Val Glu
210      215      220
Glu Asp Asp Ile Ala Met Tyr Phe Cys Gln Gln Ser Arg Lys Val Pro
225      230      235      240
Trp Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Ser Ser Ser Ala
245      250      255
Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
260      265      270
Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
275      280      285
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
290      295      300
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
305      310      315      320
Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
325      330      335
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
340      345      350
Val Arg Thr Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
355      360      365
Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
370      375      380
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
385      390      395      400
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
405      410      415
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
420      425      430
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
435      440      445
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
450      455      460
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
465      470      475      480
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
485      490      495
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
500      505      510
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
515      520      525
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
530      535      540
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
545      550      555      560
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
565      570      575
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
580      585

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<210> 7

<211> 1026

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of CkCH2CH3 (X0113)

<400> 7

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aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa 240
cacaagtctc acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaagagagc 300
ttcaacaggg gagagcgtac ggagcccaaa tcttctgaca aaactcacac atgccaccg 360
tgcccatccg gagcacctga actcctgggt ggaccgtcag tcttctctt ccccccacaa 420
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 480
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accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa 660
gccctcccag ccccatcoga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 720
caggtgtaca ccctgcccc atcccgggat gagctgacca agaaccaggt cagcctgacc 780
tgcttggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 840
ccggagaaca actacaagac cagcctccc gtgctggact ccgacggctc cttcttctc 900
tacagcaagc tcacgtgga caagagcagg tggcagcagg ggaacgtott ctcatgctcc 960
gtgatgcatg aggtctctga caaccactac acgcagaaga gcctctccct gtctccgggt 1020
aatga 1026

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<210> 8

<211> 341

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of CkCH2CH3 (X0113)

<400> 8

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Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu Arg Thr Glu Pro Lys Ser Ser
 100          105          110
Asp Lys Thr Thr His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu Leu
 115          120          125
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
 130          135          140
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 145          150          155          160
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
 165          170          175
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
 180          185          190
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
 195          200          205
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 210          215          220
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 225          230          235          240
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
 245          250          255
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 260          265          270
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 275          280          285
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 290          295          300
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 305          310          315          320

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 325          330          335
Leu Ser Pro Gly Lys
 340

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<210> 9

<211> 1839

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of Ck(YAE) Fc (N297A) 2E12 (X0244)

<400> 9

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aaggtggata acgcccctcca atcgggtaac tcccaggaga gtgccacaga gcaggacagc 180
aaggacagca cctacagcct cagcagcgag ctgacgctga gcaaagcaga ctacgagaaa 240
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agccacgaag accctgaggt caagttcaac tggtagctgg acggcgtgga ggtgcataat 540
gccaagacaa agccgcggga ggagcagtag gccagcacgt accgtgtggt cagcgtcctc 600
accgtctctc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa 660
gccctcccag ccccctcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 720
caggtgtaca cctgcccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 780
tgctgtgtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 840
ccggagaaca actacaagac cagcctccc gtgctggact ccgacggctc cttcttctct 900
tacagcaagc tcacogtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 960
gtgatgcatt aggcctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1020
aactcattat tcaaccaaga agttcaaat cccttgaccg aaagttaacg cccgaattct 1080
caggtgcagc tgaaggagtc aggaacctggc agcgtggcgc cctcacagag cctgtccatc 1140
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ccaggaagg gtctggagtg gctgggaatg atatggggtg atggaagcac agactataat 1260
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tctgacattg tgctcaacca atctccagct tctttggctg tgtctctagg tcagagagcc 1560
accatctctc ccagagccag tgaaagtgtt gaataattat tcacaagttt aatgcagtgg 1620
taccaacaga aaccaggaca gccacccaaa ctctctatct ctgctgctag caactagaa 1680
tctggggtcc ctgccaggtt tagtggcagt ggggtctgga cagactttag cctcaacatc 1740
catcctgtgg aggaggtatg tattgcaatg tatctctctc agcaaatag gaaggttcca 1800
tggacgttcg gtggaggcac caagctggaa atcaagtga 1839

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<210> 10

<211> 612

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of Ck(YAE) Fc (N297A) 2E12 (X0244)

<400> 10

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1 5 10 15
 Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr
 20 25 30
 Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35 40 45
 Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr

50 55 60
 Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65 70 75 80
 His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85 90 95
 Val Thr Lys Ser Phe Asn Arg Gly Glu Arg Thr Glu Pro Lys Ser Ser
 100 105 110
 Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu Leu
 115 120 125
 Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
 130 135 140
 Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 145 150 155 160
 Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
 165 170 175
 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser
 180 185 190
 Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
 195 200 205
 Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 210 215 220
 Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 225 230 235 240
 Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
 245 250 255
 Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 260 265 270
 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 275 280 285
 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 290 295 300
 Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 305 310 315 320
 Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 325 330 335
 Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu
 340 345 350
 Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu Lys Glu Ser Gly
 355 360 365
 Pro Gly Ser Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val
 370 375 380
 Ser Gly Phe Ser Leu Thr Gly Tyr Gly Val Asn Trp Val Arg Gln Pro
 385 390 395 400
 Pro Gly Lys Gly Leu Glu Trp Leu Gly Met Ile Trp Gly Asp Gly Ser
 405 410 415
 Thr Asp Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Thr Lys Asp
 420 425 430
 Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp
 435 440 445
 Asp Thr Ala Arg Tyr Tyr Cys Ala Arg Asp Gly Tyr Ser Asn Phe His
 450 455 460
 Tyr Tyr Val Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
 465 470 475 480
 Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 485 490 495
 Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu
 500 505 510
 Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu
 515 520 525
 Ser Val Glu Tyr Tyr Val Thr Ser Leu Met Gln Trp Tyr Gln Gln Lys
 530 535 540
 Pro Gly Gln Pro Pro Lys Leu Leu Ile Ser Ala Ala Ser Asn Val Glu
 545 550 555 560
 Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
 565 570 575

Ser Leu Asn Ile His Pro Val Glu Glu Asp Asp Ile Ala Met Tyr Phe
 580 585 590
 Cys Gln Gln Ser Arg Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys
 595 600 605
 Leu Glu Ile Lys
 610

<210> 11

<211> 1770

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of 2E12 CH1 Fc (N297A) (X0245)

<400> 11

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ccaggaaagg gtctggagtg gctgggaatg atatgggttg atggaagcac agactataat 180
tcagctctca aatccagact atcgatcacc aaggacaact ccaagagcca agttttctta 240
aaaatgaaca gtctgcaaac tgatgacaca gccagatact actgtgctcg ggaagggttat 300
agtaacttct attactatgt tatggactac tgggggtcaag gaacctcagt caccgtctcc 360
tctgggggtg gaggctctgg tggcgggtgga tccggcggag gtgggtcggg tggcggcgga 420
tctgacattg tgctcaccac atctccagct tctttggctg tgtctctagg tcagagagcc 480
accatctcct ccagagccag tgaagtgtt gaattattg tcacaagttt aatgcagtgg 540
taccacaga aaccaggaca gccacccaaa ctctctatct ctgctgctag caacgtagaa 600
tctgggggtc ctgccaagggt tagtggcagt gggctctggga cagactttag cctcaacatc 660
catctgttgg agggagatga tattgcaatg tatttctgtc agcaaagtag gaaggttcca 720
tggacgttcg gtggaggcac caagctggaa atcaagtcct cgaagcctcc caccaggggc 780
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aatcacaagc ccagcaacac caagtggtgac aagaagtcc gtacggagcc caaatcttct 1080
gacaaaactc acacatgccc accgtgccc tccggagcac ctgaactcct ggggtggaccg 1140
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gtcacatgcg tgggtgggtg cgtgagccac gaagaccctg aggtcaagtt caactggtag 1260
gtggacggcg tggaggtgca taatgccaa acaaagccgc gggaggagca gtacggcagc 1320
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tacaagtgca aggtctccaa caaagccctc ccagccccc tccagaaaac catctccaaa 1440
gccaaagggc agcccccaga accacaggtg tacaccctgc ccccatcccg ggaaggagctg 1500
accaagaacc aggtcagcct gacctgctg gtcaaaggct tctatccaag cgacatcgcc 1560
gtggagtggtg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgctgctg 1620
gactccgagc gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1680
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1740
aagagcctct cctgtctccc gggtaaatga 1770

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<210> 12

<211> 589

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of 2E12 CH1 Fc (N297A) (X0245)

<400> 12

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 1             5             10             15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Gly Tyr
 20             25             30
Gly Val Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35             40             45

```

Gly Met Ile Trp Gly Asp Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys
 50 55 60
 Ser Arg Leu Ser Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
 65 70 75 80
 Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala
 85 90 95
 Arg Asp Gly Tyr Ser Asn Phe His Tyr Tyr Val Met Asp Tyr Trp Gly
 100 105 110
 Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
 130 135 140
 Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
 145 150 155 160
 Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr Val Thr Ser
 165 170 175
 Leu Met Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
 180 185 190
 Ile Ser Ala Ala Ser Asn Val Glu Ser Gly Val Pro Ala Arg Phe Ser
 195 200 205
 Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His Pro Val Glu
 210 215 220
 Glu Asp Asp Ile Ala Met Tyr Phe Cys Gln Gln Ser Arg Lys Val Pro
 225 230 235 240
 Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ser Ser Ser Ala
 245 250 255
 Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
 260 265 270
 Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
 275 280 285
 Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
 290 295 300
 Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
 305 310 315 320
 Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
 325 330 335
 Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
 340 345 350
 Val Arg Thr Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
 355 360 365
 Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 370 375 380
 Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 385 390 395 400
 Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 405 410 415
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 420 425 430
 Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu
 435 440 445
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 450 455 460
 Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 465 470 475 480
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 485 490 495
 Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 500 505 510
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 515 520 525
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 530 535 540
 Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
 545 550 555 560
 Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn

565 570 575
 His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 580 585

<210> 13

<211> 1749

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of P2C2 Ck(YAE) Fc (N297A) (X0246)

<400> 13

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tttctgcaga gaccaggaca atctcctcag ctccctgatct atctgatgtc catgcggtgaa 180
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cctggagaga cagtcaagat ctccctgcaag gcttctggtt ataccttcac agacttttca 480
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tatttttcta cctggtctgc ttactggggc caaggggactc tggctcactgt ctctgcctcg 720
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ctctacagca agctcacctg ggacaagagc aggtggcagc aggggaacgt cttctcatgc 1680
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ggtaaatga

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<210> 14

<211> 582

<212> PRT

<213> Artificial Sequence

<220>

<223> amino acid sequence of P2C2 Ck(YAE) Fc (N297A) (X0246)

<400> 14

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Asp Ile Val Met Ile Gln Asp Glu Leu Ser Asn Pro Val Ser Ser Gly
 1           5           10           15
Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asp Lys
 20           25           30
Glu Gly Lys Thr Tyr Leu Asn Trp Phe Leu Gln Arg Pro Gly Gln Ser
 35           40           45
Pro Gln Leu Leu Ile Tyr Leu Met Ser Met Arg Glu Ser Gly Val Ser
 50           55           60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Glu Ile

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65          70          75          80
Ser Arg Val Lys Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Leu
85
Val Glu Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100
Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln
115
Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr
130
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Phe Ser
145
Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly
160
Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Arg
175
Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu
190
Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Thr
205
Trp Ser Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ser
220
225 Ser Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
235
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe
250
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
265
Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser
280
Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu
295
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
310
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Arg Thr Glu Pro Lys Ser
325
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu
340
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
355
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
370
385 Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
390
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala
405
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
420
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
435
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
450
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
465
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
480
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
495
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
510
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
525
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
540
Ser Leu Ser Pro Gly Lys
555
565
570
575
580

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<210> 15

<211> 2583

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of 2E12 CH1 Fc (N297A) H68 2E12 (X0247)

<400> 15

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ccaggaaagg gtctggagtg gctgggaatg atatggggtg atggaagcac agactataat 180
tcagctctca aatccagact atcgatcacc aaggacaact ccaagagcca agttttctta 240
aaaatgaaca gtctgcaaac tgatgacaca gccagatact actgtgctcg ggaagggtat 300
agtaactttc attactatgt tatggactac tggggtcaag gaacctcagt cacogtctcc 360
tctgggggtg gaggctctgg tggcgggtgga tcggcgaggag gtgggtcggg tggcgcgga 420
tctgacattg tggcaccaca atctccagct tctttggctg tgtctctagg tcagagagcc 480
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taccacaga aaccaggaca gccaccacaa ctctcatct ctgtgctag caacgtagaa 600
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<210> 16

<211> 860

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of 2E12 CH1 Fc (N297A) H68 2E12 (X0247)

<400> 16

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 35 40 45
 Gly Met Ile Trp Gly Asp Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys
 50 55 60
 Ser Arg Leu Ser Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
 65 70 75 80
 Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala
 85 90 95
 Arg Asp Gly Tyr Ser Asn Phe His Tyr Tyr Val Met Asp Tyr Trp Gly
 100 105 110
 Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Ser Asp Ile Val
 130 135 140
 Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
 145 150 155 160
 Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr Val Thr Ser
 165 170 175
 Leu Met Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
 180 185 190
 Ile Ser Ala Ala Ser Asn Val Glu Ser Gly Val Pro Ala Arg Phe Ser
 195 200 205
 Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His Pro Val Glu
 210 215 220
 Glu Asp Asp Ile Ala Met Tyr Phe Cys Gln Gln Ser Arg Lys Val Pro
 225 230 235 240
 Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Ser Ser Ser Ala
 245 250 255
 Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
 260 265 270
 Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
 275 280 285
 Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
 290 295 300
 Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
 305 310 315 320
 Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
 325 330 335
 Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
 340 345 350
 Val Arg Thr Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
 355 360 365
 Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 370 375 380
 Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 385 390 395 400
 Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 405 410 415
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 420 425 430
 Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu
 435 440 445
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 450 455 460
 Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 465 470 475 480
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 485 490 495
 Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys

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<211> 2547

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of P2C2 CK(YAE) Fc (N297A) H68 A2 (X0248)

<400> 17

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<210> 18

<211> 848

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of P2C2 CK(YAE) Fc (N297A) H68 A2 (X0248)

<400> 18

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Glu Gly Lys Thr Tyr Leu Asn Trp Phe Leu Gln Arg Pro Gly Gln Ser
35           40           45
Pro Gln Leu Leu Ile Tyr Leu Met Ser Met Arg Glu Ser Gly Val Ser
50           55           60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Glu Ile
65           70           75           80
Ser Arg Val Lys Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Leu
85           90           95
Val Glu Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100          105          110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gln
115          120          125
Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr
130          135          140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Phe Ser

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180          185          190
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195          200          205
Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Thr
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260          265          270
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275          280          285
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290          295          300
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305          310          315          320
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325          330          335
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Arg Thr Glu Pro Lys Ser
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Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu
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385          390          395          400
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420          425          430
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
435          440          445
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Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
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485          490          495
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500          505          510
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
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Gly Tyr Thr Lys Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
660          665          670

Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
675          680          685
Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Leu Gly Tyr Gly
690          695          700
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725          730          735
Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro
740          745          750
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755          760          765
Gly Tyr Asn His Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro
770          775          780
Lys Leu Ile Ile Tyr Asp Val Asp His Arg Pro Ser Gly Ile Ser Asn
785          790          795          800
Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser
805          810          815
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<211> 2427

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of PDL2-CH1 Fc(N297A) H68 2E12 (X0249)

<400> 19

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acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 780
cagtcctcag gactctactc cctcagcagc gtggtgacgg tgcctccag cagcttgggc 840
accagacctt acctctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 900
gttcgtacgg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccatccgga 960
gcacctgaac tcctgggtgg accgtcagtc ttctcttcc ccccaaaacc caaggacacc 1020
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cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 1140
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caggactggc tgaatggcaa ggagtacaag tgcaaggtct ccaacaaagc cctcccagcc 1260
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ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaa 1440
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accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctcctg gatgcagag 1560
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tcagggttct cattaaccgg ctatggtgta aactgggttc gccagcctcc aggaaagggt 1800
ctggagtgcc tgggaatgat atggggtgat ggaagcacag actataattc agctctcaaa 1860

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tccagactat ccatcaccaa ggacaactcc aagagccaag ttttcttaaa aatgaacagt 1920
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tactatgtta tggactactg gggcgaagga acctcagtc ccgtctcctc tgggggtgga 2040
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gccaggttta gtggcagtg gtctgggaca gactttagcc tcaacatcca tctctggag 2340
gaggatgata ttgcaatgta tttctgtcag caaagtagga aggttccatg gacgttcggt 2400
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<210> 20

<211> 808

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of PDL2-CH1 Fc(N297A) H68 2E12 (X0249)

<400> 20

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Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile Glu His Gly
1      5      10      15
Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser His Val Asn
20      25      30
Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn Asp Thr Ser
35      40      45
Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu Pro Leu Gly
50      55      60
Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp Glu Gly Gln
65      70      75      80
Tyr Gln Cys Ile Ile Ile Tyr Gly Val Ala Trp Asp Tyr Lys Tyr Leu
85      90      95
Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr His Ile Leu
100     105     110
Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln Ala Thr Gly
115     120     125
Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val Pro Ala Asn
130     135     140
Thr Ser His Ser Arg Thr Pro Glu Gly Leu Tyr Gln Val Thr Ser Val
145     150     155     160
Leu Arg Leu Lys Pro Pro Pro Gly Arg Asn Phe Ser Cys Val Phe Trp
165     170     175
Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp Leu Gln Ser
180     185     190
Gln Met Glu Pro Arg Thr His Pro Thr Ser Ser Ala Ser Thr Lys Gly
195     200     205
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
210     215     220
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
225     230     235     240
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
245     250     255
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
260     265     270
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
275     280     285
Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Arg Thr Glu
290     295     300
Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ser Gly
305     310     315     320
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
325     330     335
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
340     345     350

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Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
355 360 365
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
370 375 380
Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
385 390 395 400
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
405 410 415
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
420 425 430
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
435 440 445
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
450 455 460
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
465 470 475 480
Tyr Lys Thr Thr Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
485 490 495
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
500 505 510
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
515 520 525
Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val
530 535 540
Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu
545 550 555 560
Lys Glu Ser Gly Pro Gly Ser Val Ala Pro Ser Gln Ser Leu Ser Ile
565 570 575
Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Gly Tyr Gly Val Asn Trp
580 585 590
Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu Gly Met Ile Trp
595 600 605
Gly Asp Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser
610 615 620
Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser
625 630 635 640
Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala Arg Asp Gly Tyr
645 650 655
Ser Asn Phe His Tyr Tyr Val Met Asp Tyr Trp Gly Gln Gly Thr Ser
660 665 670
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
675 680 685
Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
690 695 700
Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys
705 710 715 720
Arg Ala Ser Glu Ser Val Glu Tyr Tyr Val Thr Ser Leu Met Gln Trp
725 730 735
Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Ser Ala Ala
740 745 750
Ser Asn Val Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser
755 760 765
Gly Thr Asp Phe Ser Leu Asn Ile His Pro Val Glu Glu Asp Asp Ile
770 775 780
Ala Met Tyr Phe Cys Gln Gln Ser Arg Lys Val Pro Trp Thr Phe Gly
785 790 795 800
Gly Gly Thr Lys Leu Glu Ile Lys
805

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<210> 21

<211> 2331

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of monolL10 Ck(YAE) Fc(N297A) H68 3D1 (X0281)

<400> 21

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gatcagctgg acaacttggt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaaag ccttgctga gatgatccag ttttacctgg aggaggtgat gccccagct 240
gagaaacaaag acccagacat caaggcccat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacgg tgggtggatcc 360
ggcggttaaga gcaaggccgt ggagcagggt aagaatgcct ttaataagct ccaagagaaa 420
ggcatctaca aagccatgag tgagtttgac atcttcatca actacataga agcctacatt 480
acaatgaaga tacgaaactc gagcactgtg gctgcaccat ctgtcttcat cttcccgcca 540
tctgagtgaag agttgaaatc tggaaactgcc tctgttgtgt gcctgctgaa ttacttctat 600
cccagagagg ccaaagtaca gtggaagggt gataacgccc tccaatcggy taactcccag 660
gagagtgcga cagagcagga cagcaaggac agcacctaca gcctcagcag cgagtgcagc 720
ctgagcaaaag cagactacga gaacacacaaa gtctacgcct gcgaagtcac ccacagggc 780
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagc gtacggagcc caactcttct 840
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tcagtcttcc tcttcccccc aaaacccaag gacacccctc tgatctcccg gacccctgag 960
gtcacatgcg tgggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtag 1020
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gccaaaggcg agccccgaga accacagggt tacaccctgc ccccatcccg ggatgagctg 1260
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatccaag cgacatcgcc 1320
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tccgtgctg 1380
gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1440
caggggaagc tctctcagc cctcgtgatg catgaggctc tgcacaacca ctacacgag 1500
aagagcctct ccctgtctcc gggttaactc ttattcaacc aagaagtcca aattcccttg 1560
accgaagtt acagcccgaa tctcaggtc cagctgcagc agtctgggcc tgagctggtg 1620
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atctattact gtgcaagagc ggcctggtat atggactact ggggtcaagg aacctcagtc 1920
accgtctcct cagggggtgg aggcctcgtg ggcgggtggc ctggcggagg tggatccgg 1980
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aactacttgg cttggtacca gcagaaacca gggcagctct ctaactgtct gatctactgg 2160
gcatacacta gggaaatctg ggtccctgat cgttcacag gcagtgagtc tgggacagat 2220
ttcactctca ccacagcag tgtgcaggct gaagacctgg cagtttatta ctgcacgcaa 2280
tcttataatc ttacacgct cggagggggg accaagctgg aaataaaata a 2331

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<210> 22

<211> 776

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of monolL10 Ck(YAE) Fc(N297A) H68 3D1 (X0281)

<400> 22

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Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1          5          10          15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20          25          30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu
35          40          45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50          55          60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65          70          75          80

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Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
 85 90 95
 Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
 100 105 110
 Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu
 115 120 125
 Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys
 130 135 140
 Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile
 145 150 155 160
 Thr Met Lys Ile Arg Asn Ser Ser Thr Val Ala Ala Pro Ser Val Phe
 165 170 175
 Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
 180 185 190
 Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
 195 200 205
 Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr
 210 215 220
 Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr
 225 230 235 240
 Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
 245 250 255
 Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
 260 265 270
 Glu Arg Thr Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
 275 280 285
 Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 290 295 300
 Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 305 310 315 320
 Val Thr Cys Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 325 330 335
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 340 345 350
 Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu
 355 360 365
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 370 375 380
 Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 385 390 395 400
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 405 410 415
 Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 420 425 430
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 435 440 445
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 450 455 460
 Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
 465 470 475 480
 Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 485 490 495
 His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe
 500 505 510
 Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser
 515 520 525
 Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Glu
 530 535 540
 Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
 545 550 555 560
 Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
 565 570 575
 Gly Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe
 580 585 590
 Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 595 600 605
 Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr Cys
 610 615 620
 Ala Arg Ala Ala Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
 625 630 635 640
 Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
 645 650 655
 Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Ser Gln Ser Pro
 660 665 670
 Ser Ser Leu Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys
 675 680 685
 Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu Ala
 690 695 700
 Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp
 705 710 715 720
 Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly
 725 730 735
 Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp
 740 745 750
 Leu Ala Val Tyr Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr Thr Phe Gly
 755 760 765
 Gly Gly Thr Lys Leu Glu Ile Lys
 770 775

<210> 23

<211> 2330

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence of monoll10CkwFc (N297A) H68 3D1 (X0282)

<400> 23

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gatcagctgg acaacttggt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
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acaatgaaga tacgaaaact gagcactgtg gctgcacat ctgtcttcat cttcccgcga 540
tctgatgagc agttgaaatc tggaaactgc tctgttgtgt gctgtgtgaa taacttctat 600
cccagagagg ccaaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 660
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 720
ctgagcaaaag cagactacga gaaacacaaa gtctacgcct gcgaagtac ccatacgggc 780
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acgtaccgtg tggtagcgt cctcacccgt ctgcacccag actggctgaa tggcaaggag 1140
tacaagtgtca aggtctccaa caaagccctc ccagccccc tgcagaaaac catctccaaa 1200
gccaaaggcc agccccgaga accacaggtg tacaccctgc ccccatcccg ggtatgagct 1260
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gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 1380
gactccgagc gctccttctt cctctacagc aagctcacgg tggacaagag caggtggcag 1440
caggggaaag tcttctcatg ctccgtgatg catgaggctc tgcaacaaca ctacacgcag 1500
aagagcctct cctgtctcc gggttaactc ttattcaacc aagaagttca aattccctg 1560
accgaaagtt acagcccga ttctcaggtc cagctgcagc agtctgggcc tgagctgggt 1620
aggcctgggg aatcagtgaa gatttccctg aagggttccg gctacacatt cactgattat 1680
gctatacagt ggtgaagca gagtcatgca aagagtctag agtggattgg agttattaat 1740
atttactatg ataatacaaa ctacaaccag aagtttaagg gcaaggccac aatgactgta 1800

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gacaaatcct ccagcacagc ctatatggaa cttgccagat tgacatctga ggattctgcc 1860
atctattact gtgcaagagc ggcctgggtat atggactact ggggtcaagg aacctcagtc 1920
accgtctcct caggggtggt aggtctctgt ggcggtggct ctggcgaggg tggatccggt 1980
ggcgggcgat ctgacattgt gctgtcacag tctccatcct ccctggctgt gtcagcagga 2040
gagaaggtca ctatgagctg caaatccagt cagagtctgc tcaacagtga aacccgagag 2100
aactacttgg cttggtacca gcagaaacca gggcagctct ctaaaactgct gatctactgg 2160
gcatccacta ggggaatctgg ggtccctgat cgcttcacag gcagtgatc tgggacagat 2220
ttcactctca ccatcagcag tgtgcaggct gaagacctgg cagtttatta ctgcacgcaa 2280
tcttataatc tttacacggt cgaggggggg accaagctgg aaataaaata 2330

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<210> 24

<211> 776

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of monoll10CkwFc (N297A) H68 3D1 (X0282)

<400> 24

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1      5      10      15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20      25      30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu
35      40      45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50      55      60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65      70      75      80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85      90      95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100     105     110
Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu
115     120     125
Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys
130     135     140
Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile
145     150     155     160
Thr Met Lys Ile Arg Asn Ser Ser Thr Val Ala Ala Pro Ser Val Phe
165     170     175
Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
180     185     190
Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
195     200     205
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
210     215     220
Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
225     230     235     240
Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
245     250     255
Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
260     265     270
Glu Arg Thr Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
275     280     285
Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
290     295     300
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
305     310     315     320
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
325     330     335
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
340     345     350
Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu

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      355      360      365
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
370      375      380
Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
385      390      395      400
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
405      410      415
Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
420      425      430
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
435      440      445
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
450      455      460
Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
465      470      475      480
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
485      490      495
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe
500      505      510
Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser
515      520      525
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Glu
530      535      540
Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
545      550      555      560
Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
565      570      575
Gly Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe
580      585      590
Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
595      600      605
Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr Cys
610      615      620
Ala Arg Ala Ala Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
625      630      635      640
Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
645      650      655
Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Ser Gln Ser Pro
660      665      670
Ser Ser Leu Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys
675      680      685
Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu Ala
690      695      700
Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp
705      710      715      720
Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly
725      730      735
Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp
740      745      750
Leu Ala Val Tyr Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr Thr Phe Gly
755      760      765
Gly Gly Thr Lys Leu Glu Ile Lys
770      775

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<210> 25

<211> 1806

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for ORN116 comprising MET021 (anti-c-Met) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 25

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atggaagcac cagcgcagct tctcttctc ctgctactct ggctcccaga taccaccggt 60
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtccac 120
atcacttgtc ggccaagtca gagcattagg aactatthaa attggtatca gcaggaacca 180
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgc aaagtgg ggtcccacatca 240
aggttcagtg gcagtggtgc tgggacagac ttcatctca coactcagcag tctgcagcct 300
gaagattttg caacttacta ctgtcaacag agttacgtta ccccgctcac tttcggcgga 360
gggaccaagg tggagatcaa agggggtgga ggctctggtg gcggtggctc tggcgagggt 420
ggatccgggtg gcggcggtc tgaagttcaa ttggttagagt ctggtggcgg tctgtttcag 480
cctggtggtt ctttactgtc ttcttgccgt gcttcoggat tcaactttctc taagtacgat 540
atgctttggg ttccccaagc tcttggtaaa ggtttggagt gggtttctta tatctatcct 600
tctggtggcc ttactgagta tgctgactcc gttaaaggct gcttcactat ctctagagac 660
aactctaaga atactctcta cttgcagatg aacagcttaa gggctgagga cagggcctg 720
tattactgtg cgagacgggc tccccgggtc ctttcttttg atatctgggg ccaagggaca 780
atggtcaccg tctcctcgag cagacccaaa tcttctgaca aaactcacac atgcccaccg 840
tgccatccg gagcacctga actcctgggt ggaccgtcag tcttctctt ccccccacaa 900
cccaaggaca cctcatgat ctcccgacc cctgaggtca catgctggtt ggtggacgtg 960
agccacgaag accctgaggt caagttaaac tggtagctgg acggcgtgga ggtgcataat 1020
gccaaagaca agcccgggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 1080
accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa 1140
gccctcccag ccccatcgca gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 1200
caggtgtaca cctgcccc atccccggat gagctgacca agaaccaggt cagcctgacc 1260
tgctgtgtca aaggctctta tccaaagcac atgcgcgtgg agtgggagag caatgggcag 1320
ccggagaaca cctacaagac cagcctccc gtgctggact ccgacggctc cttctctc 1380
tacagcaagc tcacccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1440
gtgatgcatg aggcctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1500
aaatctagag cctccaccaa gggcccatcg gtcttcccc tggcaccctc ctccaagagc 1560
acctctgggg gcacagcggc cctgggctgc ctggtaacag actactcccc cgagccgggtg 1620
acgggtgtcgt gggaactcagg cgcctgacc agcggcgtgc acacttccc ggctgtccta 1680
cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 1740
accagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 1800
gtttga 1806

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<210> 26

<211> 1797

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for ORN145 comprising : 4C04 (anti-RON) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 26

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atggaagcac cagcgcagct tctcttctc ctgctactct ggctcccaga taccaccggt 60
gacattcaga tgacccagtc tccatcctcc ctgtctgcat ctgtgggaga aagtgccac 120
atcacatgcc tggcaagtca gaccattggt acatggttag catgggtatca gcagaacca 180
gggaaatctc ctacagctcct gatctatgct gcaaccagct tggcagatgg ggtcccacatca 240
aggttcagtg ctatgtggtc tggcacaata tttctttca agatcgacag cctacagctc 300
gaagattttg taagtattta ctgtcaacaa cttacaata ctccgtggac gttcgggtgga 360
ggcaccaagc tggaaatcaa aggtggcggt ggctctggcg gaggtggatc cgtggcggtc 420
ggctctcaga tccagctgca gcagctctgga cctgagctgg tgaagcctgg gacttcagt 480
aagatatact gcaaggcttc tgactacaca ctactgact tctatatgaa ctgggtgagg 540
cagaagcctg gacagggact tgagtggatt gggaggattt atcctggaac cgataaaaact 600
agatacaatg agaaattcag ggacaaggcc atactgacog tggacacgtc ctccagcaca 660
gcctacatgc agctcagcag cctgacatca gaggacactg ctgtctattt ctgtgcaaga 720
tccgctact atggttaacta cgttgctatg gactactggg gtcaaggaaac ctacgtcacc 780
gtctcctcga gcgagcccaa atcttctgac aaaaactcaca catgcccacc gtgcccacc 840
ggagcaccctg aactcctggg tggacogtca gtcttctct tccccccaaa acccaaggac 900
accctcatga tctcccgggc cctgaggtc acatgcgtgg ttgtggacgt gagccacgaa 960
gacccagagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 1020
aagcccgagg agggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg 1080
caccaggact ggctgaatgc caaggagtac aagtgcaagg tctccaacaa agccctccca 1140
gccccatcg agaaaaccaa ctccaaagcc aaagggcagc ccgagagaac acaggtgtac 1200
accctgcccc catccggga tgagctgacc aagaaccagg tcagcctgac ctgctctggtc 1260

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aaaggcttct atccaagcga catcgccgtg gagtgggaga gcaatgggca gccggagaa 1320
aactacaaga ccacgcctcc cgtgctggac tccagcgggt ccttcttctc ctacagcaag 1380
ctcaccgtgg acaagagcag gtggcagcag gggaaagctc tctcatgctc cgtgatgcat 1440
gaggtctctg cacaaccata cagcagaag agcctctccc tgtctccggg taaatctaga 1500
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cactctggg 1560
ggcacagcgg cctgggctg ctggtcaag gactacttcc ccgagccggt gacggtgtcg 1620
tggaactcag gcgcctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 1680
ggactctact cctcagcag cgtggtgacc gtgccctcca gcagcttggg caaccagacc 1740
tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agtttga 1797

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<210> 27

<211> 1818

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for ORN146 comprising : 4C04 (anti-RON) scFv, human IgG1 SCC-P hinge, human CH2, human CH3, and human Ck (YAE)

<400> 27

```

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gacattcaga tgaccagctc tccctgcctcc cagtctgcat ctctgggaga aagtgtcacc 120
atcacatgcc tggcaagtca gaccattggt acatggttag catggtatca gcagaaacca 180
gggaaatctc ctacgctcct gatttatgct gcaaccagct tggcagatgg ggtcccatca 240
aggttcagtg ctagtggatc tggcacaata tttctttca agatcgacag cctacagtct 300
gaagattttg taagttatta ctgtcaacaa ctttacaata ctccgtggac gttcgggtgga 360
ggcaccagc tggaaatcaa aggtggcggg ggctctggcg gaggtggatc cgggtggcggc 420
ggctctcaga ctcagctgca gcagtctgga cctgagctgg tgaagcctgg gacttcagtg 480
aagatatcct gcaaggcttc tgactacaca ctcactgact totatatgaa ctgggtgagg 540
cagaagcctg aacgtggact tgagtggatt gggaggattt atcctggaac cgataaaact 600
agatacaatg agaatttcag ggacaaggcc atactgaccg tggacacgtc ctccagcaca 660
gcctacatgc agctcagcag cctgacatca gaggacactg ctgtctattt ctgtgcaaga 720
tccgcctact atggttaacta cgttgctatg gactactggg gtcaaggaaac ctcagtcacc 780
gtctcctcga gcgagcccaa atcttctgac aaaactcaca catgccacc ccgtcccatcc 840
ggagcactcg aactcctggg tggacogtca gtcttctct tcccccaaa acccaaggac 900
accctcatga tctcccgacc cctgaggtc acatgcgtgg tgggtggact gagccacgaa 960
gacctgagg tcaagttcaa ctggtaactg gacggcgtgg aggtgcataa tgccaagaca 1020
aagcccgagg agggagctg caacagcagc taccgtgtgg tcagcgtcct caccgtcctg 1080
caccagagct ggctgaatgg caaggagtac aagtgcaggg tctccaacaa agccctccca 1140
gccccatcg agaaaaccat ctccaaagcc aaagggcagc ccgagaacc acaggtgtac 1200
accctgcccc catcccgagg tgagctgacc aagaaccagg tcagcctgac ctgcctggtc 1260
aaaggtctct atccaagcga catcgccgtg gagtgggaga gcaatgggca gccggagaa 1320
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttct ctacagcaag 1380
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gaggtcctcg acaaccatc caccgagaag agcctctccc tgtctcggg taaatctaga 1500
actgtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga 1560
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aagtggtgta aggcctccca atcgggtaac tccagggaga gtgccacaga gcaggacagc 1680
aaggacagca cctacagcct cagcagcgag ctgacgtgga gcaagcaga ctacagagaa 1740
cacaagctct acgcctcgga agtcacccat cagggcctga gctcggccgt cacaagagac 1800
ttcaacaggg gagagtga 1818

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<210> 28

<211> 1806

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for ORN148 comprising : 11H09 (anti-RON) scFv, human IgG1 SCC-P hinge, human CH2, human CH3, and human Ck(YAE)

<400> 28

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gacatccaga tgaccagctc tccatcctcc ttatctgcct ctctgggaga aagagtca 120
ctcacttgct gggcaagtca ggacattggt agtagcttaa gctggtctca gcaggaacca 180
gatggtaact taaacgcct gatctactcc acatccagtt tagattctgg tgtcccaaaa 240
aggttcagtg gcagtaggtc ggggtcagat tattctctca ccatcagcag ccttgagtct 300
gaagattttg tagactatta ctgtctacaa tatgctagtt ctccgtggac gttcgggtgga 360
ggcaccaagc tggaaatcaa aggtggcggg ggctctggcg gaggtggatc cgggtggcggc 420
ggctctcagg tccagcttca gcagtctggg gctgaactgg caaaacctgg ggctcagtg 480
aagatgtcct gcaagctctc tgggtacacc tttactagot actggataca ctgggtaaaa 540
gagaggcctg gacagggtct ggaatggatt ggaatacttt atcctaccac tggttatact 600
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ctacggccct ggtacttcca tgtctggggc gcagggacca cggtcaccgt ctctcgagc 780
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aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag 1020
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aagagcaggt ggcagcaggg gaacgtcttc tcatgctcg tgatgatga ggtctgca 1440
aaccactaca cgcagaagag cctctccctg tctccgggta aatctagaac tgtggctgca 1500
ccatctgtct tcatcttccc gccatctgat gaggagttga aatctggaac tgctctgtt 1560
gtgtgcctgc tgaattactt ctatcccaga gaggccaaag tacagtggaa ggtggataac 1620
gccctccaat cgggttaactc caaggagagt gccacagagc aggcagcaga ggacagacc 1680
tacagcctca gcagcagct gacgtgagc aaagcagact acgagaaaca caaagtctac 1740
gcctgcgaag tcacccatca gggcctgagc tgcgccgtca caaagagott caacagggga 1800
gagtga 1806

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<210> 29

<211> 581

<212> PRT

<213> Artificial Sequence

<220>

<223> ORN116 mature protein comprising MET021 (anti-c-Met) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 29

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 Ser Ile Arg Asn Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Glu Pro Gly Lys Ala Pro Lys Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Ile Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Val Thr Pro Leu
 85 90 95
 Thr Phe Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Ser
 100 105 110
 Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Glu
 115 120 125
 Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
 130 135 140
 Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Tyr Asp
 145 150 155 160
 Met Leu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
 165 170 175
 Tyr Ile Tyr Pro Ser Gly Gly Leu Thr Glu Tyr Ala Asp Ser Val Lys

180 185 190
 Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
 195 200 205
 Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
 210 215 220
 Arg Arg Ala Pro Arg Ser Leu Ser Phe Asp Ile Trp Gly Gln Gly Thr
 225 230 235 240
 Met Val Thr Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
 245 250 255
 Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro
 260 265 270
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 275 280 285
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 290 295 300
 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 305 310 315 320
 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
 325 330 335
 Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 340 345 350
 Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 355 360 365
 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 370 375 380
 Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
 385 390 395 400
 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 405 410 415
 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 420 425 430
 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 435 440 445
 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 450 455 460
 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 465 470 475 480
 Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
 485 490 495
 Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
 500 505 510
 Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
 515 520 525
 Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 530 535 540
 Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
 545 550 555 560
 Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
 565 570 575
 Val Asp Lys Lys Val
 580

<210> 30

<211> 578

<212> PRT

<213> Artificial Sequence

<220>

<223> ORN145 mature protein comprising : 4C04 (anti-RON) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 30

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly

```

1      5      10      15
Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20      25      30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
35      40      45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Ala
50      55      60
Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Asp Ser Leu Gln Ser
65      70      75      80
Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Asn Thr Pro Trp
85      90      95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
100      105      110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Gln Leu Gln Gln
115      120      125
Ser Gly Pro Glu Leu Val Lys Pro Gly Thr Ser Val Lys Ile Ser Cys
130      135      140
Lys Ala Ser Asp Tyr Thr Leu Thr Asp Phe Tyr Met Asn Trp Val Arg
145      150      155      160
Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly
165      170      175
Thr Asp Lys Thr Arg Tyr Asn Glu Lys Phe Arg Asp Lys Ala Ile Leu
180      185      190
Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
195      200      205
Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Ser Ala Tyr Tyr
210      215      220
Gly Asn Tyr Val Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
225      230      235      240
Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
245      250      255
Pro Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
260      265      270
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
275      280      285
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
290      295      300
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
305      310      315      320
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
325      330      335
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
340      345      350
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
355      360      365
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
370      375      380
Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
385      390      395      400
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
405      410      415
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
420      425      430
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
435      440      445
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
450      455      460
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg
465      470      475      480
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
485      490      495
Ser Thr Ser Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
500      505      510
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
515      520      525

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
530      535      540
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
545      550      555      560
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
565      570      575

Lys Val

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<210> 31

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> ORN146 mature protein comprising : 4C04 (anti-RON) scFv, human IgG1 SCC-P hinge, human CH2, human CH3, and human Ck(YAE)

<400> 31

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Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly
1      5      10      15
Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20      25      30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Ile
35      40      45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Ala
50      55      60
Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Asp Ser Leu Gln Ser
65      70      75      80
Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Asn Thr Pro Trp
85      90      95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
100      105      110      115
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Gln Leu Gln Gln
120      125
Ser Gly Pro Glu Leu Val Lys Pro Gly Thr Ser Val Lys Ile Ser Cys
130      135      140
Lys Ala Ser Asp Tyr Thr Leu Thr Asp Phe Tyr Met Asn Trp Val Arg
145      150      155      160
Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly
165      170      175
Thr Asp Lys Thr Arg Tyr Asn Glu Lys Phe Arg Asp Lys Ala Ile Leu
180      185      190
Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
195      200      205
Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Ser Ala Tyr Tyr
210      215      220
Gly Asn Tyr Val Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
225      230      235      240
Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
245      250      255
Pro Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
260      265      270
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
275      280      285
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
290      295      300
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
305      310      315      320
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
325      330      335
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
340      345      350

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
355      360      365
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
370      375      380
Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
385      390      395      400
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
405      410      415
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
420      425      430
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
435      440      445
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
450      455      460
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg
465      470      475      480
Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
485      490      495
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr
500      505      510
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
515      520      525
Gly Asn Ser Ser Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
530      535      540
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
545      550      555      560
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
565      570      575
Val Thr Lys Ser Phe Asn Arg Gly Glu
580      585

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<210> 32

<211> 581

<212> PRT

<213> Artificial Sequence

<220>

<223> ORN148 mature protein comprising : 11H09 (anti-RON) scFv, human IgG1 SCC-P hinge, human CH2, human CH3, and human Ck(YAE)

<400> 32

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 1 5 10 15
 Glu Arg Val Ser Leu Thr Cys Arg Ala Ser Gln Asp Ile Gly Ser Ser
 20 25 30
 Leu Ser Trp Leu Gln Gln Glu Pro Asp Gly Thr Ile Lys Arg Leu Ile
 35 40 45
 Tyr Ser Thr Ser Ser Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
 50 55 60
 Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
 65 70 75 80
 Glu Asp Phe Val Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Ser Pro Trp
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
 100 105 110
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln
 115 120 125
 Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val Lys Met Ser Cys
 130 135 140
 Lys Ser Ser Gly Tyr Thr Phe Thr Ser Tyr Trp Ile His Trp Val Lys
 145 150 155 160
 Glu Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Pro Thr
 165 170 175

Thr Gly Tyr Thr Glu Ser Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu
 180 185 190
 Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
 195 200 205
 Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Phe Leu Arg Pro Trp
 210 215 220
 Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ser
 225 230 235 240
 Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ser
 245 250 255
 Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 260 265 270
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 275 280 285
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 290 295 300
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 305 310 315 320
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 325 330 335
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 340 345 350
 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 355 360 365
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 370 375 380
 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 385 390 395 400
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 405 410 415
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 420 425 430
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 435 440 445
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 450 455 460
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr Val Ala Ala
 465 470 475 480
 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 485 490 495
 Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala
 500 505 510
 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 515 520 525
 Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 530 535 540
 Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 545 550 555 560
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 565 570 575
 Phe Asn Arg Gly Glu
 580

<210> 33

<211> 1809

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for ORN160 comprising : 5D5 (anti-c-Met) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 33

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gacagatctt ccaacacagc ctacatgctg ctacagcagc tgacatctgc tgactctgca 720
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aaagtttga 1809

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<210> 34

<211> 1821

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC001 comprising : HD37 (anti-CD39), human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 34

```

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ttccccgctg tccctacagt ctcaggactc tactccctca gcagcgtggt gaccgtgccc 1740
tccagcagct tgggacccca gacctacatc tgcaacgtga atcacaagcc cagcaacacc 1800
aaggtggaca agaaagtttg a 1821

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<210> 35

<211> 1800

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC002 comprising : 2H7 (anti-CD20) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 35

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gatgctgcca cttattactg ccagcagtg agttttaacc caccacagtt cgggtgctggg 360
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gctagccagg cttatctaca gcagctctgg gctgagtcgg tgaggcctgg ggctcagtg 480
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```

<210> 36

<211> 1851

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC003 comprising : G19-4 (anti-CD3) scFv, altered human IgA1 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 36

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catggaaaga accttgagtg gattggactt attaatccat acaaaaggtct tactacctac 240
aaccagaaat tcaagggcaa ggcacatta actgtagaca agtcatccag cacagcctac 300
atggagctcc tcagctctgac atctgaagac tctgcagctc attactgtgc aagatctggg 360
tactatgggt actcggactg gtaactcgat gtctggggcg cagggaccac ggtcacctgc 420
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catcaggggc tgagctcgcc cgtcacaaag agcttcaaca ggggagagtg a 1851

```

<210> 37

<211> 1812

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC004 comprising : G19-4 (anti-CD3) scFv, altered human IgA2 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 37

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gaggtccagc tgcacacgtc tggacctgaa ctggtgaagc ctggagcttc aatgaagatt 120
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aagaccacgc ctccgtgctg ggactccgac ggtcctctt tctctacag caagctcacc 1380

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aggggagagt ga 1812

```

<210> 38

<211> 1842

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC005 comprising : G19-4 (anti-CD3) scFv, altered human IgG3 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 38

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ctgagcaaa cagactacga gaaacacaaa gtctacgctc gcgaagtcac ccatcagggc 1800
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt ga 1842

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<210> 39

<211> 1899

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC006 comprising : G19-4 (anti-CD3) scFv, altered human IgD hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 39

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atggaagcac cagcgcagct tctcttctc ctgctactct ggctcccaga taccaccggt 60
gaggtccagc tgcaacagtc tggacctgaa ctggtgaagc ctggagcttc aatgaagatt 120

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agcaaaagcag actaogagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 1860
agctcgcccc tcacaaagag ctccaacagg ggagagtga 1899

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<210> 40

<211> 1842

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC007 comprising : G19-4 (anti-CD3) scFv, altered human IgG1 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck (YAE)

<400> 40

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atggaagcac cagcgcagct tctcttctc ctgctactct ggctcccaga taccaccggt 60
gaggtccagc tgcaacagtc tggacctgaa ctggtgaagc ctggagcttc aatgaagatt 120
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```

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ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt ga 1842

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<210> 41

<211> 2115

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC008 comprising : G19-4 (anti-CD3) scFv, altered human IgE CH2 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck (YAE)

<400> 41

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catgaaaaga accttgagtg gattggactt attaatccat acaaaggctc tactacctac 240
aaccagaaat tcaagggcaa ggccacatta actgtagaca agtcatccag cacagcctac 300
atggagctcc tcagtctgac atctgaagac tctgcagctt attactgtgc aagatctggg 360
tactatggtg actcggactg gtacttcgat gtctggggcg cagggaccac ggtcacogtc 420
tcaagcggtg gcggagggtc tgggggtggc ggtccggag gtggtggctc tgcacaagac 480
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aacaggggag agtga 2115

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<210> 42

<211> 2136

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC009 comprising : G19-4 (anti-CD3) scFv, altered human IgM CH2 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck (YAE)

<400> 42

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atggaagcac cagcgcagct tctcttctc ctgctactct ggctcccaga taccaccggt 60
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tcgcccgtca caaagagctt caacagggga gagtga 2136

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<210> 43

<211> 1839

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC010 comprising : HD37 (anti-CD19) scFv, altered human IgA1 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 43

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atgaactggg tgaagcagag gcctggcag ggtcttgagt ggattggaca gatttggcct 600
ggagatgggt atactaacta caatggaaa ttcaagggtt aagccactct gactgcagac 660
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tattttctgt caagacggga gactacgacg gtaggccgtt attactatgc tatggactac 780
tggggccaag gaacctcagt caccgtctcc tcgagccctt caactccacc taccocatct 840

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cacaagccca gcaacaccaa ggtggacaag aaagtttga 1839

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<210> 44

<211> 1800

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC011 comprising : HD37 (anti-CD19) scFv, altered human IgA2 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 44

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<210> 45

<211> 1830

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC012 comprising : HD37 (anti-CD19) scFv, altered human IgG1 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 45

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accgtgccct ccagcagctt gggcacccag acctacatct gcaacgtgaa tcacaagccc 1800
agcaacacca aggtggacaa gaaagtttga 1830

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<210> 46

<211> 1830

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC013 comprising : HD37 (anti-CD19) scFv, altered human IgG3 hinge, human IgG1 CH2,

human IgG1 CH3, and human CH1

<400> 46

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```

<210> 47

<211> 1887

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC014 comprising : HD37 (anti-CD19) scFv, altered human IgD hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 47

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aacaccaagg tggacaagaa agtttga 1887

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<210> 48

<211> 2103

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC015 comprising : HD37 (anti-CD19) scFv, altered human IgE CH2 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 48

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tga 2103

```

<210> 49

<211> 2124

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC016 comprising : HD37 (anti-CD19) scFv, altered human IgM CH2 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 49

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accaaggtgg acaagaaagt ttga 2124

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<210> 50

<211> 1788

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC017 comprising : P2C2 (anti-CD79b) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 50

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```

<210> 51

<211> 1812

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC018 comprising : M0042 (anti-HLA-DR) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 51

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<210> 52

<211> 1833

<212> DNA

<213> Artificial Sequence

<220>

<223> Nucleotide sequence for TSC019 comprising : G19-4 (anti-CD3) scFv, human IgG1 SCC-P hinge, human CH2, human CH3, and human Ck (YAE)

<400> 52

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gaggtccagc tgcaactgac tggacctgaa ctgggtgaag ctggagcttc aatgaagatt 120
tcttgcaagg cctctggtta ctcatctact ggctacatcg tgaactggct gaagcagagc 180
catggaaaga accttgagtg gattggactt attaatccat acaaaaggtct tactacctac 240
aaccagaaat tcaaggggcaa ggccacatta actgtagaca agtcatccag cacagcctac 300
atggagctcc tcagttctgac atctgaagac tctgcagttc attactgtgc aagatctggg 360
tactatgggt actcggactg gtacttcgat gtctggggcg caggggaccac ggtcaccgtc 420

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tcaagcgggt gcggagggtc tgggggtggc ggatccggag gtgggtggctc tgcacaagac 480
atccagatga cacagactac atcctccctg tctgcctctc tgggagacag agtcaccatc 540
agtgcagggt caagtcagga cattcgcaat tatttaaact ggatcagca gaaaccagat 600
ggaaactgta aactcctgat ctaactacaca tcaagattac actcaggagt ccatcaagg 660
ttcagttggc gtgggtctgg aacagattat tctctcacca ttgccaacct gcaaccagaa 720
gatattgcca cttacttttg ccaacagggt aatacgcttc cgtggacgtt cgggtggaggc 780
accaaaactg taaccaaacc ctgcagcgag cccaaatctt ctgacaaaac tcacacatgc 840
ccaccgtgcc catccggagc acctgaactc ctgggtggac cgtcagttct cctcttcccc 900
ccaaaaccca aggaacacct catgatctcc cggacccctg aggtcacatg cgtgggtggtg 960
gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggagcg cgtggaggtg 1020
cataatgccg agacaaagcc gcgggagggg cagtacaaca gcacgtaccg tgtggtcagc 1080
gtcctcaccg tcttgcaacc ggaactggctg aatggcaagg agtacaagtg caaggtctcc 1140
aaccagagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1200
gaaccacagg tgtacaccct gcccccattc cgggatgagc tgaccaagaa ccaggtcagc 1260
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gggcagccgg agaacaacta caagaccacg cctccgtgct tggactccga cggctccttc 1380
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tgctccgtga tgcagtgagg tctgcacaac cactacacgc agaagacct ctccctgtct 1500
ccgggtaaat ctagaactgt ggctgcacca tctgtcttca tcttcccgcc atctgatgag 1560
cagttgaaat ctggaactgc ctctgtgtgt tgctgctga attacttcta tcccagagag 1620
gccaaagtac agtggaaagt ggataacgcc ctccaatcgg gtaactccca ggagagtgcc 1680
acagagcagg acagcaaggg cagcacctac agcctcagca gcgagctgac gctgagcaaa 1740
gcagactacg agaaacacaa agtctacgcc tgcgaagtc cccatcaggg cctgagctcg 1800
cccgctacaa agagcttcaa caggggagag tga 1833

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<210> 53

<211> 582

<212> PRT

<213> Artificial Sequence

<220>

<223> ORN160 mature protein comprising : 5D5 (anti-c-Met) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 53

Asp Phe Met Met Ser Gln Ser Pro Ser Ser Leu Thr Val Ser Val Gly
 1 5 10 15
 Glu Lys Val Thr Val Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Thr
 20 25 30
 Ser Ser Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45
 Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60
 Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 Ile Thr Ser Val Lys Ala Asp Asp Leu Ala Val Tyr Tyr Cys Gln Gln
 85 90 95
 Tyr Tyr Ala Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu
 100 105 110
 Lys Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser
 115 120 125
 Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Ala
 130 135 140
 Ser Val Lys Met Ser Cys Arg Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 145 150 155 160
 Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 165 170 175
 Gly Met Ile Asp Pro Ser Asn Ser Asp Thr Arg Phe Asn Pro Asn Phe
 180 185 190
 Lys Asp Lys Ala Thr Leu Asn Val Asp Arg Ser Ser Asn Thr Ala Tyr
 195 200 205
 Met Leu Leu Ser Ser Leu Thr Ser Ala Asp Ser Ala Val Tyr Tyr Cys
 210 215 220
 Ala Thr Tyr Gly Ser Tyr Val Ser Pro Leu Asp Tyr Trp Gly Gln Gly

225 230 235 240
 Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr
 245 250 255
 His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly
 260 265 270
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 275 280 285
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 290 295 300
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 305 310 315 320
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 325 330 335
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 340 345 350
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 355 360 365
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 370 375 380
 Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
 385 390 395 400
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 405 410 415
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 420 425 430
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 435 440 445
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 450 455 460
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 465 470 475 480
 Gly Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 485 490 495
 Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 500 505 510
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 515 520 525
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 530 535 540
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 545 550 555 560
 Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 565 570 575
 Lys Val Asp Lys Lys Val
 580

<210> 54

<211> 586

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC001 mature protein comprising : HD37 (anti-CD39), human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 54

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
 20 25 30
 Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
 35 40 45
 Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro

50 55 60
 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65 70 75 80
 Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
 85 90 95
 Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
 100 105 110
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
 115 120 125
 Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
 130 135 140
 Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
 145 150 155 160
 Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
 165 170 175
 Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
 180 185 190
 Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
 195 200 205
 Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
 210 215 220
 Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
 225 230 235 240
 Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
 245 250 255
 Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu
 260 265 270
 Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 275 280 285
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 290 295 300
 Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
 305 310 315 320
 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
 325 330 335
 Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
 340 345 350
 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
 355 360 365
 Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 370 375 380
 Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
 385 390 395 400
 Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 405 410 415
 Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 420 425 430
 Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 435 440 445
 Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 450 455 460
 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 465 470 475 480
 Ser Leu Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val
 485 490 495
 Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 500 505 510
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 515 520 525
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 530 535 540
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 545 550 555 560
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 565 570 575

Pro Ser Asn Thr Lys Val Asp Lys Lys Val
 580 585

<210> 55

<211> 579

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC002 mature protein comprising : 2H7 (anti-CD20) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 55

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Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1      5      10      15
Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Val Ser Tyr Met
20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35      40      45
Ala Pro Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50      55      60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65      70      75      80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
85      90      95
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Asp Gly Gly Gly Ser Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln Ala Tyr Leu Gln Gln
115      120      125
Ser Gly Ala Glu Ser Val Arg Pro Gly Ala Ser Val Lys Met Ser Cys
130      135      140
Lys Ala Ser Gly Tyr Phe Thr Ser Tyr Asn Met His Trp Val Lys
145      150      155      160
Gln Thr Pro Arg Gln Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly
165      170      175
Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu
180      185      190
Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
195      200      205
Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Val Val Tyr Tyr
210      215      220
Ser Asn Ser Tyr Trp Phe Asp Val Trp Gly Thr Gly Thr Thr Val
225      230      235      240
Thr Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys
245      250      255
Pro Pro Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
260      265      270
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
275      280      285
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
290      295      300
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
305      310      315      320
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
325      330      335
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
340      345      350
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
355      360      365
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
370      375      380
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
385      390      395      400

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
405      410      415
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
420      425      430
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
435      440      445
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
450      455      460
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
465      470      475      480
Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
485      490      495
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
500      505      510
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
515      520      525
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
530      535      540
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
545      550      555      560
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
565      570      575
Lys Lys Val

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<210> 56

<211> 596

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC003 mature protein comprising : G19-4 (anti-CD3) scFv, altered human IgA1 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck (YAE)

<400> 56

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30
 Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
 35 40 45
 Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
 100 105 110
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
 115 120 125
 Gly Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
 130 135 140
 Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
 145 150 155 160
 Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
 165 170 175
 Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
 180 185 190
 Leu His Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
 195 200 205
 Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
 210 215 220

 Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
 225 230 235 240
 Thr Lys Leu Val Thr Lys Arg Ser Ser Pro Ser Thr Pro Pro Thr Pro
 245 250 255
 Ser Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Cys Pro Pro Cys Pro
 260 265 270
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 275 280 285
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 290 295 300
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 305 310 315 320
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 325 330 335
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 340 345 350
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 355 360 365
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 370 375 380
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
 385 390 395 400
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 405 410 415
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 420 425 430
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 435 440 445
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 450 455 460
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 465 470 475 480
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr Val Ala Ala Pro
 485 490 495
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
 500 505 510
 Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys
 515 520 525
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
 530 535 540
 Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
 545 550 555 560
 Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
 565 570 575
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
 580 585 590
 Asn Arg Gly Glu
 595

<210> 57

<211> 583

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC004 mature protein comprising : G19-4 (anti-CD3) scFv, altered human IgA2 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck (YAE)

<400> 57

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30

Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
 35 40 45
 Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
 100 105 110
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
 115 120 125
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
 130 135 140
 Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
 145 150 155 160
 Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
 165 170 175
 Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
 180 185 190
 Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
 195 200 205
 Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
 210 215 220
 Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
 225 230 235 240
 Thr Lys Leu Val Thr Lys Arg Ser Ser Pro Pro Pro Pro Cys Pro
 245 250 255
 Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 260 265 270
 Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 275 280 285
 Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 290 295 300
 Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 305 310 315 320
 Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 325 330 335
 Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 340 345 350
 Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 355 360 365
 Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 370 375 380
 Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 385 390 395 400
 Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 405 410 415
 Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 420 425 430
 Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 435 440 445
 Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 450 455 460
 Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr Val
 465 470 475 480
 Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
 485 490 495
 Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg
 500 505 510
 Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
 515 520 525
 Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
 530 535 540
 Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys

545 550 555 560
 Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
 565 570 575
 Lys Ser Phe Asn Arg Gly Glu
 580

<210> 58

<211> 593

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC005 mature protein comprising : G19-4 (anti-CD3) scFv, altered human IgG3 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck (YAE)

<400> 58

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30
 Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
 35 40 45
 Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
 100 105 110
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
 115 120 125
 Gly Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
 130 135 140
 Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
 145 150 155 160
 Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
 165 170 175
 Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
 180 185 190
 Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
 195 200 205
 Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
 210 215 220
 Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
 225 230 235 240
 Thr Lys Leu Val Thr Lys Arg Ser Ser Glu Pro Lys Ser Ser Asp Thr
 245 250 255
 Pro Pro Pro Ser Pro Arg Ser Pro Cys Pro Pro Cys Pro Ala Pro Glu
 260 265 270
 Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 275 280 285
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 290 295 300
 Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
 305 310 315 320
 Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
 325 330 335
 Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
 340 345 350
 Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
 355 360 365
 Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu

370 375 380
 Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
 385 390 395 400
 Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 405 410 415
 Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 420 425 430
 Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 435 440 445
 Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 450 455 460
 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 465 470 475 480
 Ser Leu Ser Pro Gly Lys Ser Arg Thr Val Ala Ala Pro Ser Val Phe
 485 490 495
 Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
 500 505 510
 Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
 515 520 525
 Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr
 530 535 540
 Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr
 545 550 555 560
 Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
 565 570 575
 Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
 580 585 590
 Glu

<210> 59

<211> 612

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC006 mature protein comprising : G19-4 (anti-CD3) scFv, altered human IgD hinge, human IgG1 CH2, human IgG1 CH3, and human Ck (YAE)

<220>

<221> VARIANT

<222> 375

<223> Xaa = Any Amino Acid

<400> 59

Glu Val Gln Leu Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30
 Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
 35 40 45
 Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
 100 105 110
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
 115 120 125
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
 130 135 140

Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
 145 150 155 160
 Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
 165 170 175
 Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
 180 185 190
 Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
 195 200 205
 Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
 210 215 220
 Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
 225 230 235 240
 Thr Lys Leu Val Thr Lys Arg Ser Ser Glu Ser Pro Lys Ala Gln Ala
 245 250 255
 Ser Ser Val Pro Thr Ala Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys
 260 265 270
 Ala Thr Thr Ala Pro Ala Thr Thr Arg Asn Thr Cys Pro Pro Cys Pro
 275 280 285
 Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 290 295 300
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 305 310 315 320
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 325 330 335
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 340 345 350
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 355 360 365
 Gln Asp Trp Leu Asn Gly Xaa Glu Tyr Lys Cys Lys Val Ser Asn Lys
 370 375 380
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 385 390 395 400
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
 405 410 415
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 420 425 430
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 435 440 445
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 450 455 460
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 465 470 475 480
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 485 490 495
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr Val Ala Ala Pro
 500 505 510
 Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
 515 520 525
 Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys
 530 535 540
 Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
 545 550 555 560
 Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
 565 570 575
 Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
 580 585 590
 Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
 595 600 605
 Asn Arg Gly Glu
 610

<210> 60

<211> 593

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC007 mature protein comprising : G19-4 (anti-CD3) scFv, altered human IgG1 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck (YAE)

<400> 60

```

Glu Val Gln Leu Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1      5      10      15
Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20     25     30
Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35     40     45
Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
50     55     60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Ala Tyr
65     70     75     80
Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85     90     95
Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
100    105    110
Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
115    120    125
Gly Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
130    135    140
Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
145    150    155    160
Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
165    170    175
Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
180    185    190
Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
195    200    205
Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
210    215    220
Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
225    230    235    240
Thr Lys Leu Val Thr Lys Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys
245    250    255
Thr His Thr Ser Pro Pro Ser Pro Cys Pro Pro Cys Pro Ala Pro Glu
260    265    270
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
275    280    285
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
290    295    300
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
305    310    315    320
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
325    330    335
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
340    345    350
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
355    360    365
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
370    375    380
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
385    390    395    400
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
405    410    415
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
420    425    430
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
435    440    445
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
450    455    460
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
465    470    475    480
Ser Leu Ser Pro Gly Lys Ser Arg Thr Val Ala Ala Pro Ser Val Phe
485    490    495
Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
500    505    510
Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
515    520    525
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr
530    535    540
Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr
545    550    555    560
Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
565    570    575
Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
580    585    590
Glu

```

<210> 61

<211> 684

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC008 mature protein comprising : G19-4 (anti-CD3) scFv, altered human IgE CH2 hinge (SEQ ID NO:757), human IgG1

CH2, human IgG1 CH3, and human Ck (YAE)

<400> 61

Glu Val Gln Leu Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30
 Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
 35 40 45
 Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
 100 105 110
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
 115 120 125
 Gly Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
 130 135 140
 Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
 145 150 155 160
 Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
 165 170 175
 Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
 180 185 190
 Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
 195 200 205
 Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
 210 215 220
 Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
 225 230 235 240
 Thr Lys Leu Val Thr Lys Arg Ser Ser Ser Arg Asp Phe Thr Pro Pro
 245 250 255

Thr Val Lys Ile Leu Gln Ser Ser Ser Asp Gly Gly Gly His Phe Pro
 260 265 270
 Pro Thr Ile Gln Leu Leu Cys Leu Val Ser Gly Tyr Thr Pro Gly Thr
 275 280 285
 Ile Asn Ile Thr Trp Leu Glu Asp Gly Gln Val Met Asp Val Asp Leu
 290 295 300
 Ser Thr Ala Ser Thr Thr Gln Glu Gly Glu Leu Ala Ser Thr Gln Ser
 305 310 315 320
 Glu Leu Thr Leu Ser Gln Lys His Trp Leu Ser Asp Arg Thr Tyr Thr
 325 330 335
 Cys Gln Val Thr Tyr Gln Gly His Thr Phe Glu Asp Ser Thr Lys Lys
 340 345 350
 Ser Ala Cys Pro Pro Cys Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro
 355 360 365
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 370 375 380
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 385 390 395 400
 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 405 410 415
 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
 420 425 430
 Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 435 440 445
 Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 450 455 460
 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 465 470 475 480
 Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
 485 490 495
 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 500 505 510
 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Val Leu
 515 520 525
 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 530 535 540
 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 545 550 555 560
 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 565 570 575
 Lys Ser Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
 580 585 590
 Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
 595 600 605
 Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala
 610 615 620
 Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys
 625 630 635 640
 Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp
 645 650 655
 Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
 660 665 670
 Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
 675 680

<210> 62

<211> 691

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC009 mature protein comprising : G19-4 (anti-CD3) scFv, altered human IgM CH2 hinge, human IgG1 CH2, human IgG1 CH3, and human Ck (YAE)

<400> 62

```

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1      5      10      15
Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20      25      30
Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35      40      45
Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
50      55      60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65      70      75      80
Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
100     105     110
Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
115     120     125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
130     135     140
Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
145     150     155     160
Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
165     170     175
Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
180     185     190
Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
195     200     205
Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
210     215     220
Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
225     230     235     240
Thr Lys Leu Val Thr Lys Arg Ser Ser Ile Ala Glu Leu Pro Pro Lys
245     250     255
Val Ser Val Phe Val Pro Pro Arg Asp Gly Phe Phe Gly Asn Pro Arg
260     265     270
Lys Ser Lys Leu Ile Cys Gln Ala Thr Gly Phe Ser Pro Arg Gln Ile
275     280     285
Gln Val Ser Trp Leu Arg Glu Gly Lys Gln Val Gly Ser Gly Val Thr
290     295     300
Thr Asp Gln Val Gln Ala Glu Ala Lys Glu Ser Gly Pro Thr Thr Tyr
305     310     315     320
Lys Val Thr Ser Thr Leu Thr Ile Lys Glu Ser Asp Trp Leu Ser Gln
325     330     335
Ser Met Phe Thr Cys Arg Val Asp His Arg Gly Leu Thr Phe Gln Gln
340     345     350
Asn Ala Ser Ser Met Ser Val Pro Cys Pro Pro Cys Pro Ser Gly Ala
355     360     365
Pro Glu Leu 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 His Glu Asp Pro Glu Val Lys 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
Tyr 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 Ala
450     455     460
Leu Pro Ala Pro 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 Arg Asp Glu Leu Thr
485     490     495
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser

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      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 Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln 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 Pro Gly Lys Ser Arg Thr Val Ala Ala Pro Ser
      580      585      590
Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
      595      600      605
Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys Val
      610      615      620
Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
      625      630      635      640
Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Glu
      645      650      655
Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
      660      665      670
Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
      675      680      685
Arg Gly Glu
      690

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<210> 63

<211> 592

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC010 mature protein comprising : HD37 (anti-CD19) scFv, altered human IgA1 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 63

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
 20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
 35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
 50      55      60
Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
 85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala

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      210      215      220
Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Pro Ser Thr Pro
      245      250      255
Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Cys Pro
      260      265      270
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
      275      280      285
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
      290      295      300
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
      305      310      315      320
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
      325      330      335
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
      340      345      350
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
      355      360      365
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
      370      375      380
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
      385      390      395      400
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
      405      410      415
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
      420      425      430
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
      435      440      445
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
      450      455      460
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
      465      470      475      480
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Ala Ser
      485      490      495
Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
      500      505      510
Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
      515      520      525
Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
      530      535      540
His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
      545      550      555      560
Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
      565      570      575
Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
      580      585      590

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<210> 64

<211> 579

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC011 mature protein comprising : HD37 (anti-CD19) scFv, altered human IgA2 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 64

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
      20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro

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      35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
 50      55      60
Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
      85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Pro Pro Pro Pro
245      250      255
Pro Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
260      265      270
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
275      280      285
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
290      295      300
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
305      310      315      320
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
325      330      335
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
340      345      350
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
355      360      365
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
370      375      380
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
385      390      395      400
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
405      410      415
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
420      425      430
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
435      440      445
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
450      455      460
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
465      470      475      480
Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
485      490      495
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
500      505      510
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
515      520      525
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
530      535      540
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
545      550      555      560

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
565      570      575
Lys Lys Val

```

<210> 65

<211> 589

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC012 mature protein comprising : HD37 (anti-CD19) scFv, altered human IgG1 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 65

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
245      250      255
Ser Asp Lys Thr His Thr Ser Pro Pro Ser Pro Cys Pro Pro Cys Pro
260      265      270
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
275      280      285
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
290      295      300
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
305      310      315      320
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
325      330      335
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
340      345      350
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
355      360      365
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
370      375      380

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
385      390      395      400
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
405      410      415
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
420      425      430
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
435      440      445
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
450      455      460
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
465      470      475      480
Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly
485      490      495
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
500      505      510
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
515      520      525
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
530      535      540
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
545      550      555      560
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
565      570      575
Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
580      585

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<210> 66

<211> 589

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC013 mature protein comprising : HD37 (anti-CD19) scFv, altered human IgG3 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 66

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205

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Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
245      250      255
Ser Asp Thr Pro Pro Pro Ser Pro Arg Ser Pro Cys Pro Pro Cys Pro
260      265      270
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
275      280      285
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
290      295      300
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
305      310      315      320
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
325      330      335
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
340      345      350
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
355      360      365
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
370      375      380
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
385      390      395      400
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
405      410      415
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
420      425      430
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
435      440      445
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
450      455      460
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
465      470      475      480
Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly
485      490      495
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
500      505      510
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
515      520      525
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
530      535      540
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
545      550      555      560
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
565      570      575
Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
580      585

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<210> 67

<211> 608

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC014 mature protein comprising : HD37 (anti-CD19) scFv, altered human IgD hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 67

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20      25      30

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Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
 35 40 45
 Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
 50 55 60
 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65 70 75 80
 Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
 85 90 95
 Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
 100 105 110
 Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
 115 120 125
 Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
 130 135 140
 Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
 145 150 155 160
 Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
 165 170 175
 Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
 180 185 190
 Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
 195 200 205
 Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
 210 215 220
 Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
 225 230 235 240
 Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Ser Pro Lys
 245 250 255
 Ala Gln Ala Ser Ser Val Pro Thr Ala Gln Pro Gln Ala Glu Gly Ser
 260 265 270
 Leu Ala Lys Ala Thr Thr Ala Pro Ala Thr Thr Arg Asn Thr Cys Pro
 275 280 285
 Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 290 295 300
 Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 305 310 315 320
 Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 325 330 335
 Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 340 345 350
 Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 355 360 365
 Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 370 375 380
 Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 385 390 395 400
 Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 405 410 415
 Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 420 425 430
 Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 435 440 445
 Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 450 455 460
 Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 465 470 475 480
 Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 485 490 495
 Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Ala Ser
 500 505 510
 Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
 515 520 525
 Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
 530 535 540
 Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
 545 550 555 560
 His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
 565 570 575
 Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
 580 585 590
 Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
 595 600 605

<210> 68

<211> 680

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC015 mature protein comprising : HD37 (anti-CD19) scFv, altered human IgE CH2 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 68

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Ser Arg Asp Phe
245      250      255
Thr Pro Pro Thr Val Lys Ile Leu Gln Ser Ser Ser Asp Gly Gly Gly
260      265      270
His Phe Pro Pro Thr Ile Gln Leu Leu Cys Leu Val Ser Gly Tyr Thr
275      280      285
Pro Gly Thr Ile Asn Ile Thr Trp Leu Glu Asp Gly Gln Val Met Asp
290      295      300
Val Asp Leu Ser Thr Ala Ser Thr Thr Gln Glu Gly Glu Leu Ala Ser
305      310      315      320
Thr Gln Ser Glu Leu Thr Leu Ser Gln Lys His Trp Leu Ser Asp Arg
325      330      335
Thr Tyr Thr Cys Gln Val Thr Tyr Gln Gly His Thr Phe Glu Asp Ser
340      345      350
Thr Lys Lys Ser Ala Cys Pro Pro Cys Ser Gly Ala Pro Glu Leu Leu

355      360      365
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
370      375      380
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser
385      390      395      400
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
405      410      415
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
420      425      430
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
435      440      445
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
450      455      460
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
465      470      475      480
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
485      490      495
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
500      505      510
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
515      520      525
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
530      535      540
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
545      550      555      560
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
565      570      575
Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
580      585      590
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
595      600      605
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
610      615      620
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
625      630      635      640
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
645      650      655
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
660      665      670
Asn Thr Lys Val Asp Lys Lys Val
675      680

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<210> 69

<211> 687

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC016 mature protein comprising : HD37 (anti-CD19) scFv, altered human IgM CH2 hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 69

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1           5           10           15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
          20           25           30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
          35           40           45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
          50           55           60
Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65          70          75          80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr

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          85           90           95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
          100          105          110
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
          115          120          125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
          130          135          140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
          145          150          155          160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
          165          170          175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
          180          185          190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
          195          200          205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
          210          215          220
Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
          225          230          235          240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Ile Ala Glu Leu
          245          250          255
Pro Pro Lys Val Ser Val Phe Val Pro Pro Arg Asp Gly Phe Phe Gly
          260          265          270
Asn Pro Arg Lys Ser Lys Leu Ile Cys Gln Ala Thr Gly Phe Ser Pro
          275          280          285
Arg Gln Ile Gln Val Ser Trp Leu Arg Glu Gly Lys Gln Val Gly Ser
          290          295          300
Gly Val Thr Thr Asp Gln Val Gln Ala Glu Ala Lys Glu Ser Gly Pro
          305          310          315          320
Thr Thr Tyr Lys Val Thr Ser Thr Leu Thr Ile Lys Glu Ser Asp Trp
          325          330          335
Leu Ser Gln Ser Met Phe Thr Cys Arg Val Asp His Arg Gly Leu Thr
          340          345          350
Phe Gln Gln Asn Ala Ser Ser Met Ser Val Pro Cys Pro Pro Cys Pro
          355          360          365
Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
          370          375          380
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
          385          390          395          400
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
          405          410          415
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
          420          425          430
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
          435          440          445
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
          450          455          460
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
          465          470          475          480
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
          485          490          495
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
          500          505          510
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
          515          520          525
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
          530          535          540
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
          545          550          555          560
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
          565          570          575
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Ala Ser Thr
          580          585          590
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
          595          600          605

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Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
610          615          620
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
625          630          635          640
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
          645          650          655
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
          660          665          670
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
          675          680          685

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<210> 70

<211> 575

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC017 mature protein comprising : P2C2 (anti-CD79b) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3 and human CH1

<400> 70

```

Asp Ile Val Met Ile Gln Asp Glu Leu Ser Asn Pro Val Ser Ser Gly
 1           5           10           15
Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asp Lys
 20           25           30
Glu Gly Lys Thr Tyr Leu Asn Trp Phe Leu Gln Arg Pro Gly Gln Ser
 35           40           45
Pro Gln Leu Leu Ile Tyr Leu Met Ser Met Arg Glu Ser Gly Val Ser
 50           55           60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Glu Ile
 65           70           75           80
Ser Arg Val Lys Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Leu
 85           90           95
Val Glu Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100           105           110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln
115           120           125
Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr
130           135           140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Phe Ser
145           150           155           160
Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly
165           170           175
Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Arg
180           185           190
Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu
195           200           205
Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Thr
210           215           220
Trp Ser Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ser
225           230           235           240
Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
245           250           255
Ser Gly Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
260           265           270
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
275           280           285
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
290           295           300
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305           310           315           320
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
325           330           335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
340           345           350
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
355           360           365
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
370           375           380
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385           390           395           400
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
405           410           415
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
420           425           430
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
435           440           445
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
450           455           460
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Ala Ser Thr
465           470           475           480
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
485           490           495
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
500           505           510
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
515           520           525
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
530           535           540
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
545           550           555           560
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
565           570           575

```

<210> 71

<211> 583

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC018 mature protein comprising : M0042 (anti-HLA-DR) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human CH1

<400> 71

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
 20           25           30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Val
 35           40           45
Tyr Ser Val Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50           55           60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
 65           70           75           80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Phe
 85           90           95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Gly Gly Gly Gly Ser
100           105           110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
115           120           125
Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
130           135           140
Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr Tyr
145           150           155           160
Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
165           170           175

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Tyr Ile Gly Pro Ser Gly Gly Phe Thr Ala Tyr Ala Asp Ser Val Lys
180           185           190
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
195           200           205
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
210           215           220
Arg Asp Gly Trp Val Gly Ser Glu Asn Tyr Ser Gly Met Asp Val Trp
225           230           235
Gly Gln Gly Thr Thr Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys
240           245           250           255
Thr His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly
260           265           270
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
275           280           285
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
290           295           300
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
305           310           315           320
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
325           330           335
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
340           345           350
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
355           360           365
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
370           375           380
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
385           390           395           400
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
405           410           415
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
420           425           430
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
435           440           445
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
450           455           460
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
465           470           475           480
Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
485           490           495
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
500           505           510
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
515           520           525
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
530           535           540
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
545           550           555           560
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
565           570           575
Thr Lys Val Asp Lys Lys Val
580

```

<210> 72

<211> 590

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC019 mature protein comprising : G19-4 (anti-CD3) scFv, human IgG1 SCC-P hinge, human CH2, human CH3, and

human Ck (YAE)

<400> 72

```

Glu Val Gln Leu Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1      5      10      15
Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20     25     30
Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35     40     45
Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
50     55     60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65     70     75     80
Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85     90     95
Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
100    105    110
Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
115    120    125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
130    135    140
Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
145    150    155    160
Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
165    170    175
Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
180    185    190
Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
195    200    205
Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
210    215    220
Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
225    230    235    240
Thr Lys Leu Val Thr Lys Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys
245    250    255
Thr His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly
260    265    270
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
275    280    285
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
290    295    300
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
305    310    315    320
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
325    330    335
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
340    345    350
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
355    360    365
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
370    375    380
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
385    390    395    400
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
405    410    415
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
420    425    430
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
435    440    445
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
450    455    460
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
465    470    475    480
Pro Gly Lys Ser Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
485    490    495
Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
500    505    510
Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp

```

```

515      520      525
Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp
530    535    540
Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys
545    550    555    560
Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
565    570    575
Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
580    585    590

```

<210> 73

<211> 2292

<212> DNA

<213> Artificial Sequence

<220>

<223> 4C04 (anti-RON) x G19-4 (anti-CD3) Scorpion DNA sequence (SO266)

<400> 73

```

atggaagcac cagcgcagct tctcttctc ctgctactct ggctcccaga taccaccggt 60
gacattcaga tgaccagtc tctgcctcc cagtctgcat ctctgggaga aagtgtcacc 120
atcacatgcc tggcaagtca gaccattggt acatggttag catggtatca gcagaaacca 180
gggaaatctc ctacgctcct gatttatgct gcaaccagct tggcagatgg ggtcccatca 240
aggttcagtg ctagtggatc tggcacaata ttttcttca agatcgacag cctacagtct 300
gaagattttg taagttatta ctgtcaacaa ctttacaata ctccgtggac gttcgggtgga 360
ggcaccagc tggaaatcaa aggtggcggg ggctctggcg gaggtggatc cgggtggcggc 420
ggctctcaga tccagctgca gcagtctgga cctgagctgg tgaagcctgg gacttcagtg 480
aagatatcct gcaaggcttc tgactacaca ctactgact tctatatgaa ctgggtgagg 540
cagaagcctg gacagggact tgagtggatt gggaggattt atcctggaac cgataaaact 600
agatacaatg agaatttcag ggacaaggcc atactgaccg tggacacgtc ctccagcaca 660
gcctacatgc agctcagcag cctgacatca gaggacactg ctgtctatct ctgtgcaaga 720
tcgcctact atggtaacta cgttgcctat gactactggg gtcaaggaa ctcagtcacc 780
gtctcctcga gcgagcccaa atcttctgac aaaactcaca catgcccacc gtgcccagca 840
cctgaactcc tgggtggacc gtcagtcttc ctcttcccc caaaacccaa ggacaccctc 900
atgatctccc ggacccctga ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct 960
gaggtcaagt tcaactggta cgtggacggc gtggaggtgc ataagccaa gacaagccg 1020
cgggaggagc agtacaacag cactacactg gtggtcagcg tctcaccct cctgcaccag 1080
gactggctga atggcaagga gtacaagtgc aaggtctcca acaagccct cccagccccc 1140
atcgagaaaa ccatctccaa agccaaaggg cagccccgag aaccacaggt gtacaccctg 1200
ccccatccc gggatgagct gaccaagaac caggtcagcc tgacctgctt ggtcaaaggc 1260
ttctatccaa gcgacatcgc cgtggagtgg gagagcaatg ggagccggg gaacaactac 1320
aagaccacgc tgcctgctc ggactccgac ggctcctct tctctacag caagctcacc 1380
gtggacaaga gcaggtggca gcagggaac gtcttctcat gctcctgat gcatgaggct 1440
ctgcacaacc actacacgca gaagagctc tcctgtctc cgggtcagag gcacaacaat 1500
tcttccctga atacaggaa tcagatggca ggtcattctc cgaattctga ggtccagctg 1560
caacagctct gacctgaact ggtgaagcct ggagctcaa tgaagattc ctgcaaggcc 1620
tctggttact cattcactgg ctacatcgtg aactggctga agcagagcca tggaaagaac 1680
cttgagtggg ttggacttat taatccatc aaaggtctta ctacctcaa ccagaaattc 1740
aagggcaagg ccacattaac tgtagacaag tcatccagca cagcctacat ggagctcctc 1800
agtctgacat ctgaagactc tgcagtctat tactgtgcaa gatctgggta ctatgggtgac 1860
tcggactggt acttcgatgt ctggggcgca gggaccacgg tcacctctc aagcgggtggc 1920
ggagggtctg ggggtggcgg atccggaggt ggtggtctg cacaagacat ccagatgaca 1980
cagactacat cctcctgtc tgcctctctg ggagacagag tcacctcag ttgcagggca 2040
agtcaggaca ttocgaatta tttaaaactg tatcagcaga aaccagatgg aactgttaaa 2100
ctcctgatct actacacatc aagattacac tcaggagtcc catcaaggtt cagtggcagt 2160
gggtctggaa cagattatc tctcaccatt gccaacctgc aaccagaaga tattgccact 2220
tacttttgcc aacagggtaa tacgcttcg tggacgttcg gtggaggcac caaactggta 2280
acaaacgat aa 2292

```

<210> 74

<211> 743

<212> PRT

<213> Artificial Sequence

<220>

<223> 4C04 (anti-RON) x G19-4 (anti-CD3) Scorpion mature protein sequence (SO266)

<400> 74

```

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly
1      5      10      15
Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20      25      30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Ile
35      40      45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Ala
50      55      60
Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Asp Ser Leu Gln Ser
65      70      75      80
Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Asn Thr Pro Trp
85      90      95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
100      105      110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Gln Leu Gln Gln
115      120      125
Ser Gly Pro Glu Leu Val Lys Pro Gly Thr Ser Val Lys Ile Ser Cys
130      135      140
Lys Ala Ser Asp Tyr Thr Leu Thr Asp Phe Tyr Met Asn Trp Val Arg
145      150      155      160
Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly
165      170      175
Thr Asp Lys Thr Arg Tyr Asn Glu Lys Phe Arg Asp Lys Ala Ile Leu
180      185      190
Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
195      200      205
Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Ser Ala Tyr Tyr
210      215      220
Gly Asn Tyr Val Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
225      230      235      240
Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
245      250      255
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
260      265      270
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
275      280      285
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
290      295      300
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
305      310      315      320
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
325      330      335
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
340      345      350
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
355      360      365
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
370      375      380
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
385      390      395      400
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
405      410      415
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
420      425      430
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
435      440      445
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
450      455      460
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Arg His Asn Asn

465      470      475      480
Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn Ser
485      490      495
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
500      505      510
Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
515      520      525
Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
530      535      540
Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
545      550      555      560
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
565      570      575
Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
580      585      590
Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
595      600      605
Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
610      615      620
Gly Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
625      630      635      640
Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
645      650      655
Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
660      665      670
Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
675      680      685
Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Thr
690      695      700
Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
705      710      715      720
Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
725      730      735
Thr Lys Leu Val Thr Lys Arg
740

```

<210> 75

<400> 75

000

<210> 76

<400> 76

000

<210> 77

<211> 510

<212> PRT

<213> Artificial Sequence

<220>

<223> Mutated M0039

<220>

<221> SIGNAL

<222> (1)...(22)

<400> 77

Met	Asp	Phe	Gln	Val	Gln	Ile	Phe	Ser	Phe	Leu	Leu	Ile	Ser	Ala	Ser
	-20					-15						-10			
Val	Ile	Met	Ser	Arg	Gly	Val	Gln	Val	Gln	Leu	Lys	Glu	Ser	Gly	Pro
	-5				1					5				10	
Gly	Leu	Val	Ala	Pro	Ser	Gln	Ser	Leu	Ser	Ile	Thr	Cys	Thr	Val	Ser

```

      15      20      25
Gly Phe Ser Leu Thr Gly Tyr Gly Val Asn Trp Val Arg Gln Pro Pro
   30   35   40
Gly Lys Gly Leu Glu Trp Leu Gly Met Ile Trp Gly Asp Gly Ser Thr
   45   50   55
Asp Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Thr Lys Asp Asn
   60   65   70
Ser Lys Ser Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp
   75   80   85   90
Thr Ala Arg Tyr Tyr Cys Ala Arg Asp Gly Tyr Ser Asn Phe His Tyr
   95  100  105
Tyr Val Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
  110  115  120
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
  125  130  135
Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
  140  145  150
Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
  155  160  165  170
Val Glu Tyr Tyr Val Thr Ser Leu Met Gln Trp Tyr Gln Gln Lys Pro
  175  180  185
Gly Gln Pro Pro Lys Leu Leu Ile Ser Ala Ala Ser Asn Val Glu Ser
  190  195  200
Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser
  205  210  215
Leu Asn Ile His Pro Val Glu Glu Asp Asp Ile Ala Met Tyr Phe Cys
  220  225  230
Gln Gln Ser Arg Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu
  235  240  245  250
Glu Ile Lys Arg Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr
  255  260  265
Ser Pro Pro Ser Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
  270  275  280
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
  285  290  295
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
  300  305  310
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
  315  320  325  330
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
  335  340  345
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
  350  355  360
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
  365  370  375
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
  380  385  390
Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
  395  400  405  410
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
  415  420  425
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
  430  435  440
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
  445  450  455
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
  460  465  470
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
  475  480  485

```

<210> 78

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> H68 linker (scorpion linker derived from NKG2D)

<400> 78

```

Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
  1      5      10      15
Ser Pro Asn Ser
      20

```

<210> 79

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> VH of A2

<400> 79


```

gaagttcaat tgttagagtc tgggtggcggc cttgttcagc ctgggtgggtc tttacgtctt 60
tcttgcgctg cttccggatt cactttctct ttttaccaga tgcattgggt tcgccaagct 120
cctggtaaag gtttggagtg ggtttctggt atctatcctt ctgggtgggta tactaagtat 180
gctgactccg ttaaaggctg cttcactatc tctagagaca actotaagaa tactctctac 240
ttgcagatga acagcttaag ggctgaggac actgcagtct actattgtgc gagagatcta 300
gggtacggca gtagctggtta ctactttgac tactgggggc agggaacctt ggtcacgctc 360
tcaagc

```

<210> 80

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> VH of A2

<400> 80

```

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 Phe Tyr
20      25      30
Gln Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35      40      45
Ser Gly Ile Tyr Pro Ser Gly Gly Tyr Thr Lys Tyr Ala Asp Ser Val
50      55      60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65      70      75      80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Asp Leu Gly Tyr Gly Ser Ser Trp Tyr Tyr Phe Asp Tyr Trp
100      105      110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115      120

```

<210> 81

<400> 81

000

<210> 82

<400> 82

000

<210> 83

<211> 330

<212> DNA

<213> Artificial Sequence

<220>

<223> VL of A2

<400> 83

```

cagagcgcctt tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60
tctctcagtg gaaccgacag tgacgttggt ggttataacc atgtctcctg gtaccaacaa 120
cacccaggca aggcccccaa actcataatt tatgatgtcg atcatcgcc ctcagggatac 180
tctaaccgctt tctctggctc caagtctggc aacacggcct ccoctgacct cctctgggctc 240
caggctgagg acgaggctga ttattactgc agctcatata gaagcggtag cacttatgtc 300
ttcggaactg ggaccaaggt caccgtccta
330

```

<210> 84

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> VL of A2

<400> 84

```

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 Ser Gly Thr Asp Ser Asp Val Gly Gly Tyr
20      25      30
Asn His Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35      40      45
Ile Ile Tyr Asp Val Asp His Arg Pro Ser Gly Ile 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 Arg Ser Gly
85      90      95
Ser Thr Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100     105     110

```

<210> 85

<211> 741

<212> DNA

<213> Artificial Sequence

<220>

<223> A2 scFv

<400> 85

```

gaagttcaat tgtagagtc tggtagcggt ctgttcagc ctggtggttc tttacgtctt 60
tcttgccgtg cttccggatt cactttctct tttaccaga tgcattgggt tcgccaagct 120
cctggtaaag gtttggagtg ggtttctggt atctatcctt ctggtggcta tactaagtat 180
gctgactccg ttaaaggctg cttcactatc tctagagaca actctaagaa tactctctac 240
ttgcagatga acagcttaag ggctgaggac actgcagtct actattgtgc gagagatcta 300
gggtacggca gtactgtgta ctactttgac tactggggcc agggaaccct ggtcaccgtc 360
tcaagcgggt gcggcggttc ggggggtggc ggaagtggag gtggagggag tcagagcgct 420
ttgactcagc ctgcctcogt gtctgggtct cctggacagt cgatcaccat ctctgcagt 480
ggaaccgaca gtgacgttgg tggttataac catgtctcct ggtaccaaca acaccaggc 540
aaggcccca aactcataat ttatgatgac gatcatcggc cctcagggat ctctaaccgt 600
ttctctggct ccaagtcttg caacacggcc tccctgacca tctctgggct ccaggctgag 660
gacgagcgct attattactg cagctcatat agaagcggtg gcacttatgt cttcggaact 720
gggaccaagg tcacgcctct a                                     741

```

<210> 86

<211> 247

<212> PRT

<213> Artificial Sequence

<220>

<223> A2 scFv

<400> 86

```

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 Phe Tyr
20      25      30
Gln Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35      40      45
Ser Gly Ile Tyr Pro Ser Gly Gly Tyr Thr Lys Tyr Ala Asp Ser Val
50      55      60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65      70      75      80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Asp Leu Gly Tyr Gly Ser Ser Trp Tyr Tyr Phe Asp Tyr Trp
100     105     110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115     120     125
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro
130     135     140
Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Ser
145     150     155     160
Gly Thr Asp Ser Asp Val Gly Gly Tyr Asn His Val Ser Trp Tyr Gln
165     170     175
Gln His Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp Val Asp His
180     185     190
Arg Pro Ser Gly Ile Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn
195     200     205
Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp
210     215     220
Tyr Tyr Cys Ser Ser Tyr Arg Ser Gly Ser Thr Tyr Val Phe Gly Thr
225     230     235     240
Gly Thr Lys Val Thr Val Leu
245

```

<210> 87

<211> 603

<212> DNA

<213> Artificial Sequence

<220>

<223> PLD ECD

<400> 87

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ttattcacag tgacagtccc taaggaactg tacataatag agcatggcag caatgtgacc 60
ctggaatgca actttgacac tgggaagtcac gtgaaccttg gagcaataac agccagtttg 120
caaaagtggtg aaaatgatac atccccacac cgtgaaagag ccactttgct ggaggagcag 180
ctgcccttag ggaaggcctc gtccacata cctcaagtcc aagtgaggga cgaaggacag 240
taccaatgca taatcatcta tggggtcgcc tgggaactaca agtacctgac tctgaaagtc 300
aaagcttcct acaggaaaaat aaacactcac atcctaaaagg ttccagaaaac agatgaggta 360
gagctacact gccagggtac aggttatcct ctggcagaag tatcctggcc aaacgtcagc 420
gttcctgccca acaccagcca ctccaggacc cctgaaggcc tctaccaggt caccagtgtt 480
ctgcgcctaa agccaccccc tggcagaaac ttcagctgtg tgttctggaa tactcacgtg 540
aggggaactta ctttggccag cattgacctt caaagtcaga tggaaaccag gacccatcca 600
acc 603

```

<210> 88

<211> 201

<212> PRT

<213> Artificial Sequence

<220>

<223> PLD ECD

<400> 88

```

Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile Glu His Gly
 1          5          10          15
Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser His Val Asn
 20         25         30
Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn Asp Thr Ser
 35         40         45
Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu Pro Leu Gly
 50         55         60
Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp Glu Gly Gln
 65         70         75         80
Tyr Gln Cys Ile Ile Tyr Gly Val Ala Trp Asp Tyr Lys Tyr Leu
 85         90         95
Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr His Ile Leu
100        105        110
Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln Ala Thr Gly
115        120        125
Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val Pro Ala Asn
130        135        140
Thr Ser His Ser Arg Thr Pro Glu Gly Leu Tyr Gln Val Thr Ser Val
145        150        155        160
Leu Arg Leu Lys Pro Pro Gly Arg Asn Phe Ser Cys Val Phe Trp
165        170        175
Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp Leu Gln Ser
180        185        190
Gln Met Glu Pro Arg Thr His Pro Thr
195        200

```

<210> 89

<211> 498

<212> DNA

<213> Artificial Sequence

<220>

<223> monolL10

<400> 89

```

agcccaggcc agggcaccca gtctgagaac agctgcaccc acttcccagg caacctgcct 60
aacatgcttc gagatctccg agatgccttc agcagagtga agactttctt tcaaatgaag 120
gatcagctgg acaacttggt gttaaaggag tccttgctgg aggactttta gggttacctg 180
ggttgccaag ccttgctcga gatgatccag ttttacctgg aggaggtgat gcccgaagct 240
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttcct gtgaaaacgg tggtagatcc 360
ggcggttaaga gcaaggccgt ggagcaggtg aagaatgcct ttaataagct ccaagagaaa 420
ggcatctaca aagccatgag tgagtttgac atcttcatca actacataga agcctacatt 480
acaatgaaga tacgaaac

```

<210> 90

<211> 166

<212> PRT

<213> Artificial Sequence

<220>

<223> monolL10

<400> 90

```

Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1          5          10          15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
          20          25          30

```

```

Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35          40          45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50          55          60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65          70          75          80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
          85          90          95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100         105         110
Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu
115         120         125
Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys
130         135         140
Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile
145         150         155         160
Thr Met Lys Ile Arg Asn
          165

```

<210> 91

<211> 348

<212> DNA

<213> Artificial Sequence

<220>

<223> VH of 3D1

<400> 91

```

caggtccagc tgcagcagtc tgggcctgag ctggtgaggc ctggggaatc agtgaagatt 60
tcttgcaagg gttcoggota cacattcact gattatgcta tacagtgggt gaagcagagt 120
catgcaaaga gtctagagtg gattggagtt attaatattt actatgataa tacaaactac 180
aaccagaagt ttaaggggcaa ggccacaatg actgtagaca aatcctccag cacagcctat 240
atggaacttg ccagattgac atctgaggat tctgccatct attactgtgc aagagcggcc 300
tggtatatgg actactgggg tcaaggaacc tcagtcacog tctcctca 348

```

<210> 92

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> VH of 3D1

<400> 92

```

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Glu
1          5          10          15
Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
20          25          30
Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
35          40          45
Gly Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe
50          55          60
Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65          70          75          80
Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr Cys
          85          90          95
Ala Arg Ala Ala Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
100         105         110
Thr Val Ser Ser
          115

```

<210> 93

<400> 93

000

<210> 94

<400> 94

000

<210> 95
 <211> 336
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> VL of 3D1

<400> 95
 gacattgtgc tgtcacagtc tccatcctcc ctggctgtgt cagcaggaga gaaggctcact 60
 atgagctgca aatccagtc gagtctgtct aacagtagaa cccgagagaa ctacttggct 120
 tgggtaccagc agaaaccagg gcagtctcct aaactgctga tctactgggc atccactagg 180
 gaatctgggg tccctgatcg cttcacaggc agtggatctg ggacagattt cactctcacc 240
 atcagcagtg tgcaggctga agacctggca gtttattact gcacgcaatc ttataatctt 300
 tacacgttcg gaggggggac caagctggaa ataaaa 336

<210> 96
 <211> 112
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL of 3D1

<400> 96
 Asp Ile Val Leu Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly
 1 5 10 15
 Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
 20 25 30
 Arg Thr Arg Glu Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45
 Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60
 Pro Asp Arg Phe Thr Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Thr Gln
 85 90 95
 Ser Tyr Asn Leu Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 97
 <211> 744
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> 3D1 scFv

<400> 97
 caggtccagc tgcagcagtc tgggcctgag ctggtgaggc ctggggaatc agtgaagatt 60
 tctcgcaagg gttcoggcta cacattcact gattatgcta tacagtgggt gaagcagagt 120
 catgcaaaga cttctagagt gattggagtt attaatattt actatgataa tacaaactac 180
 aaccagaagt ttaagggcaa ggccacaatg actgtagaca aatcctccag cacagcctat 240
 atggaacttg ccagattgac atctgaggat tctgccatct attactgtgc aagagcggcc 300
 tgggtatatg actactgggg tcaaggaacc tcagtcaccg tctcctcagg ggggtggaggc 360
 tctggtggcg gtggctcttg cggaggtgga tcgggtggcg gcggatctga cattgtgctg 420
 tcacagtcct catcctcctt ggctgtgtca gcaggagaga aggtcactat gagctgcaaa 480
 tccagtcaga gtctgctcaa cagtagaacc cgagagaact acttggtctt gtaccagcag 540

 aaaccagggc agtctcctaa actgctgata tactgggcat ccactaggga atctggggtc 600
 cctgatcgct tcacaggcag tggatctggg acagatttca ctctcaccat cagcagtggtg 660
 caggctgaag acctggcagt ttattactgc acgcaatctt ataatcttta caggttcgga 720
 ggggggacca agctggaaat aaaa 744

<210> 98
 <211> 248
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 3D1 scFv

<400> 98

```

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Glu
1      5      10      15
Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
20      25      30
Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
35      40      45
Gly Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser Ser Thr Ala Tyr
65      70      75      80
Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr Cys
85      90      95
Ala Arg Ala Ala Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
100      105      110
Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
115      120      125
Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Ser Gln Ser Pro
130      135      140
Ser Ser Leu Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys
145      150      155      160
Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu Ala
165      170      175
Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp
180      185      190
Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly
195      200      205
Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp
210      215      220
Leu Ala Val Tyr Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr Thr Phe Gly
225      230      235      240
Gly Gly Thr Lys Leu Glu Ile Lys
245

```

<210> 99

<211> 247

<212> PRT

<213> Artificial Sequence

<220>

<223> MET021 scFv

<400> 99

```

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 Ser Ile Arg Asn Tyr
20      25      30
Leu Asn Trp Tyr Gln Gln Glu Pro Gly Lys Ala Pro Lys Leu Leu Ile
35      40      45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50      55      60

Ser Gly Ser Gly Thr Asp Phe Ile Leu Thr Ile Ser Ser Leu Gln Pro
65      70      75      80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Val Thr Pro Leu
85      90      95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
100      105      110
Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
115      120      125
Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
130      135      140
Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Tyr Asp
145      150      155      160
Met Leu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
165      170      175
Tyr Ile Tyr Pro Ser Gly Gly Leu Thr Glu Tyr Ala Asp Ser Val Lys
180      185      190
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
195      200      205
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
210      215      220
Arg Arg Ala Pro Arg Ser Leu Ser Phe Asp Ile Trp Gly Gln Gly Thr
225      230      235      240
Met Val Thr Val Ser Ser
245

```

<210> 100

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> VH of MET021 scFv

<400> 100

```

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 Lys Tyr
20      25      30
Asp Met Leu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35      40      45
Ser Tyr Ile Tyr Pro Ser Gly Gly Leu Thr Glu Tyr Ala Asp Ser Val
50      55      60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65      70      75      80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Arg Ala Pro Arg Ser Leu Ser Phe Asp Ile Trp Gly Gln Gly
100      105      110
Thr Met Val Thr Val Ser Ser Ser
115      120

```

<210> 101

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL of MET021 scFv

<400> 101

```

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 Ser Ile Arg Asn Tyr

20      25      30
Leu Asn Trp Tyr Gln Gln Glu Pro Gly Lys Ala Pro Lys Leu Leu Ile
35      40      45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50      55      60
Ser Gly Ser Gly Thr Asp Phe Ile Leu Thr Ile Ser Ser Leu Gln Pro
65      70      75      80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Val Thr Pro Leu
85      90      95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100      105

```

<210> 102

<211> 249

<212> PRT

<213> Artificial Sequence

<220>

<223> G19-4 scFv

<400> 102

```

Glu Val Gln Leu Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1      5      10      15
Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20      25      30
Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35      40      45
Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
50      55      60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65      70      75      80
Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
100      105      110
Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
115      120      125
Gly Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
130      135      140
Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
145      150      155      160
Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
165      170      175
Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
180      185      190
Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
195      200      205
Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
210      215      220
Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
225      230      235      240
Thr Lys Leu Val Thr Lys Arg Ser Ser
245

```

<210> 103

<211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VH of G19-4

<400> 103
 Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30
 Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
 35 40 45
 Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
 100 105 110
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 104
 <211> 112
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VL of G19-4

<400> 104
 Ala Gln Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser
 1 5 10 15
 Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Arg
 20 25 30
 Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu
 35 40 45
 Leu Ile Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe
 50 55 60
 Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ala Asn Leu
 65 70 75 80
 Gln Pro Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu
 85 90 95
 Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Val Thr Lys Arg Ser Ser
 100 105 110

<210> 105
 <211> 252
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> HD37 scFv

<400> 105
 Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
 20 25 30
 Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
 35 40 45
 Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
 50 55 60
 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65 70 75 80
 Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
 85 90 95
 Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly


```

      100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Gln
      115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
      130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
      145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
      165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
      180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
      195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
      210      215      220
Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
      225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser
      245      250

```

<210> 106

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> VH of 2E12 scFv

<400> 106

```

Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Ser Val Ala Pro Ser Gln
 1      5      10      15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Gly Tyr
      20      25      30
Gly Val Asn Trp Val Arg Gln Pro Gly Lys Gly Leu Glu Trp Leu
      35      40      45
Gly Met Ile Trp Gly Asp Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys
      50      55      60
Ser Arg Leu Ser Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
      65      70      75      80
Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala
      85      90      95
Arg Asp Gly Tyr Ser Asn Phe His Tyr Tyr Val Met Asp Tyr Trp Gly
      100      105      110
Gln Gly Thr Ser Val Thr Val Ser Ser
      115      120

```

<210> 107

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> VL of 2E12 scFv

<400> 107

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr
      20      25      30
Val Thr Ser Leu Met Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
      35      40      45
Lys Leu Leu Ile Ser Ala Ala Ser Asn Val Glu Ser Gly Val Pro Ala
      50      55      60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
65      70      75      80
Pro Val Glu Glu Asp Asp Ile Ala Met Tyr Phe Cys Gln Gln Ser Arg
      85      90      95
Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
      100      105      110

```

<210> 108

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker of 2E12 scFv

<400> 108

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> 109

<211> 252

<212> PRT

<213> Artificial Sequence

<220>

<223> full length 2E12 scFv

<400> 109

Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Ser Val Ala Pro Ser Gln
 1 5 10 15
 Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Gly Tyr
 20 25 30
 Gly Val Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45
 Gly Met Ile Trp Gly Asp Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys
 50 55 60
 Ser Arg Leu Ser Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
 65 70 75 80
 Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala
 85 90 95
 Arg Asp Gly Tyr Ser Asn Phe His Tyr Tyr Val Met Asp Tyr Trp Gly
 100 105 110
 Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Asp Ile Val
 130 135 140
 Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
 145 150 155 160
 Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr Val Thr Ser
 165 170 175
 Leu Met Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
 180 185 190
 Ile Ser Ala Ala Ser Asn Val Glu Ser Gly Val Pro Ala Arg Phe Ser
 195 200 205
 Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His Pro Val Glu
 210 215 220
 Glu Asp Asp Ile Ala Met Tyr Phe Cys Gln Gln Ser Arg Lys Val Pro
 225 230 235 240
 Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 245 250

<210> 110

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Signal peptide of 2E12 scFv

<400> 110

Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
 1 5 10 15
 Val Ile Met Ser Arg Gly
 20

<210> 111

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Signal peptide in various single chain fusion proteins (X01xx)

<400> 111

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Trp Leu Pro
 1 5 10 15
 Asp Thr Thr Gly
 20

<210> 112

<211> 107

<212> PRT

<213> Homo sapiens

<400> 112

```

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1      5      10
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20      25      30
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35      40      45
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50      55      60
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65      70      75      80
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85      90      95
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100      105

```

<210> 113

<211> 106

<212> PRT

<213> Homo sapiens

<400> 113

```

Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser
1      5      10      15
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20      25      30
Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro

35      40      45
Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
50      55      60
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65      70      75      80
Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85      90      95
Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100      105

```

<210> 114

<211> 98

<212> PRT

<213> Homo sapiens

<400> 114

```

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1      5      10      15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20      25      30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35      40      45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50      55      60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65      70      75      80
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85      90      95
Lys Val

```

<210> 115

<211> 110

<212> PRT

<213> Homo sapiens

<400> 115

```

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1      5      10      15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20      25      30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35      40      45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50      55      60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65      70      75      80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85      90      95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100      105      110

```

<210> 116

<211> 107

<212> PRT

<213> Homo sapiens

<400> 116

```

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 1          5          10          15
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
          20          25          30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 35          40          45
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 50          55          60
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 65          70          75          80
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 85          90          95
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
          100          105

```

<210> 117

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> VH of HD37

<400> 117

```

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
 1          5          10          15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
          20          25          30
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
          35          40          45
Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
          50          55          60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Thr Ala Tyr
 65          70          75          80
Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys
          85          90          95
Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
          100          105          110
Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser
          115          120          125

```

<210> 118

<400> 118

000

<210> 119

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> VL of HD37

<400> 119

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1          5          10          15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
          20          25          30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
          35          40          45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
          50          55          60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65          70          75          80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
          85          90          95

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
          100          105          110

```

<210> 120

<211> 249

<212> PRT

<213> Artificial Sequence

<220>

<223> M0042 scFv (VL-VH)

<400> 120

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
 20           25           30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Ser Lys Leu Leu Val
 35           40           45
Tyr Ser Val Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50           55           60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
 65           70           75           80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Phe
 85           90           95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Gly Gly Gly Ser
100           105           110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly
115           120           125
Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
130           135           140
Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr Tyr
145           150           155           160
Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
165           170           175
Tyr Ile Gly Pro Ser Gly Gly Phe Thr Ala Tyr Ala Asp Ser Val Lys
180           185           190
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
195           200           205
Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
210           215           220
Arg Asp Gly Trp Val Gly Ser Glu Asn Tyr Ser Gly Met Asp Val Trp
225           230           235           240
Gly Gln Gly Thr Thr Val Ser Ser Ser
245

```

<210> 121

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> VH of M0042

<400> 121

```

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 His Tyr
 20           25           30
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35           40           45
Ser Tyr Ile Gly Pro Ser Gly Gly Phe Thr Ala Tyr Ala Asp Ser Val
 50           55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65           70           75           80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85           90           95
Ala Arg Asp Gly Trp Val Gly Ser Glu Asn Tyr Ser Gly Met Asp Val
100           105           110
Trp Gly Gln Gly Thr Thr Val Ser Ser
115           120

```

<210> 122

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> VL of M0042

<400> 122

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20     25     30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Val
35     40     45
Tyr Ser Val Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50     55     60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
65     70     75     80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Phe
85     90     95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100    105

```

<210> 123

<400> 123

000

<210> 124

<400> 124

000

<210> 125

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> NKG2D Linker

<400> 125

```

Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1      5      10      15
Ser Pro Asn Ser
20

```

<210> 126

<400> 126

000

<210> 127

<400> 127

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<210> 128

<400> 128

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<210> 129

<400> 129

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<210> 137

<400> 137

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<210> 138

<400> 138

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<210> 139

<400> 139

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<210> 140

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human C1 sequence used in constructing Interceptors

<400> 140

Gln	Pro	Lys	Ala	Asn	Pro	Thr	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu
1				5					10				15		
Glu	Leu	Gln	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe
		20						25				30			
Tyr	Pro	Gly	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Pro	Val
		35				40					45				
Lys	Ala	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys
	50					55					60				
Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser
65					70					75				80	
His	Arg	Ser	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu
			85						90					95	
Lys	Thr	Val	Ala	Pro	Thr	Glu	Ser	Ser							
			100					105							

<210> 141

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck sequence used in constructing Interceptors

<400> 141

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35      40      45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50      55      60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100      105

```

<210> 142

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N29A substitution

<400> 142

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Ala Asn Phe Tyr
20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35      40      45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50      55      60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100      105

```

<210> 143

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N30A substitution

<400> 143

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Ala Phe Tyr
20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35      40      45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50      55      60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100      105

```

<210> 144

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with Q52A substitution

<400> 144


```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Ala Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 145

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A substitution

<400> 145

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95

```

```

Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 146

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with T56A substitution

<400> 146

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Val Ala Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 147

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with S68A substitution

<400> 147

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ala Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 148

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with T70A substitution

<400> 148

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 149

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A N29A substitution

<400> 149

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Ala Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 150

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A N30A substitution

<400> 150

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Ala Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50      55      60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100      105

```

<210> 151

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A Q52A substitution

<400> 151

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45
Gly Asn Ser Ala Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50      55      60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100      105

```

<210> 152

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A S68A substitution

<400> 152

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50      55      60
Tyr Ser Leu Ala Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100      105

```

<210> 153

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A T70A substitution

<400> 153

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr

```

```

      50      55      60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
      85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
      100      105

```

<210> 154

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A N29A N30A substitution

<400> 154

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Ala Ala Phe Tyr
      20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
      35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
      50      55      60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
      85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
      100      105

```

<210> 155

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A N29A S68A substitution

<400> 155

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Ala Asn Phe Tyr
      20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
      35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
      50      55      60
Tyr Ser Leu Ala Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
      85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
      100      105

```

<210> 156

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A S68A T70A substitution

<400> 156

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
      20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
      35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
      50      55      60
Tyr Ser Leu Ala Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
      85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
      100      105

```

<210> 157

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55A Q52A S68A substitution

<400> 157

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Ala Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ala Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100          105

```

<210> 158

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N29R V55A T70A substitution

<400> 158

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Arg Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100          105

```

<210> 159

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N29AK V55A T70A substitution

<400> 159

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Lys Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100          105

```

<210> 160

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N29W V55A T70A substitution

<400> 160

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Trp Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 161

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N29Y V55A T70A substitution

<400> 161

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Tyr Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 162

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with S68K V55A substitution

<400> 162

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Lys Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 163

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with S68E V55A substitution

<400> 163

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
50      55      60
Tyr Ser Leu Glu Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100      105

```

<210> 164

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with S68Q V55A substitution

<400> 164

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
50      55      60
Tyr Ser Leu Glu Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100      105

```

<210> 165

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with T70E V55A substitution

<400> 165

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
50      55      60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100      105

```

<210> 166

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with Q52L N29A N30A substitution

<400> 166

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Ala Ala Phe Tyr
20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35      40      45
Gly Asn Ser Leu Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr

```

```

      50              55              60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65              70              75              80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
      85              90              95
Val Thr Lys Ser Phe Asn Arg Gly Glu
      100              105

```

<210> 167

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N30R V55A T70A substitution

<400> 167

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1              5              10              15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Arg Phe Tyr
      20              25              30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
      35              40              45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
      50              55              60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65              70              75              80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
      85              90              95
Val Thr Lys Ser Phe Asn Arg Gly Glu
      100              105

```

<210> 168

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N30K V55A T70A substitution

<400> 168

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1              5              10              15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Lys Phe Tyr
      20              25              30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
      35              40              45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
      50              55              60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65              70              75              80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
      85              90              95
Val Thr Lys Ser Phe Asn Arg Gly Glu
      100              105

```

<210> 169

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N30W V55A T70A substitution

<400> 169

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1              5              10              15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Trp Phe Tyr
      20              25              30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
      35              40              45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
      50              55              60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65              70              75              80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
      85              90              95
Val Thr Lys Ser Phe Asn Arg Gly Glu
      100              105

```


<210> 170
 <211> 105
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Altered human Ck with N30E V55A T70A substitution

<400> 170

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Glu Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 171
 <211> 105
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Altered human Ck with N30G V55A T70A substitution

<400> 171

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Gly Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Ala Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 172
 <211> 105
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Altered human Ck with V55R N29A N30A substitution

<400> 172

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Ala Ala Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Arg Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 173
 <211> 105
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Altered human Ck with V55W N29A N30A substitution

<400> 173

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1           5           10           15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Ala Ala Phe Tyr
           20           25           30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
           35           40           45
Gly Asn Ser Gln Glu Ser Trp Thr Glu Gln Asp Ser Lys Asp Ser Thr
           50           55           60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65           70           75           80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
           85           90           95
Val Thr Lys Ser Phe Asn Arg Gly Glu
           100          105

```

<210> 174

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with V55E N29A N30A substitution

<400> 174

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1           5           10           15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Ala Ala Phe Tyr
           20           25           30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
           35           40           45
Gly Asn Ser Gln Glu Ser Glu Thr Glu Gln Asp Ser Lys Asp Ser Thr
           50           55           60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65           70           75           80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
           85           90           95
Val Thr Lys Ser Phe Asn Arg Gly Glu
           100          105

```

<210> 175

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N29W N30Y V55A T70E (WYAE) substitution

<400> 175

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1           5           10           15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Trp Tyr Phe Tyr
           20           25           30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
           35           40           45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
           50           55           60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65           70           75           80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
           85           90           95
Val Thr Lys Ser Phe Asn Arg Gly Glu
           100          105

```

<210> 176

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N29Y N30Y V55A T70E (YYAE) substitution

<400> 176

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Tyr Tyr Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50      55      60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100      105

```

<210> 177

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N30E V55A T70E (EAE) substitution

<400> 177

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Glu Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50      55      60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100      105

```

<210> 178

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck with N30Y V55A T70E (YAE) substitution

<400> 178

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50      55      60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100      105

```

<210> 179

<400> 179

000

<210> 180

<400> 180

000

<210> 181

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Portion of human IgG1 hinge

<400> 181

Cys Pro Pro Cys
1

<210> 182

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> VL of P2C2 scFv

<400> 182

Asp	Ile	Val	Met	Ile	Gln	Asp	Glu	Leu	Ser	Asn	Pro	Val	Ser	Ser	Gly
1				5					10					15	
Glu	Ser	Val	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Lys	Ser	Leu	Leu	Asp	Lys
			20					25					30		
Glu	Gly	Lys	Thr	Tyr	Leu	Asn	Trp	Phe	Leu	Gln	Arg	Pro	Gly	Gln	Ser
		35				40					45				
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Met	Ser	Met	Arg	Glu	Ser	Gly	Val	Ser
	50					55				60					
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Glu	Ile
65			70						75					80	
Ser	Arg	Val	Lys	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Gln	Gln	Leu
			85						90				95		
Val	Glu	Tyr	Pro	Trp	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys
			100				105						110		

<210> 183

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker of P2C2 scFv

<400> 183

Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
1				5					10					15

<210> 184

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> VH of P2C2 scFv

<400> 184

Gln	Ile	Gln	Leu	Val	Gln	Ser	Gly	Pro	Glu	Leu	Lys	Lys	Pro	Gly	Glu
1				5					10					15	
Thr	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Phe
			20					25					30		
Ser	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Lys	Trp	Met
		35				40					45				
Gly	Trp	Ile	Asn	Thr	Glu	Thr	Gly	Glu	Pro	Thr	Tyr	Ala	Asp	Asp	Phe
	50				55					60					
Arg	Gly	Arg	Phe	Ala	Phe	Ser	Leu	Glu	Thr	Ser	Ala	Ser	Thr	Ala	Tyr
65			70						75					80	
Leu	Gln	Ile	Asn	Asn	Leu	Lys	Asn	Glu	Asp	Thr	Ala	Thr	Tyr	Phe	Cys
			85					90					95		
Thr	Trp	Ser	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ala
			100				105						110		

<210> 185

<211> 239

<212> PRT

<213> Artificial Sequence

<220>

<223> full length of P2C2 scFv

<400> 185

```

Asp Ile Val Met Ile Gln Asp Glu Leu Ser Asn Pro Val Ser Ser Gly
1      5      10      15
Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asp Lys
20     25     30
Glu Gly Lys Thr Tyr Leu Asn Trp Phe Leu Gln Arg Pro Gly Gln Ser
35     40     45
Pro Gln Leu Leu Ile Tyr Leu Met Ser Met Arg Glu Ser Gly Val Ser
50     55     60
Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Glu Ile
65     70     75     80
Ser Arg Val Lys Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Leu
85     90     95
Val Glu Tyr Pro Trp Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
100    105    110
Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln
115    120    125
Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr
130    135    140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Phe Ser
145    150    155    160
Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly
165    170    175
Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Arg
180    185    190
Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu
195    200    205
Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Thr
210    215    220
Trp Ser Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
225    230    235

```

<210> 186

<211> 102

<212> PRT

<213> Homo sapiens

<400> 186

```

Ala Ser Pro Thr Ser Pro Lys Val Phe Pro Leu Ser Leu Cys Ser Thr
1      5      10      15
Gln Pro Asp Gly Asn Val Val Ile Ala Cys Leu Val Gln Gly Phe Phe
20     25     30
Pro Gln Glu Pro Leu Ser Val Thr Trp Ser Glu Ser Gly Gln Gly Val
35     40     45
Thr Ala Arg Asn Phe Pro Pro Ser Gln Asp Ala Ser Gly Asp Leu Tyr
50     55     60
Thr Thr Ser Ser Gln Leu Thr Leu Pro Ala Thr Gln Cys Leu Ala Gly
65     70     75     80

Lys Ser Val Thr Cys His Val Lys His Tyr Thr Asn Pro Ser Gln Asp
85     90     95
Val Thr Val Pro Cys Pro
100

```

<210> 187

<211> 102

<212> PRT

<213> Homo sapiens

<400> 187

```

Ala Ser Pro Thr Ser Pro Lys Val Phe Pro Leu Ser Leu Asp Ser Thr
1      5      10      15
Pro Gln Asp Gly Asn Val Val Val Ala Cys Leu Val Gln Gly Phe Phe
20     25     30
Pro Gln Glu Pro Leu Ser Val Thr Trp Ser Glu Ser Gly Gln Asn Val
35     40     45
Thr Ala Arg Asn Phe Pro Pro Ser Gln Asp Ala Ser Gly Asp Leu Tyr
50     55     60
Thr Thr Ser Ser Gln Leu Thr Leu Pro Ala Thr Gln Cys Pro Asp Gly
65     70     75     80
Lys Ser Val Thr Cys His Val Lys His Tyr Thr Asn Pro Ser Gln Asp
85     90     95
Val Thr Val Pro Cys Pro
100

```

<210> 188

<211> 101

<212> PRT

<213> Homo sapiens

<400> 188

```

Ala Pro Thr Lys Ala Pro Asp Val Phe Pro Ile Ile Ser Gly Cys Arg
 1          5          10          15
His Pro Lys Asp Asn Ser Pro Val Val Leu Ala Cys Leu Ile Thr Gly
 20          25          30
Tyr His Pro Thr Ser Val Thr Val Thr Trp Tyr Met Gly Thr Gln Ser
 35          40          45
Gln Pro Gln Arg Thr Phe Pro Glu Ile Gln Arg Arg Asp Ser Tyr Tyr
 50          55          60
Met Thr Ser Ser Gln Leu Ser Thr Pro Leu Gln Gln Trp Arg Gln Gly
 65          70          75          80
Glu Tyr Lys Cys Val Val Gln His Thr Ala Ser Lys Ser Lys Lys Glu
 85          90          95
Ile Phe Arg Trp Pro
100

```

<210> 189

<211> 103

<212> PRT

<213> Homo sapiens

<400> 189

```

Ala Ser Thr Gln Ser Pro Ser Val Phe Pro Leu Thr Arg Cys Cys Lys
 1          5          10          15
Asn Ile Pro Ser Asn Ala Thr Ser Val Thr Leu Gly Cys Leu Ala Thr
 20          25          30
Gly Tyr Phe Pro Glu Pro Val Met Val Thr Cys Asp Thr Gly Ser Leu
 35          40          45
Asn Gly Thr Thr Met Thr Leu Pro Ala Thr Thr Leu Thr Leu Ser Gly
 50          55          60
His Tyr Ala Thr Ile Ser Leu Leu Thr Val Ser Gly Ala Trp Ala Lys
 65          70          75          80
Gln Met Phe Thr Cys Arg Val Ala His Thr Pro Ser Ser Thr Asp Trp
 85          90          95
Val Asp Asn Lys Thr Phe Ser
100

```

<210> 190

<211> 98

<212> PRT

<213> Homo sapiens

<400> 190

```

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1          5          10          15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20          25          30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35          40          45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50          55          60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
 65          70          75          80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85          90          95
Thr Val

```

<210> 191

<211> 98

<212> PRT

<213> Homo sapiens

<400> 191

```

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1          5          10          15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20          25          30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35          40          45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50          55          60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65          70          75          80
Tyr Thr Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85          90          95
Arg Val

```

<210> 192

<211> 98

<212> PRT

<213> Homo sapiens

<400> 192

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1 5 10 15
 Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
 65 70 75 80
 Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Arg Val

<210> 193

<400> 193

000

<210> 194

<211> 104

<212> PRT

<213> Homo sapiens

<400> 194

Gly Ser Ala Ser Ala Pro Thr Leu Phe Pro Leu Val Ser Cys Glu Asn
 1 5 10 15
 Ser Pro Ser Asp Thr Ser Ser Val Ala Val Gly Cys Leu Ala Gln Asp
 20 25 30
 Phe Leu Pro Asp Ser Ile Thr Leu Ser Trp Lys Tyr Lys Asn Asn Ser
 35 40 45
 Asp Ile Ser Ser Thr Arg Gly Phe Pro Ser Val Leu Arg Gly Gly Lys
 50 55 60
 Tyr Ala Ala Thr Ser Gln Val Leu Leu Pro Ser Lys Asp Val Met Gln
 65 70 75 80
 Gly Thr Asp Glu His Val Val Cys Lys Val Gln His Pro Asn Gly Asn
 85 90 95
 Lys Glu Lys Asn Val Pro Leu Pro
 100

<210> 195

<211> 101

<212> PRT

<213> Homo sapiens

<400> 195

Cys Cys His Pro Arg Leu Ser Leu His Arg Pro Ala Leu Glu Asp Leu
 1 5 10 15
 Leu Leu Gly Ser Glu Ala Asn Leu Thr Cys Thr Leu Thr Gly Leu Arg
 20 25 30
 Asp Ala Ser Gly Val Thr Phe Thr Trp Thr Pro Ser Ser Gly Lys Ser
 35 40 45
 Ala Val Gln Gly Pro Pro Glu Arg Asp Leu Cys Gly Cys Tyr Ser Val
 50 55 60
 Ser Ser Val Leu Pro Gly Cys Ala Glu Pro Trp Asn His Gly Lys Thr
 65 70 75 80
 Phe Thr Cys Thr Ala Ala Tyr Pro Glu Ser Lys Thr Pro Leu Thr Ala
 85 90 95
 Thr Leu Ser Lys Ser
 100

<210> 196

<211> 101

<212> PRT

<213> Homo sapiens

<400> 196

Cys Cys His Pro Arg Leu Ser Leu His Arg Pro Ala Leu Glu Asp Leu
 1 5 10 15
 Leu Leu Gly Ser Glu Ala Asn Leu Thr Cys Thr Leu Thr Gly Leu Arg

```

      20      25      30
Asp Ala Ser Gly Ala Thr Phe Thr Trp Thr Pro Ser Ser Gly Lys Ser
      35      40      45
Ala Val Gln Gly Pro Pro Glu Arg Asp Leu Cys Gly Cys Tyr Ser Val
      50      55      60
Ser Ser Val Leu Pro Gly Cys Ala Gln Pro Trp Asn His Gly Glu Thr
      65      70      75      80
Phe Thr Cys Thr Ala Ala His Pro Glu Leu Lys Thr Pro Leu Thr Ala
      85      90      95
Asn Ile Thr Lys Ser
      100

```

<210> 197

<211> 108

<212> PRT

<213> Homo sapiens

<400> 197

```

Glu Cys Pro Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro
1      5      10      15
Ala Val Gln Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe
      20      25      30
Val Val Gly Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala
      35      40      45
Gly Lys Val Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His
      50      55      60
Ser Asn Gly Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser
      65      70      75      80
Leu Trp Asn Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser
      85      90      95
Leu Pro Pro Gln Arg Leu Met Ala Leu Arg Glu Pro
      100      105

```

<210> 198

<211> 107

<212> PRT

<213> Homo sapiens

<400> 198

```

Val Cys Ser Arg Asp Phe Thr Pro Pro Thr Val Lys Ile Leu Gln Ser
1      5      10      15
Ser Cys Asp Gly Gly His Phe Pro Pro Thr Ile Gln Leu Leu Cys
      20      25      30
Leu Val Ser Gly Tyr Thr Pro Gly Thr Ile Asn Ile Thr Trp Leu Glu
      35      40      45
Asp Gly Gln Val Met Asp Val Asp Leu Ser Thr Ala Ser Thr Thr Gln
      50      55      60
Glu Gly Glu Leu Ala Ser Thr Gln Ser Glu Leu Thr Leu Ser Gln Lys
      65      70      75      80
His Trp Leu Ser Asp Arg Thr Tyr Thr Cys Gln Val Thr Tyr Gln Gly
      85      90      95
His Thr Phe Glu Asp Ser Thr Lys Lys Cys Ala
      100      105

```

<210> 199

<211> 109

<212> PRT

<213> Homo sapiens

<400> 199

```

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1      5      10      15

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
      20      25      30
Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
      35      40      45
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
      50      55      60
Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
      65      70      75      80
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
      85      90      95
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
      100      105

```

<210> 200

<211> 110

<212> PRT

<213> Homo sapiens

<400> 200


```

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 1          5          10          15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 20
Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr
 35          40          45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 50          55          60
Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
 65          70          75          80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 85          90          95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
 100          105          110

```

<210> 201

<211> 110

<212> PRT

<213> Homo sapiens

<400> 201

```

Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 1          5          10          15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 20
Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
 35          40          45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 50          55          60
Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 65          70          75          80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 85          90          95
Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
 100          105          110

```

<210> 202

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human Ck region + T70E, N29A, N30A, V55A

<400> 202

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Ala Ala Phe Tyr
 20
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100          105

```

<210> 203

<211> 112

<212> PRT

<213> Homo sapiens

<400> 203

```

Val Ile Ala Glu Leu Pro Pro Lys Val Ser Val Phe Val Pro Pro Arg
 1          5          10          15
Asp Gly Phe Phe Gly Asn Pro Arg Lys Ser Lys Leu Ile Cys Gln Ala
 20
Thr Gly Phe Ser Pro Arg Gln Ile Gln Val Ser Trp Leu Arg Glu Gly
 35          40          45
Lys Gln Val Gly Ser Gly Val Thr Thr Asp Gln Val Gln Ala Glu Ala
 50          55          60
Lys Glu Ser Gly Pro Thr Thr Tyr Lys Val Thr Ser Thr Leu Thr Ile
 65          70          75          80
Lys Glu Ser Asp Trp Leu Gly Gln Ser Met Phe Thr Cys Arg Val Asp
 85          90          95
His Arg Gly Leu Thr Phe Gln Gln Asn Ala Ser Ser Met Cys Val Pro
 100          105          110

```

<210> 204

<211> 131

<212> PRT

<213> Homo sapiens

<400> 204

```

Gly Asn Thr Phe Arg Pro Glu Val His Leu Leu Pro Pro Pro Ser Glu
 1          5          10          15
Glu Leu Ala Leu Asn Glu Leu Val Thr Leu Thr Cys Leu Ala Arg Gly
 20          25          30
Phe Ser Pro Lys Asp Val Leu Val Arg Trp Leu Gln Gly Ser Gln Glu
 35          40          45
Leu Pro Arg Glu Lys Tyr Leu Thr Trp Ala Ser Arg Gln Glu Pro Ser
 50          55          60
Gln Gly Thr Thr Thr Phe Ala Val Thr Ser Ile Leu Arg Val Ala Ala
 65          70          75          80
Glu Asp Trp Lys Lys Gly Asp Thr Phe Ser Cys Met Val Gly His Glu
 85          90          95
Ala Leu Pro Leu Ala Phe Thr Gln Lys Thr Ile Asp Arg Leu Ala Gly
100          105          110
Lys Pro Thr His Val Asn Val Ser Val Val Met Ala Glu Val Asp Gly
115          120          125
Thr Cys Tyr
130

```

<210> 205

<211> 131

<212> PRT

<213> Homo sapiens

<400> 205

```

Gly Asn Thr Phe Arg Pro Glu Val His Leu Leu Pro Pro Pro Ser Glu
 1          5          10          15
Glu Leu Ala Leu Asn Glu Leu Val Thr Leu Thr Cys Leu Ala Arg Gly
 20          25          30
Phe Ser Pro Lys Asp Val Leu Val Arg Trp Leu Gln Gly Ser Gln Glu
 35          40          45
Leu Pro Arg Glu Lys Tyr Leu Thr Trp Ala Ser Arg Gln Glu Pro Ser
 50          55          60
Gln Gly Thr Thr Thr Phe Ala Val Thr Ser Ile Leu Arg Val Ala Ala
 65          70          75          80
Glu Asp Trp Lys Lys Gly Asp Thr Phe Ser Cys Met Val Gly His Glu
 85          90          95
Ala Leu Pro Leu Ala Phe Thr Gln Lys Thr Ile Asp Arg Leu Ala Gly
100          105          110
Lys Pro Thr His Val Asn Val Ser Val Val Met Ala Glu Val Asp Gly
115          120          125
Thr Cys Tyr
130

```

<210> 206

<211> 117

<212> PRT

<213> Homo sapiens

<400> 206

```

Ala Ala Gln Ala Pro Val Lys Leu Ser Leu Asn Leu Leu Ala Ser Ser
 1          5          10          15
Asp Pro Pro Glu Ala Ala Ser Trp Leu Leu Cys Glu Val Ser Gly Phe
 20          25          30
Ser Pro Pro Asn Ile Leu Leu Met Trp Leu Glu Asp Gln Arg Glu Val
 35          40          45
Asn Thr Ser Gly Phe Ala Pro Ala Arg Pro Pro Pro Gln Pro Arg Ser
 50          55          60
Thr Thr Phe Trp Ala Trp Ser Val Leu Arg Val Pro Ala Pro Pro Ser
 65          70          75          80
Pro Gln Pro Ala Thr Tyr Thr Cys Val Val Ser His Glu Asp Ser Arg
 85          90          95
Thr Leu Leu Asn Ala Ser Arg Ser Leu Glu Val Ser Tyr Val Thr Asp
100          105          110
His Gly Pro Met Lys
115

```

<210> 207

<211> 108

<212> PRT

<213> Homo sapiens

<400> 207

```

Asp Ser Asn Pro Arg Gly Val Ser Ala Tyr Leu Ser Arg Pro Ser Pro
 1          5          10          15
Phe Asp Leu Phe Ile Arg Lys Ser Pro Thr Ile Thr Cys Leu Val Val
 20          25          30
Asp Leu Ala Pro Ser Lys Gly Thr Val Asn Leu Thr Trp Ser Arg Ala
 35          40          45
Ser Gly Lys Pro Val Asn His Ser Thr Arg Lys Glu Glu Lys Gln Arg
 50          55          60

Asn Gly Thr Leu Thr Val Thr Ser Thr Leu Pro Val Gly Thr Arg Asp
 65          70          75          80
Trp Ile Glu Gly Glu Thr Tyr Gln Cys Arg Val Thr His Pro His Leu
 85          90          95
Pro Arg Ala Leu Met Arg Ser Thr Thr Lys Thr Ser
 100          105

```

<210> 208

<211> 107

<212> PRT

<213> Homo sapiens

<400> 208

```

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
 1          5          10          15
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 20          25          30
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 35          40          45
Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
 50          55          60
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 65          70          75          80
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 85          90          95
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 100          105

```

<210> 209

<211> 107

<212> PRT

<213> Homo sapiens

<400> 209

```

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
 1          5          10          15
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 20          25          30
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu
 35          40          45
Asn Asn Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
 50          55          60
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 65          70          75          80
Asn Ile Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe
 85          90          95
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 100          105

```

<210> 210

<211> 107

<212> PRT

<213> Homo sapiens

<400> 210

```

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
 1          5          10          15
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 20          25          30
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 35          40          45
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 50          55          60
Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
 65          70          75          80
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 85          90          95
Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
 100          105

```

<210> 211

<211> 7

<212> PRT

<213> Homo sapiens

<400> 211

Glu Arg Lys Cys Cys Val Glu
 1 5

<210> 212

<211> 106

<212> PRT

<213> Homo sapiens

<400> 212

Asp Gln Asp Thr Ala Ile Arg Val Phe Ala Ile Pro Pro Ser Phe Ala
 1 5 10 15
 Ser Ile Phe Leu Thr Lys Ser Thr Lys Leu Thr Cys Leu Val Thr Asp
 20 25 30
 Leu Thr Thr Tyr Asp Ser Val Thr Ile Ser Trp Thr Arg Gln Asn Gly
 35 40 45
 Glu Ala Val Lys Thr His Thr Asn Ile Ser Glu Ser His Pro Asn Ala
 50 55 60
 Thr Phe Ser Ala Val Gly Glu Ala Ser Ile Cys Glu Asp Asp Trp Asn
 65 70 75 80
 Ser Gly Glu Arg Phe Thr Cys Thr Val Thr His Thr Asp Leu Pro Ser
 85 90 95
 Pro Leu Lys Gln Thr Ile Ser Arg Pro Lys
 100 105

<210> 213

<211> 110

<212> PRT

<213> Homo sapiens

<400> 213

Gly Pro Arg Ala Ala Pro Glu Val Tyr Ala Phe Ala Thr Pro Glu Trp
 1 5 10 15
 Pro Gly Ser Arg Asp Lys Arg Thr Leu Ala Cys Leu Ile Gln Asn Phe
 20 25 30
 Met Pro Glu Asp Ile Ser Val Gln Trp Leu His Asn Glu Val Gln Leu
 35 40 45
 Pro Asp Ala Arg His Ser Thr Thr Gln Pro Arg Lys Thr Lys Gly Ser
 50 55 60
 Gly Phe Phe Val Phe Ser Arg Leu Glu Val Thr Arg Ala Glu Trp Glu
 65 70 75 80
 Gln Lys Asp Glu Phe Ile Cys Arg Ala Val His Glu Ala Ala Ser Pro
 85 90 95
 Ser Gln Thr Val Gln Arg Ala Val Ser Val Asn Pro Gly Lys
 100 105 110

<210> 214

<211> 131

<212> PRT

<213> Homo sapiens

<400> 214

Gly Val Ala Leu His Arg Pro Asp Val Tyr Leu Leu Pro Pro Ala Arg
 1 5 10 15
 Glu Gln Leu Asn Leu Arg Glu Ser Ala Thr Ile Thr Cys Leu Val Thr
 20 25 30
 Gly Phe Ser Pro Ala Asp Val Phe Val Gln Trp Met Gln Arg Gly Gln
 35 40 45
 Pro Leu Ser Pro Glu Lys Tyr Val Thr Ser Ala Pro Met Pro Glu Pro
 50 55 60
 Gln Ala Pro Gly Arg Tyr Phe Ala His Ser Ile Leu Thr Val Ser Glu
 65 70 75 80
 Glu Glu Trp Asn Thr Gly Glu Thr Tyr Thr Cys Val Val Ala His Glu
 85 90 95
 Ala Leu Pro Asn Arg Val Thr Glu Arg Thr Val Asp Lys Ser Thr Gly
 100 105 110
 Lys Pro Thr Leu Tyr Asn Val Ser Leu Val Met Ser Asp Thr Ala Gly
 115 120 125
 Thr Cys Tyr
 130

<210> 215

<211> 19

<212> PRT

<213> Homo sapiens

<400> 215

Val Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro
 1 5 10 15
 Ser Pro Ser

<210> 216

<211> 6

<212> PRT

<213> Homo sapiens

<400> 216

Val Pro Pro Pro Pro Pro
 1 5

<210> 217

<211> 58

<212> PRT

<213> Homo sapiens

<400> 217

Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala Gln Pro Gln
 1 5 10 15
 Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala Thr Thr Arg
 20 25 30
 Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys Glu Lys Glu
 35 40 45
 Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro
 50 55

<210> 218

<400> 218

000

<210> 219

<211> 12

<212> PRT

<213> Homo sapiens

<400> 219

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
 1 5 10

<210> 220

<211> 62

<212> PRT

<213> Homo sapiens

<400> 220

Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro Arg Cys
 1 5 10 15
 Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
 20 25 30
 Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu
 35 40 45
 Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
 50 55 60

<210> 221

<211> 12

<212> PRT

<213> Homo sapiens

<400> 221

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro
 1 5 10

<210> 222

<211> 34

<212> PRT

<213> Homo sapiens

<400> 222

```

Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala Gln Pro Gln
 1      5      10      15
Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala Thr Thr Arg
 20      25      30
Asn Thr

```

<210> 223

<211> 106

<212> PRT

<213> Homo sapiens

<400> 223

```

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
 1      5      10      15
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
 20      25      30
Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
 35      40      45
Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn

```

```

      50      55      60
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65      70      75      80
Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
      85      90      95
Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100      105

```

<210> 224

<211> 106

<212> PRT

<213> Homo sapiens

<400> 224

```

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
 1      5      10      15
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
 20      25      30
Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
 35      40      45
Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50      55      60
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65      70      75      80
Ser His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
      85      90      95
Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100      105

```

<210> 225

<211> 106

<212> PRT

<213> Homo sapiens

<400> 225

```

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
 1      5      10      15
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
 20      25      30
Phe Tyr Pro Gly Ala Val Lys Val Ala Trp Lys Ala Asp Gly Ser Pro
 35      40      45
Val Asn Thr Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50      55      60
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65      70      75      80
Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
      85      90      95
Glu Lys Thr Val Ala Pro Ala Glu Cys Ser
100      105

```

<210> 226

<211> 106

<212> PRT

<213> Homo sapiens

<400> 226

```

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
 1          5          10          15
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Val Ser Asp
 20          25          30
Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
 35          40          45

Val Lys Val Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
 50          55          60
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
 65          70          75          80
Ser His Arg Ser Tyr Ser Cys Arg Val Thr His Glu Gly Ser Thr Val
 85          90          95
Glu Lys Thr Val Ala Pro Ala Glu Cys Ser
 100          105

```

<210> 227

<211> 10

<212> PRT

<213> Homo sapiens

<400> 227

```

Glu Pro Lys Ser Cys Asp Lys Thr His Thr
 1          5          10

```

<210> 228

<211> 5

<212> PRT

<213> Homo sapiens

<400> 228

```

Cys Pro Pro Cys Pro
 1          5

```

<210> 229

<400> 229

000

<210> 230

<400> 230

000

<210> 231

<400> 231

000

<210> 232

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human IgG1 hinge (CSC-P)

<400> 232

```

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Ser Pro Pro Cys Pro
 1          5          10          15

```

<210> 233

<400> 233

000

<210> 234

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human IgG1 hinge (CCS-P)

<400> 234

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Pro
1				5					10					15

<210> 235

<400> 235

000

<210> 236

<400> 236

000

<210> 237

<400> 237

000

<210> 238

<400> 238

000

<210> 239

<400> 239

000

<210> 240

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human IgG1 hinge (CCS-S)

<400> 240

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Ser
1				5					10					15

<210> 241

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Stalk region of CD69

<400> 241

Gln	Tyr	Asn	Cys	Pro	Gly	Gln	Tyr	Thr	Phe	Ser	Met
1				5					10		

<210> 242

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Stalk region of CD72

<400> 242

Pro	Phe	Phe	Thr	Cys	Gly	Ser	Ala	Asp	Thr	Cys
1				5					10	

<210> 243

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Stalk region of CD94

<400> 243

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

<210> 244

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Stalk region of NKG2A

<400> 244

Gln	Arg	His	Asn	Asn	Ser	Ser	Leu	Asn	Thr	Arg	Thr	Gln	Lys	Ala	Arg
1				5				10						15	
His	Cys														

<210> 245

<211> 12

<212> PRT

<213> Homo sapiens

<400> 245

Glu	Leu	Lys	Thr	Pro	Leu	Gly	Asp	Thr	Thr	His	Thr
1				5				10			

<210> 246

<211> 10

<212> PRT

<213> Homo sapiens

<400> 246

Glu	Pro	Lys	Ser	Cys	Asp	Thr	Pro	Pro	Pro
1				5				10	

<210> 247

<211> 7

<212> PRT

<213> Homo sapiens

<400> 247

Glu	Ser	Lys	Tyr	Gly	Pro	Pro
1				5		

<210> 248

<211> 5

<212> PRT

<213> Homo sapiens

<400> 248

Cys	Pro	Arg	Cys	Pro
1				5

<210> 249

<211> 5

<212> PRT

<213> Homo sapiens

<400> 249

Cys Pro Ser Cys Pro
1 5

<210> 250

<211> 17

<212> PRT

<213> Homo sapiens

<400> 250

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

<210> 251

<211> 15

<212> PRT

<213> Homo sapiens

<400> 251

Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
1 5 10 15

<210> 252

<211> 24

<212> PRT

<213> Homo sapiens

<400> 252

Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys Glu Lys Glu Glu Gln
1 5 10 15
Glu Glu Arg Glu Thr Lys Thr Pro
20

<210> 253

<211> 107

<212> PRT

<213> Homo sapiens

<400> 253

Val Cys Ser Arg Asp Phe Thr Pro Pro Thr Val Lys Ile Leu Gln Ser
1 5 10 15
Ser Ser Asp Gly Gly Gly His Phe Pro Pro Thr Ile Gln Leu Leu Cys
20 25 30
Leu Val Ser Gly Tyr Thr Pro Gly Thr Ile Asn Ile Thr Trp Leu Glu
35 40 45
Asp Gly Gln Val Met Asp Val Asp Leu Ser Thr Ala Ser Thr Thr Gln
50 55 60
Glu Gly Glu Leu Ala Ser Thr Gln Ser Glu Leu Thr Leu Ser Gln Lys
65 70 75 80
His Trp Leu Ser Asp Arg Thr Tyr Thr Cys Gln Val Thr Tyr Gln Gly
85 90 95
His Thr Phe Glu Asp Ser Thr Lys Lys Cys Ala
100 105

<210> 254

<211> 112

<212> PRT

<213> Homo sapiens

<400> 254

Val Ile Ala Glu Leu Pro Pro Lys Val Ser Val Phe Val Pro Pro Arg
1 5 10 15
Asp Gly Phe Phe Gly Asn Pro Arg Lys Ser Lys Leu Ile Cys Gln Ala
20 25 30
Thr Gly Phe Ser Pro Arg Gln Ile Gln Val Ser Trp Leu Arg Glu Gly
35 40 45
Lys Gln Val Gly Ser Gly Val Thr Thr Asp Gln Val Gln Ala Glu Ala
50 55 60
Lys Glu Ser Gly Pro Thr Thr Tyr Lys Val Thr Ser Thr Leu Thr Ile
65 70 75 80
Lys Glu Ser Asp Trp Leu Gly Gln Ser Met Phe Thr Cys Arg Val Asp
85 90 95
His Arg Gly Leu Thr Phe Gln Gln Asn Ala Ser Ser Met Cys Val Pro
100 105 110

<210> 255

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Altered human CH2 upper hinge like sequence of IgE

<400> 255

```

Val Cys Ser Arg Asp Phe Thr Pro Pro Thr Val Lys Ile Leu Gln Ser
 1      5      10      15
Ser Ser Asp Gly Gly His Phe Pro Pro Thr Ile Gln Leu Leu Cys
 20      25      30
Leu Val Ser Gly Tyr Thr Pro Gly Thr Ile Asn Ile Thr Trp Leu Glu
 35      40      45
Asp Gly Gln Val Met Asp Val Asp Leu Ser Thr Ala Ser Thr Thr Gln
 50      55      60
Glu Gly Glu Leu Ala Ser Thr Gln Ser Glu Leu Thr Leu Ser Gln Lys
 65      70      75      80
His Trp Leu Ser Asp Arg Thr Tyr Thr Cys Gln Val Thr Tyr Gln Gly
 85      90      95
His Thr Phe Glu Asp Ser Thr Lys Lys Ser Ala
 100      105

```

<210> 256

<211> 268

<212> PRT

<213> Artificial Sequence

<220>

<223> 5D5 scFv (VLVH)

<220>

<221> SIGNAL

<222> (10)...(20)

<400> 256

```

Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Trp Leu Pro
-20      -15      -10      -5
Asp Thr Thr Gly Asp Phe Met Met Ser Gln Ser Pro Ser Ser Leu Thr
 1      5      10
Val Ser Val Gly Glu Lys Val Thr Val Ser Cys Lys Ser Ser Gln Ser
 15      20      25
Leu Leu Tyr Thr Ser Ser Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
 30      35      40
Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg
 45      50      55      60
Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
 65      70      75
Phe Thr Leu Thr Ile Thr Ser Val Lys Ala Asp Asp Leu Ala Val Tyr
 80      85      90
Tyr Cys Gln Gln Tyr Tyr Ala Tyr Pro Trp Thr Phe Gly Gly Gly Thr
 95      100      105
Lys Leu Glu Leu Lys Gly Gly Gly Ser Gly Gly Gly Ser Gly
 110      115      120
Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val
 125      130      135      140
Arg Pro Gly Ala Ser Val Lys Met Ser Cys Arg Ala Ser Gly Tyr Thr
 145      150      155
Phe Thr Ser Tyr Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln Gly
 160      165      170
Leu Glu Trp Ile Gly Met Ile Asp Pro Ser Asn Ser Asp Thr Arg Phe
 175      180      185
Asn Pro Asn Phe Lys Asp Lys Ala Thr Leu Asn Val Asp Arg Ser Ser
 190      195      200
Asn Thr Ala Tyr Met Leu Leu Ser Ser Leu Thr Ser Ala Asp Ser Ala
 205      210      215      220
Val Tyr Tyr Cys Ala Thr Tyr Gly Ser Tyr Val Ser Pro Leu Asp Tyr
 225      230      235
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser
 240      245

```

<210> 257

<211> 248

<212> PRT

<213> Artificial Sequence

<220>

<223> 5D5 scFv (VLVH) mature protein without the signal peptide

<400> 257

```

Asp Phe Met Met Ser Gln Ser Pro Ser Ser Leu Thr Val Ser Val Gly
1      5      10      15
Glu Lys Val Thr Val Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Thr
20      25      30
Ser Ser Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35      40      45
Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50      55      60
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

```

```

65      70      75      80
Ile Thr Ser Val Lys Ala Asp Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85      90      95
Tyr Tyr Ala Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu
100     105     110
Lys Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser
115     120     125
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Ala
130     135     140
Ser Val Lys Met Ser Cys Arg Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
145     150     155     160
Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
165     170     175
Gly Met Ile Asp Pro Ser Asn Ser Asp Thr Arg Phe Asn Pro Asn Phe
180     185     190
Lys Asp Lys Ala Thr Leu Asn Val Asp Arg Ser Ser Asn Thr Ala Tyr
195     200     205
Met Leu Leu Ser Ser Leu Thr Ser Ala Asp Ser Ala Val Tyr Tyr Cys
210     215     220
Ala Thr Tyr Gly Ser Tyr Val Ser Pro Leu Asp Tyr Trp Gly Gln Gly
225     230     235     240
Thr Ser Val Thr Val Ser Ser Ser
245

```

<210> 258

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> 5D5 VH

<400> 258

```

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Ala
1      5      10      15
Ser Val Lys Met Ser Cys Arg Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20      25      30
Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Met Ile Asp Pro Ser Asn Ser Asp Thr Arg Phe Asn Pro Asn Phe
50      55      60
Lys Asp Lys Ala Thr Leu Asn Val Asp Arg Ser Ser Asn Thr Ala Tyr
65      70      75      80
Met Leu Leu Ser Ser Leu Thr Ser Ala Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Thr Tyr Gly Ser Tyr Val Ser Pro Leu Asp Tyr Trp Gly Gln Gly
100     105     110
Thr Ser Val Thr Val Ser Ser Ser
115     120

```

<210> 259

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> 5D5 VL

<400> 259

```

Asp Phe Met Met Ser Gln Ser Pro Ser Ser Leu Thr Val Ser Val Gly
1      5      10      15
Glu Lys Val Thr Val Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Thr
20      25      30

Ser Ser Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35      40      45
Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50      55      60
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65      70      75      80
Ile Thr Ser Val Lys Ala Asp Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85      90      95
Tyr Tyr Ala Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu
100     105     110
Lys

```

<210> 260

<211> 792

<212> DNA

<213> Artificial Sequence

<220>

<223> 4C04 anti-Ron scFv with signal peptide and junction amino acids SSS at carboxy-terminus

<400> 260

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gacattcaga  tgaccocagt  tcctgcctcc  cagtctgcat  ctctgggaga  aagtgtcacc  120
atcacatgcc  tggcaagtca  gaccattggt  acatggtag  catgggtatca  gcagaaacca  180
gggaaatctc  ctccagctcc  gatttatgct  gcaaccagct  tggcagatgg  ggtcccatca  240
aggttcagt  ctagtggatc  tggcacaaaa  ttttctttca  agatcgacag  cctacagtct  300
gaagattttg  taagtattta  ctgtcaacaa  ctttacaata  ctccgtggac  gttcggtgga  360
ggcaccgaag  tggaaatcaa  aggtggcggt  ggctctggcg  gaggtggatc  cggtggcggc  420
ggctctcaga  tccagctgca  gcagtctgga  cctgagctgg  tgaagcctgg  gacttcagt  480
aagatatcct  gcaaggcttc  tgactacaca  ctcaactgact  tctatatgaa  ctgggtgagg  540
cagaagcctg  gacagggact  tgagtggatt  gggaggattt  atcctggaac  cgataaaact  600
agatacaatg  agaattcag  ggacaaggcc  atactgacog  tggacacgtc  ctccagcaca  660
gcctacatgc  agctcagcag  cctgacatca  gaggacactg  ctgtctattt  ctgtgcaaga  720
tccgcctact  atggttaact  cgttgctatg  gactactggg  gtcaaggaa  ctcagtcacc  780
gtctcctcga  gc  792

```

<210> 261

<211> 244

<212> PRT

<213> Artificial Sequence

<220>

<223> 4C04 anti-Ron scFv with signal peptide and junction amino acids SSS at carboxy-terminus

<400> 261

```

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly
1      5      10      15
Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20     25     30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
35     40     45
Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Ala
50     55     60
Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Asp Ser Leu Gln Ser
65     70     75     80
Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Asn Thr Pro Trp
85     90     95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
100    105    110    115
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Gln Leu Gln Gln
120    125

Ser Gly Pro Glu Leu Val Lys Pro Gly Thr Ser Val Lys Ile Ser Cys
130    135    140
Lys Ala Ser Asp Tyr Thr Leu Thr Asp Phe Tyr Met Asn Trp Val Arg
145    150    155    160
Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly
165    170    175
Thr Asp Lys Thr Arg Tyr Asn Glu Lys Phe Arg Asp Lys Ala Ile Leu
180    185    190
Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
195    200    205
Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Ser Ala Tyr Tyr
210    215    220
Gly Asn Tyr Val Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
225    230    235    240
Val Ser Ser Ser

```

<210> 262

<211> 2115

<212> DNA

<213> Artificial Sequence

<220>

<223> 4C04 anti-Ron single chain polypeptide (4C04 scFv-CH1-CH2-CH3-Ck with signal peptide)

<400> 262

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atggaagcac cagcgcagct tctcttctc ctgctactct ggctcccaga taccaccggt 60
gacattcaga tgacccagtc tctgcctccc cagtctgcat ctctgggaga aagtgtcacc 120
atcacatgcc tggcaagtca gaccattggt acatgggttag catgggtatca gcagaacca 180
gggaaatctc ctacgctcct gatttatgct gcaaccagct tggcagatgg ggtcccatca 240
aggttcagtg ctagtggatc tggcacaata ttttctttca agatcgacag cctacagtct 300
gaagattttg taagtattta ctgtcaacaa ctttacaata ctccgtggac gttcggtgga 360
ggcaccagc tggaaatcaa aggtggcggt ggctctggcg gaggtggatc cgggtggcgg 420
ggctctcaga tccagctgca gcagtctgga cctgagctgg tgaagcctgg gacttcagtg 480
aagatatcct gcaaggcttc tgactacaca ctactgact tctatatgaa ctgggtgagg 540
cagaagcctg gacagggact tgagtggatt gggaggattt atcctggaac cgataaaact 600
agatacaatg agaaattcag ggacaaggcc atactgaccg tggacacgtc ctccagcaca 660
gcctacatgc agctcagcag cctgacatca gaggacactg ctgtctattt ctgtgcaaga 720
tcgcctact atggtaacta cgttgctatg gactactggg gtcaaggaaac ctacgtcacc 780
gtctcctcga gcgcctccac caagggccca tccgtcttcc ccttgccacc ctccctcaag 840
agcactctg ggggcacagc ggccctgggc tgccctggta aggactactt ccccgagccg 900
gtgacgggtg cgtggaactc aggcgccctg accagcggcg tgcacacctt cccggctgtc 960
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aaagtctcga cggagcccaa atcttctgac aaaactcaca catgcccacc gtgcccatcc 1140
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accctcatga tctcccgagc cctgaggtc acatgcgtgg tgggtggact gagccacgaa 1260
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aagcccgagg agggagcag caacagcacg taccgtgtgg tcagcgtcct caccgtcctg 1380
caccagagct ggctgaatgg caaggagtac aagtgcagg tctccaacaa agccctccca 1440
gccccatcg agaaaaccat ctccaaagcc aaaggcgagc cccgagaacc acaggtgtac 1500
accctgcccc catcccgagg tgagctgacc aagaaccagg tcagcctgac ctgcctggtc 1560
aaaggcttct atccaagcga catcgccgtg gagtgggaga gcaatgggca gccgggagac 1620
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttct ctacagcaag 1680
ctcaccgtgg acaagagcag gtggcagcag gggaaactgt tctcatgtgc cgtgatgcat 1740
gaggtctcgc acaaccacta cagcagaag agcctctccc tgtctccggg taaatctaga 1800
actgtggctg caccatctgt ctctatcttc ccgccatctg atgagcagtt gaaatctgga 1860
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtg 1920
aaggtggata acgcctccca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 1980
aaggacagca cctacagcct cagcagcacc ctgacgtgta gcaagcaga ctacagagaa 2040
cacaagtctc acgcctgcga agtcacccat cagggcctga gctcgccctg cacaagagac 2100
ttcaacaggg gagag 2115

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<210> 263

<400> 263

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<210> 264

<400> 264

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<210> 265

<211> 240

<212> PRT

<213> Artificial Sequence

<220>

<223> 11H09 anti-RON scFv mature protein without the signal peptide but with junction amino acids SSS at carboxy-terminus

<400> 265

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1      5      10      15
Glu Arg Val Ser Leu Thr Cys Arg Ala Ser Gln Asp Ile Gly Ser Ser
20     25     30
Leu Ser Trp Leu Gln Gln Glu Pro Asp Gly Thr Ile Lys Arg Leu Ile
35     40     45
Tyr Ser Thr Ser Ser Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
50     55     60
Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65     70     75     80
Glu Asp Phe Val Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Ser Pro Trp
85     90     95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
100    105    110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln
115    120    125
Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val Lys Met Ser Cys
130    135    140
Lys Ser Ser Gly Tyr Thr Phe Thr Ser Tyr Trp Ile His Trp Val Lys
145    150    155    160
Glu Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Pro Thr
165    170    175
Thr Gly Tyr Thr Glu Ser Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu
180    185    190
Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
195    200    205
Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Phe Leu Leu Arg Pro Trp
210    215    220
Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser Ser
225    230    235    240

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<210> 266

<400> 266
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<210> 295

<400> 295

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<210> 296

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-c-Met Light Chain Complementarity Determining Region

<400> 296

Arg	Ala	Ser	Gln	Ser	Ile	Arg	Asn	Tyr	Leu	Asn
1				5					10	

<210> 297

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-c-Met Light Chain Complementarity Determining Region

<400> 297

Ala	Ala	Ser	Ser	Leu	Gln	Ser
1				5		

<210> 298

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-c-Met Light Chain Complementarity Determining Region

<400> 298

Gln	Gln	Ser	Tyr	Val	Thr	Pro	Leu	Thr
1					5			

<210> 299

<400> 299

000

<210> 300

<400> 300

000

<210> 301

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> OKT3 VH amino acid sequence

<400> 301

```

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
 1           5           10           15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
 20           25           30
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35           40           45
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
 50           55           60
Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
 65           70           75           80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85           90           95
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100           105           110
Thr Thr Val Thr Val Ser Ser
115

```

<210> 302

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> OKT3 VL amino acid sequence

<400> 302

```

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
 1           5           10           15
Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
 20           25           30
Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
 35           40           45
Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser
 50           55           60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu
 65           70           75           80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
 85           90           95
Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn
100           105

```

<210> 303

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> BC3 VH amino acid sequence

<400> 303

```

Gln Val Gln Leu Gln Gln Ser Ala Ala Glu Leu Ala Arg Pro Gly Ala
 1           5           10           15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
 20           25           30
Thr Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35           40           45
Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Ile Gly Tyr Ser Gln Lys Phe
 50           55           60
Lys Asp Lys Thr Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65           70           75           80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85           90           95
Ala Arg Ser Lys Val Tyr Tyr Asp Tyr Asp Val Tyr Ser Met Asp Tyr
100           105           110
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115           120

```

<210> 304

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> BC3 VL amino acid sequence

<400> 304

```
Gln Ile Ile Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
 1           5           10           15
Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
 20           25           30
His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
 35           40           45
Asp Thr Ser Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
 50           55           60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
 65           70           75           80
Asp Ala Ala Thr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
 85           90           95
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100           105
```

<210> 305

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<223> G1 N297A CH2-CH3 (N297ST - A297ST)

<400> 305

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 1           5           10           15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 20           25           30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 35           40           45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 50           55           60
Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 65           70           75           80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 85           90           95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100           105           110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
115           120           125
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130           135           140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145           150           155           160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165           170           175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180           185           190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195           200           205
Lys Ser Leu Ser Leu Ser Pro Gly Lys
210           215
```

<210> 306

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> IgG1 AA N297A CH2CH3 (Ala substitutions at 234, 235, 237 and 297; 236 deleted)

<400> 306

```

Ala Pro Glu Ala Ala Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1      5      10      15
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
20      25      30
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
35      40      45
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
50      55      60
Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
65      70      75      80
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
85      90      95
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
100      105      110
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
115      120      125
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
130      135      140
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145      150      155      160
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
165      170      175
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
180      185      190
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
195      200      205
Ser Leu Ser Leu Ser Pro Gly Lys
210      215

```

<210> 307

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> G2 AA N297A CH2CH3 (Ala substitution at 234, 236 and 297)

<400> 307

```

Ala Pro Glu Ala Ala Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1      5      10      15
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
20      25      30
Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
35      40      45

Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
50      55      60
Phe Ala Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
65      70      75      80
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
85      90      95
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
100      105      110
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
115      120      125
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
130      135      140
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145      150      155      160
Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
165      170      175
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
180      185      190
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
195      200      205
Ser Leu Ser Leu Ser Pro Gly Lys
210      215

```

<210> 308

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> G4 AA N297A CH2CH3 (Ala substitutions at 234, 235, 237 and 297; 236 deleted)

<400> 308

```

Ala Pro Glu Ala Ala Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1      5      10      15
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
20      25      30
Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
35      40      45
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
50      55      60
Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
65      70      75      80
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
85      90      95
Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
100     105     110
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
115     120     125
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
130     135     140
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145     150     155     160
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
165     170     175
Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
180     185     190
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
195     200     205
Ser Leu Ser Leu Ser Pro Gly Lys
210     215

```

<210> 309

<211> 153

<212> PRT

<213> Artificial Sequence

<220>

<223> DeltaCH2 (glCH3 only)

<400> 309

```

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
1      5      10      15
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20      25      30
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35      40      45
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50      55      60
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65      70      75      80
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85      90      95
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Thr Gly Leu Asn Asp
100     105     110
Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu Asp Tyr Lys Asp Asp
115     120     125
Asp Asp Lys Asp Tyr Lys Asp Asp Asp Lys Asp Tyr Lys Asp Asp
130     135     140
Asp Asp Lys His His His His His His
145     150

```

<210> 310

<211> 246

<212> PRT

<213> Artificial Sequence

<220>

<223> BC3-VH-VL amino acid sequence (includes g4s linker)

<400> 310

```

Gln Val Gln Leu Gln Gln Ser Ala Ala Glu Leu Ala Arg Pro Gly Ala
1      5      10      15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20      25      30
Thr Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Ser Gly Tyr Ile Gly Tyr Ser Gln Lys Phe
50      55      60
Lys Asp Lys Thr Thr Leu Thr Ala Asp Lys Ser Ser Thr Ala Tyr
65      70      75      80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Ser Lys Val Tyr Tyr Asp Tyr Asp Val Tyr Ser Met Asp Tyr
100     105     110
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser
115     120     125
Gly Gly Gly Gly Ser Gly Gly Gly Ser Ala Gln Gln Ile Ile Leu
130     135     140
Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr
145     150     155     160
Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met His Trp Tyr Gln
165     170     175
Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys
180     185     190

```

```

Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr
195     200     205
Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr
210     215     220
Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Ala Gly
225     230     235     240
Thr Lys Leu Glu Leu Lys
245

```

<210> 311

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> OKT3-VH-VL amino acid sequence (includes g4s linker)

<400> 311

```

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1      5      10      15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20      25      30
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Thr Ala Tyr
65      70      75      80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100     105     110
Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115     120     125
Ser Gly Gly Gly Gly Ser Ala Gln Gln Ile Val Leu Thr Gln Ser Pro
130     135     140
Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Ser
145     150     155     160
Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Ser Gly
165     170     175
Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly
180     185     190
Val Pro Ala His Phe Arg Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu
195     200     205
Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
210     215     220
Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu
225     230     235     240
Ile Asn

```

<210> 312

<211> 244

<212> PRT

<213> Artificial Sequence

<220>

<223> H57 VH-Linker-VL (without leader)

<400> 312

```

Glu Val Tyr Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Ser
 1          5          10          15
Ser Leu Lys Val Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Phe
          20          25          30

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35          40          45
Gly Arg Ile Lys Asn Lys Pro Asn Asn Tyr Ala Thr Glu Tyr Ala Asp
 50          55          60
Ser Val Arg Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Arg Asn Ser
 65          70          75          80
Ile Tyr Leu Gln Met Asn Arg Leu Arg Val Asp Asp Thr Ala Ile Tyr
          85          90          95
Tyr Cys Thr Arg Ala Gly Arg Phe Asp His Phe Asp Tyr Trp Gly Gln
          100          105          110
Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly
          115          120          125
Gly Ser Gly Gly Gly Gly Ser Ala Gln Tyr Glu Leu Ile Gln Pro Ser
          130          135          140
Ser Ala Ser Val Thr Val Gly Glu Thr Val Lys Ile Thr Cys Ser Gly
          145          150          155          160
Asp Gln Leu Pro Lys Asn Phe Ala Tyr Trp Phe Gln Gln Lys Ser Asp
          165          170          175
Lys Asn Ile Leu Leu Leu Ile Tyr Met Asp Asn Lys Arg Pro Ser Gly
          180          185          190
Ile Pro Glu Arg Phe Ser Gly Ser Thr Ser Gly Thr Thr Ala Thr Leu
          195          200          205
Thr Ile Ser Gly Ala Gln Pro Glu Asp Glu Ala Ala Tyr Tyr Cys Leu
          210          215          220
Ser Ser Tyr Gly Asp Asn Asn Asp Leu Val Phe Gly Ser Gly Thr Gln
          225          230          235          240
Leu Thr Val Leu

```

<210> 313

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> H57 Null2 SMIP - VH amino acid

<400> 313

```

Glu Val Tyr Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Ser
 1          5          10          15
Ser Leu Lys Val Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Phe
          20          25          30
Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45
Gly Arg Ile Lys Asn Lys Pro Asn Asn Tyr Ala Thr Glu Tyr Ala Asp
          50          55          60
Ser Val Arg Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Arg Asn Ser
          65          70          75          80
Ile Tyr Leu Gln Met Asn Arg Leu Arg Val Asp Asp Thr Ala Ile Tyr
          85          90          95
Tyr Cys Thr Arg Ala Gly Arg Phe Asp His Phe Asp Tyr Trp Gly Gln
          100          105          110
Gly Thr Met Val Thr Val Ser Ser
          115          120

```

<210> 314

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> Mouse IGHG2c mutated CH2 (alanine substitutions at positions L234, L235, G237, E318, K320 and K322)

<400> 314

```

Ala Pro Asp Ala Ala Gly Ala Pro Ser Val Phe Ile Phe Pro Pro Lys
 1          5          10          15
Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Met Val Thr Cys Val
          20          25          30
Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe
          35          40          45
Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu
          50          55          60
Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His
          65          70          75          80
Gln Asp Trp Met Ser Gly Lys Ala Phe Ala Cys Ala Val Asn Asn Arg
          85          90          95
Ala Leu Pro Ser Pro Ile Glu Lys Thr Ile Ser Lys Pro Arg
          100          105          110

```

<210> 315

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> H57 Null2 SMIP - VL amino acid sequence

<400> 315

```

Tyr Glu Leu Ile Gln Pro Ser Ser Ala Ser Val Thr Val Gly Glu Thr
 1      5      10      15
Val Lys Ile Thr Cys Ser Gly Asp Gln Leu Pro Lys Asn Phe Ala Tyr
 20      25      30
Trp Phe Gln Gln Lys Ser Asp Lys Asn Ile Leu Leu Ile Tyr Met
 35      40      45
Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Thr
 50      55      60
Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Gly Ala Gln Pro Glu Asp
 65      70      75      80
Glu Ala Ala Tyr Tyr Cys Leu Ser Ser Tyr Gly Asp Asn Asn Asp Leu
 85      90      95
Val Phe Gly Ser Gly Thr Gln Leu Thr Val Leu
 100      105

```

<210> 316

<400> 316

000

<210> 317

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> 2C11 Null2 SMIP - VH amino acid

<400> 317

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Lys
 1      5      10      15
Ser Leu Lys Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Gly Tyr
 20      25      30
Gly Met His Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Glu Ser Val
 35      40      45
Ala Tyr Ile Thr Ser Ser Ser Ile Asn Ile Lys Tyr Ala Asp Ala Val
 50      55      60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Leu Leu Phe
 65      70      75      80
Leu Gln Met Asn Ile Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
 85      90      95
Ala Arg Phe Asp Trp Asp Lys Asn Tyr Trp Gly Gln Gly Thr Met Val
 100      105      110
Thr Val Ser Ser
 115

```

<210> 318

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> 2C11 Null2 SMIP - VL amino acid

<400> 318

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Pro Ala Ser Leu Gly
 1      5      10      15
Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
 20      25      30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35      40      45
Tyr Tyr Thr Asn Lys Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
 50      55      60
Ser Gly Ser Gly Arg Asp Ser Ser Phe Thr Ile Ser Ser Leu Glu Ser
 65      70      75      80
Glu Asp Ile Gly Ser Tyr Tyr Cys Gln Gln Tyr Tyr Asn Tyr Pro Trp
 85      90      95
Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys
 100      105

```


<210> 319

<211> 240

<212> PRT

<213> Artificial Sequence

<220>

<223> 2C11 VH-Linker-VL (without leader)

<400> 319

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Lys
 1          5          10          15
Ser Leu Lys Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Gly Tyr
 20          25          30
Gly Met His Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Glu Ser Val
 35          40          45
Ala Tyr Ile Thr Ser Ser Ser Ile Asn Ile Lys Tyr Ala Asp Ala Val
 50          55          60
Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Leu Leu Phe
 65          70          75          80
Leu Gln Met Asn Ile Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
 85          90          95
Ala Arg Phe Asp Trp Asp Lys Asn Tyr Trp Gly Gln Gly Thr Met Val
100          105          110
Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
115          120          125
Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
130          135          140
Pro Ala Ser Leu Gly Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Gln

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

```

<210> 320

<211> 110

<212> PRT

<213> Mus musculus

<220>

<223> Human IGHG2c CH2 domain

<400> 320

```

Ala Pro Asp Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys
 1          5          10          15
Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Met Val Thr Cys Val
 20          25          30
Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe
 35          40          45
Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu
 50          55          60
Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His
 65          70          75          80
Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Arg
 85          90          95
Ala Leu Pro Ser Pro Ile Glu Lys Thr Ile Ser Lys Pro Arg
100          105          110

```

<210> 321

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<223> HM1 (IgM CH3:IgG1 CH3) without C-terminal tail

<400> 321

```

Asp Gln Asp Thr Ala Ile Arg Val Phe Ala Ile Pro Pro Ser Phe Ala
1      5      10      15
Ser Ile Phe Leu Thr Lys Ser Thr Lys Leu Thr Cys Leu Val Thr Asp
20      25      30
Leu Thr Thr Tyr Asp Ser Val Thr Ile Ser Trp Thr Arg Gln Asn Gly
35      40      45
Glu Ala Val Lys Thr His Thr Asn Ile Ser Glu Ser His Pro Asn Ala
50      55      60
Thr Phe Ser Ala Val Gly Glu Ala Ser Ile Cys Glu Asp Asp Trp Asn
65      70      75      80
Ser Gly Glu Arg Phe Thr Cys Thr Val Thr His Thr Asp Leu Pro Ser
85      90      95
Pro Leu Lys Gln Thr Ile Ser Arg Pro Lys Gly Gln Pro Arg Glu Pro
100     105     110
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
115     120     125

```

```

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
130     135     140
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
145     150     155     160
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
165     170     175
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
180     185     190
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
195     200     205
Leu Ser Pro Gly Lys
210

```

<210> 322

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> IgG4 AA CH2

<400> 322

```

Ala Pro Glu Ala Ala Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1      5      10      15
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
20      25      30
Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
35      40      45
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
50      55      60
Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
65      70      75      80
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
85      90      95
Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
100     105

```

<210> 323

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<223> Human IgG1 CH2 CH3 Null2

<400> 323

```

Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
1      5      10      15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20      25      30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35      40      45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50      55      60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65      70      75      80
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
85      90      95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100     105     110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
115     120     125

```

```

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130      135      140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145      150      155      160
Tyr Lys Thr Thr Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165      170      175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180      185      190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195      200      205
Lys Ser Leu Ser Leu Ser Pro Gly Lys
210      215

```

<210> 324

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> IgG1 N297A CH2

<400> 324

```

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1      5      10      15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20      25      30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35      40      45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50      55      60
Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65      70      75      80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85      90      95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100      105      110

```

<210> 325

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> IgG1 AA CH2

<400> 325

```

Ala Pro Glu Ala Ala Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1      5      10      15
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
20      25      30
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
35      40      45
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
50      55      60
Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
65      70      75      80
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
85      90      95
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100      105

```

<210> 326

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> IgG2 AA CH2

<400> 326

```

Ala Pro Glu Ala Ala Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1      5      10      15
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
20      25      30
Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
35      40      45
Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
50      55      60
Phe Ala Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
65      70      75      80
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
85      90      95
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
100      105

```

<210> 327

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Cris7-VH murine hybridoma Amino Acid

<220>

<221> ACT_SITE

<222> (31)...(35)

<223> complementarity-determining region

<220>

<221> ACT_SITE

<222> (50)...(66)

<223> complementarity-determining region

<220>

<221> ACT_SITE

<222> (100)...(110)

<223> complementarity-determining region

<400> 327

```

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1      5      10      15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
20      25      30
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65      70      75      80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Ser Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100      105      110
Gln Gly Thr Leu Val Thr Val Ser Ala
115      120

```

<210> 328

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Cris7-VL murine hybridoma Amino Acid

<220>

<221> ACT_SITE

<222> (24)...(33)

<223> complementarity-determining region

<220>

<221> ACT_SITE

<222> (49)...(55)

<223> complementarity-determining region

<220>

<221> ACT_SITE

<222> (88)...(96)

<223> complementarity-determining region

<400> 328

```

Gln Val Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Phe Pro Gly
 1          5          10          15
Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
          20          25          30
Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
          35          40          45
Asp Ser Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
          50          55          60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Thr Glu
65          70          75          80
Asp Ala Ala Thr Tyr Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr
          85          90          95
Phe Gly Gly Gly Thr Lys Leu Gln Ile Thr Arg
          100          105

```

<210> 329

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7 VL.1

<220>

<221> ACT_SITE

<222> (24)...(33)

<223> complementarity-determining region

<220>

<221> ACT_SITE

<222> (49)...(55)

<223> complementarity-determining region

<220>

<221> ACT_SITE

<222> (88)...(96)

<223> complementarity-determining region

<400> 329

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1          5          10          15
Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
          20          25          30
Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
          35          40          45
Asp Ser Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
          50          55          60
Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65          70          75          80
Asp Phe Ala Thr Tyr Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr
          85          90          95
Phe Gly Gly Gly Thr Lys Leu Gln Ile Thr Arg
          100          105

```

<210> 330

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7 VL.2

<400> 330

```

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 Ser Ala Ser Ser Val Ser Tyr Met
20      25      30
Asn Trp Tyr Gln Gln Thr Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
35      40      45
Asp Ser Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50      55      60
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65      70      75      80
Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr
85      90      95
Phe Gly Gln Gly Thr Lys Leu Gln Ile Thr Arg
100      105

```

<210> 331

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7 VH.1

<220>

<221> ACT_SITE

<222> (31)...(35)

<223> complementarity-determining region

<220>

<221> ACT_SITE

<222> (50)...(66)

<223> complementarity-determining region

<220>

<221> ACT_SITE

<222> (100)...(110)

<223> complementarity-determining region

<400> 331

```

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 Arg Ser
20      25      30
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Ala Tyr
65      70      75      80
Met Gln Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100      105      110
Gln Gly Thr Leu Val Thr Val Ser Ser
115      120

```

<210> 332

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7 VH.2

<400> 332

```

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1           5           10           15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20           25           30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35           40           45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50           55           60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Lys Asn Thr Ala Tyr
 65           70           75           80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85           90           95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
 100          105          110
Gln Gly Thr Leu Val Thr Val Ser Ser
 115          120

```

<210> 333

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCRIS7 VH.3

<400> 333

```

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1           5           10           15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20           25           30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35           40           45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50           55           60
Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65           70           75           80

Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85           90           95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
 100          105          110
Gln Gly Thr Pro Val Thr Val Ser Ser
 115          120

```

<210> 334

<211> 245

<212> PRT

<213> Artificial Sequence

<220>

<223> Cris7-(VH-VL)

<220>

<221> SITE

<222> (122)...(138)

<223> Linker

<400> 334

```

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1      5      10      15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
20      25      30
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65      70      75      80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Ser Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100     105     110
Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly Gly Gly Ser Gly Gly
115     120     125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Gln Val Val Leu Thr Gln
130     135     140
Ser Pro Ala Ile Met Ser Ala Phe Pro Gly Glu Lys Val Thr Met Thr
145     150     155     160
Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
165     170     175
Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180     185     190
Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr
195     200     205
Ser Leu Thr Ile Ser Ser Met Glu Thr Glu Asp Ala Ala Thr Tyr Tyr
210     215     220
Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
225     230     235     240
Leu Gln Ile Thr Arg
245

```

<210> 335

<211> 245

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7-(VH1-VL1)

<220>

<221> SITE

<222> (122)...(138)

<223> Linker

<400> 335

```

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 Arg Ser
20      25      30
Thr Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65      70      75      80
Met Gln Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100     105     110
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115     120     125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130     135     140
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
145     150     155     160
Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
165     170     175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180     185     190
Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr
195     200     205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
210     215     220
Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
225     230     235     240
Leu Gln Ile Thr Arg
245

```

<210> 336

<211> 245

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7-(VH1-VL2)

<220>

<221> SITE

<222> (122)...(138)

<223> Linker

<400> 336

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 Arg Ser
 20 25 30
 Thr Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50 55 60
 Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Gln Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95
 Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
 130 135 140
 Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
 145 150 155 160
 Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Thr
 165 170 175
 Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
 180 185 190
 Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
 195 200 205
 Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr
 210 215 220
 Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gln Gly Thr Lys
 225 230 235 240
 Leu Gln Ile Thr Arg
 245

<210> 337

<211> 245

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7-(VH2-VL1)

<220>

<221> SITE

<222> (122)...(138)

<223> Linker

<400> 337

```

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1      5      10      15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
20      25      30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Lys Asn Thr Ala Tyr
65      70      75      80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100     105     110
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
115     120     125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130     135     140
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
145     150     155     160
Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
165     170     175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180     185     190
Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr
195     200     205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
210     215     220

Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
225     230     235     240
Leu Gln Ile Thr Arg
245

```

<210> 338

<211> 245

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7-(VH2-V1,2)

<220>

<221> SITE

<222> (122)...(138)

<223> Linker

<400> 338

```

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1      5      10      15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
20      25      30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Lys Asn Thr Ala Tyr
65      70      75      80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100     105     110
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
115     120     125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130     135     140
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
145     150     155     160
Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Thr
165     170     175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180     185     190
Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Thr Asp Phe
195     200     205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr
210     215     220
Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gln Gly Thr Lys
225     230     235     240
Leu Gln Ile Thr Arg
245

```

<210> 339

<211> 245

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7-(VH3-VL1)

<220>

<221> SITE

<222> (122)...(138)

<223> Liniker

<400> 339

```

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1          5          10          15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20          25          30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35          40          45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50          55          60
Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65          70          75          80
Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85          90          95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100          105          110
Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115          120          125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130          135          140
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
145          150          155          160
Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
165          170          175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180          185          190
Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr
195          200          205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
210          215          220
Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
225          230          235          240
Leu Gln Ile Thr Arg
245

```

<210> 340

<211> 245

<212> PRT

<213> Artificial Sequence

<220>

<223> HuCris7-(VH3-V1,2)

<220>

<221> SITE

<222> (122)...(138)

<223> Linker

<400> 340

```

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1          5          10          15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20          25          30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35          40          45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50          55          60
Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65          70          75          80
Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85          90          95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100          105          110

```

```

Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125
Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130 135 140
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
145 150 155 160
Cys Ser Ala Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Thr
165 170 175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180 185 190
Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
195 200 205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr
210 215 220
Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gln Gly Thr Lys
225 230 235 240
Leu Gln Ile Thr Arg
245

```

<210> 341

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> Half null CH2-CH3 regions

<400> 341

```

Pro Asp Ala Ala Gly Ala Pro Ser Val Phe Ile Phe Pro Pro Lys Ile
1 5 10 15
Lys Asp Val Leu Met Ile Ser Leu Ser Pro Met Val Thr Cys Val Val
20 25 30
Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val
35 40 45
Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp
50 55 60
Tyr Ala Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln
65 70 75 80
Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Arg Ala
85 90 95
Leu Pro Ser Pro Ile Glu Lys Thr Ile Ser Lys Pro Arg Gly Pro Val
100 105 110
Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Ala Glu Glu Met Thr
115 120 125
Lys Lys Glu Phe Ser Leu Thr Cys Met Ile Thr Gly Phe Leu Pro Ala
130 135 140
Glu Ile Ala Val Asp Trp Thr Ser Asn Gly Arg Thr Glu Gln Asn Tyr
145 150 155 160
Lys Asn Thr Ala Thr Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr
165 170 175
Ser Lys Leu Arg Val Gln Lys Ser Thr Trp Glu Arg Gly Ser Leu Phe
180 185 190
Ala Cys Ser Val Val His Glu Gly Leu His Asn His Leu Thr Thr Lys
195 200 205
Thr Ile Ser Arg Ser Leu Gly Lys
210 215

```

<210> 342

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<223> HM2 (mouse CH3mu-CH3gamma) without C-terminal tail

<400> 342

```

Ser Pro Ser Thr Asp Ile Leu Thr Phe Thr Ile Pro Pro Ser Phe Ala
1      5      10      15
Asp Ile Phe Leu Ser Lys Ser Ala Asn Leu Thr Cys Leu Val Ser Asn
20      25      30
Leu Ala Thr Tyr Glu Thr Leu Asn Ile Ser Trp Ala Ser Gln Ser Gly
35      40      45
Glu Pro Leu Glu Thr Lys Ile Lys Ile Met Glu Ser His Pro Asn Gly
50      55      60
Thr Phe Ser Ala Lys Gly Val Ala Ser Val Cys Val Glu Asp Trp Asn
65      70      75      80
Asn Arg Lys Glu Phe Val Cys Thr Val Thr His Arg Asp Leu Pro Ser
85      90      95
Pro Gln Lys Lys Phe Ile Ser Lys Pro Asn Gly Pro Val Arg Ala Pro
100     105     110
Gln Val Tyr Val Leu Pro Pro Pro Ala Glu Glu Met Thr Lys Lys Glu
115     120     125
Phe Ser Leu Thr Cys Met Ile Thr Gly Phe Leu Pro Ala Glu Ile Ala
130     135     140
Val Asp Trp Thr Ser Asn Gly Arg Thr Glu Gln Asn Tyr Lys Asn Thr
145     150     155     160
Ala Thr Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu
165     170     175
Arg Val Gln Lys Ser Thr Trp Glu Arg Gly Ser Leu Phe Ala Cys Ser
180     185     190
Val Val His Glu Gly Leu His Asn His Leu Thr Thr Lys Thr Ile Ser
195     200     205
Arg Ser Leu Gly Lys
210

```

<210> 343

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> huamn IgG4 AA CH2 with alanine substitutions at F234 and N297

<400> 343

```

Ala Pro Glu Ala Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1      5      10      15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20      25      30
Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
35      40      45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50      55      60
Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65      70      75      80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85      90      95
Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
100     105     110

```

<210> 344

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> human IgG4 AA CH2 with alanine substitutions at L235 and N297

<400> 344

```

Ala Pro Glu Phe Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1      5      10      15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20      25      30
Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
35      40      45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50      55      60
Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65      70      75      80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85      90      95
Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
100     105     110

```

<210> 345

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> human IgG4 AA CH2 with alanine substitutions at G236 and N297

<400> 345

```

Ala Pro Glu Phe Leu Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 1           5           10           15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 20           25           30
Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
 35           40           45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 50           55           60
Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 65           70           75           80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 85           90           95
Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
 100          105          110

```

<210> 346

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> human IgG4 AA CH2 with alanine substitutions at G237 and N297

<400> 346

```

Ala Pro Glu Phe Leu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
 1           5           10           15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 20           25           30
Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
 35           40           45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 50           55           60
Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 65           70           75           80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 85           90           95
Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
 100          105          110

```

<210> 347

<400> 347

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<210> 348

<400> 348

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<210> 349

<400> 349

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<210> 377

<400> 377

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<210> 378

<400> 378

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<210> 379

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 134

<400> 379

Glu	Pro	Met	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10				15	

<210> 380

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 135

<400> 380

Glu	Pro	Met	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10				15	

<210> 381

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 136

<400> 381

Glu	Pro	Met	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro
1				5					10				15	

<210> 382

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 137

<400> 382

Glu	Pro	Met	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Pro
1				5					10				15	

<210> 383

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 138

<400> 383

Glu	Pro	Met	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro
1				5					10				15	

<210> 384

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 139

<400> 384

Glu	Pro	Met	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Pro
1				5					10				15	

<210> 385

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 140

<400> 385

Glu	Pro	Met	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Pro
1				5					10					15

<210> 386

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 141

<400> 386

Glu	Pro	Met	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Ser
1				5					10					15

<210> 387

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 142

<400> 387

Glu	Pro	Met	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Ser
1				5					10					15

<210> 388

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 143

<400> 388

Glu	Pro	Met	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Ser
1				5					10					15

<210> 389

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 144

<400> 389

Glu	Pro	Met	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Ser
1				5					10					15

<210> 390

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 145

<400> 390

Glu	Pro	Met	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Ser
1				5					10					15

<210> 391

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 146

<400> 391

Glu	Pro	Met	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Pro
1				5					10					15

<210> 392

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 147

<400> 392

Glu	Pro	Met	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Ser
1				5					10					15

<210> 393

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 148

<400> 393

Glu	Pro	Thr	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 394

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 149

<400> 394

Glu	Pro	Thr	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 395

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 150

<400> 395

Glu	Pro	Thr	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro
1				5					10					15

<210> 396

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 151

<400> 396

Glu	Pro	Thr	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Pro
1				5					10					15

<210> 397

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 152

<400> 397

Glu	Pro	Thr	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro
1				5					10					15

<210> 398

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 153

<400> 398

Glu	Pro	Thr	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Pro
1				5					10					15

<210> 399

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 154

<400> 399

Glu	Pro	Thr	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Pro
1				5					10					15

<210> 400

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 155

<400> 400

Glu	Pro	Thr	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Ser
1				5					10					15

<210> 401

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 156

<400> 401

Glu	Pro	Thr	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Ser
1				5					10					15

<210> 402

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 157

<400> 402

Glu	Pro	Thr	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Ser
1				5					10					15

<210> 403

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 158

<400> 403

Glu	Pro	Thr	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Ser
1				5					10					15

<210> 404

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 159

<400> 404

Glu	Pro	Thr	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Ser
1				5					10					15

<210> 405

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 160

<400> 405

Glu	Pro	Thr	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Ser
1				5					10					15

<210> 406

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 161

<400> 406

Glu	Pro	Thr	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Ser
1				5					10					15

<210> 407

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 162

<400> 407

```

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

```

<210> 408

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 163

<400> 408

```

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

```

<210> 409

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 164

<400> 409

```

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

```

<210> 410

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 165

<400> 410

```

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

```

<210> 411

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 166

<400> 411

```

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

```

<210> 412

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker 167

<400> 412

```

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

```

<210> 413

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

<220>
 <223> Linker 168

<400> 413
 Glu Pro Ala Ser Cys Asp Lys Thr His Thr Ser Pro Pro Ser Pro
 1 5 10 15

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Glu	Pro	Ala	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Ser
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Glu	Pro	Ala	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Ser
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Glu	Pro	Ala	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Ser
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<223> Linker 176

<400> 421

Glu	Pro	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
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<400> 422

Glu	Pro	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
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Glu	Pro	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro
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Glu Pro Ser Cys Asp Lys Thr His Thr Cys Pro Pro Ser Pro
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<223> Linker 180

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Glu Pro Ser Ser Asp Lys Thr His Thr Ser Pro Pro Cys Pro
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<223> Linker 181

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Glu Pro Ser Ser Asp Lys Thr His Thr Cys Pro Pro Ser Pro
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<223> Linker 182

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Glu Pro Ser Cys Asp Lys Thr His Thr Ser Pro Pro Ser Pro
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<223> Linker 183

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Glu Pro Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Ser
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Glu Pro Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Ser
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 Glu Pro Ser Cys Asp Lys Thr His Thr Ser Pro Pro Cys Ser
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 Glu Pro Ser Cys Asp Lys Thr His Thr Cys Pro Pro Ser Ser
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 Glu Pro Ser Ser Asp Lys Thr His Thr Ser Pro Pro Cys Ser
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<400> 433
 Glu Pro Ser Ser Asp Lys Thr His Thr Cys Pro Pro Ser Ser
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<223> Anti-c-Met Heavy Chain Complementarity Determining Region

<400> 464

Lys	Tyr	Asp	Met	Leu
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<210> 465

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<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-c-Met Heavy Chain Complementarity Determining Region

<400> 465

Tyr	Ile	Tyr	Pro	Ser	Gly	Gly	Leu	Thr	Glu	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 466

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<223> Anti-c-Met Heavy Chain Complementarity Determining Region

<400> 466

Arg	Ala	Pro	Arg	Ser	Leu	Ser	Phe	Asp	Ile
1				5					10

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<213> Artificial Sequence

<220>

<223> Human IgG1 CH2 with L235A, E318A, K320A and K322A substitutions

<400> 595

Ala	Pro	Glu	Leu	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
1				5					10					15	
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
			20					25					30		
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
			35				40					45			
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
	50					55					60				
Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
65					70					75					80
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Ala	Tyr	Ala	Cys	Ala	Val	Ser	Asn	Lys
			85					90						95	
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys		
			100					105					110		

<210> 596

<211> 110

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<220>

<223> Human IgG1 CH2 with L234A, L235A, G237A, E318A, K320A and K322A

<400> 596

Ala	Pro	Glu	Ala	Ala	Gly	Ala	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
1				5					10					15	
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val
			20					25					30		
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
			35				40					45			
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu
	50					55					60				
Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His
65					70					75					80
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Ala	Tyr	Ala	Cys	Ala	Val	Ser	Asn	Lys
			85					90						95	
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys		
			100					105					110		

<210> 597

<400> 597

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<210> 598

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<220>

<223> Junction amino acids

<400> 598

Arg Asp Gln
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<210> 599

<211> 4

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<213> Artificial Sequence

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<223> Junction amino acids

<400> 599

Ser Ala Ser Ser
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<210> 600

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<223> Junction amino acids

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Ser Ser Ser
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<210> 601

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<212> PRT

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<223> NKG2D Linker

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Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1 5 10 15
Ser

<210> 602

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-RON mAb 4C04 light chain

<400> 602

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ala	Ser	Gln	Ser	Ala	Ser	Leu	Gly
1				5					10					15	
Glu	Ser	Val	Thr	Ile	Thr	Cys	Leu	Ala	Ser	Gln	Thr	Ile	Gly	Thr	Trp
		20					25					30			
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Gln	Leu	Leu	Ile
		35					40					45			
Tyr	Ala	Ala	Thr	Ser	Leu	Ala	Asp	Gly	Val	Pro	Ser	Arg	Phe	Ser	Ala
	50				55				60						
Ser	Gly	Ser	Gly	Thr	Lys	Phe	Ser	Phe	Lys	Ile	Asp	Ser	Leu	Gln	Ser
	65			70				75						80	
Glu	Asp	Phe	Val	Ser	Tyr	Tyr	Cys	Gln	Gln	Leu	Tyr	Asn	Thr	Pro	Trp
			85					90						95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
		100					105								

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<220>

<223> Anti-RON mAb 4C04 heavy chain

<400> 603

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Gln Ile Gln Leu Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Thr
 1           5           10           15
Ser Val Lys Ile Ser Cys Lys Ala Ser Asp Tyr Thr Leu Thr Asp Phe
 20           25           30
Tyr Met Asn Trp Val Arg Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
 35           40           45
Gly Arg Ile Tyr Pro Gly Thr Asp Lys Thr Arg Tyr Asn Glu Lys Phe
 50           55           60
Arg Asp Lys Ala Ile Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr
 65           70           75           80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys
 85           90           95
Ala Arg Ser Ala Tyr Tyr Gly Asn Tyr Val Ala Met Asp Tyr Trp Gly
100           105           110
Gln Gly Thr Ser Val Thr Val Ser Ser
115           120

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<210> 604

<211> 6

<212> PRT

<213> Artificial Sequence

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<223> Anti-RON mAb 4C04 light chain CDR1

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Gln Thr Ile Gly Thr Trp
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<210> 605

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<212> PRT

<213> Artificial Sequence

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<223> Anti-RON mAb 4C04 light chain CDR2

<400> 605

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Ala Ala Thr
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<223> Anti-RON mAb 4C04 light chain CDR3

<400> 606

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Gln Gln Leu Tyr Asn Thr Pro Trp Thr
 1           5

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<210> 607

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<220>

<223> Anti-RON mAb 4C04 heavy chain CDR1

<400> 607

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Asp Tyr Thr Leu Thr Asp Phe Tyr
 1           5

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<210> 608

<211> 8

<212> PRT

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<223> Anti-RON mAb 4C04 heavy chain CDR2

<400> 608

Ile Tyr Pro Gly Thr Asp Lys Thr
1 5

<210> 609

<211> 14

<212> PRT

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<220>

<223> Anti-RON mAb 4C04 heavy chain CDR3

<400> 609

Ala Arg Ser Ala Tyr Tyr Gly Asn Tyr Val Ala Met Asp Tyr
1 5 10

<210> 610

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-RON mAb 11H09 light chain

<400> 610

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15
Glu Arg Val Ser Leu Thr Cys Arg Ala Ser Gln Asp Ile Gly Ser Ser
20 25 30
Leu Ser Trp Leu Gln Gln Glu Pro Asp Gly Thr Ile Lys Arg Leu Ile
35 40 45
Tyr Ser Thr Ser Ser Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
50 55 60
Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80
Glu Asp Phe Val Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Ser Pro Trp
85 90 95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

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<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-RON mAb 11H09 heavy chain

<400> 611

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Met Ser Cys Lys Ser Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Trp Ile His Trp Val Lys Glu Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45
Gly Tyr Ile Tyr Pro Thr Thr Gly Tyr Thr Glu Ser Asn Gln Lys Phe
50 55 60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Ala Tyr
65 70 75 80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95
Phe Leu Leu Arg Pro Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr
100 105 110
Val Thr Val Ser Ser
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<210> 612

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-RON mAb 11H09 light chain CDR1

<400> 612

Gln	Asp	Ile	Gly	Ser	Ser
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<210> 613

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-RON mAb 11H09 light chain CDR2

<400> 613

Ser	Thr	Ser
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<210> 614

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<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-RON mAb 11H09 light chain CDR3

<400> 614

Leu	Gln	Tyr	Ala	Ser	Ser	Pro	Trp	Thr
1				5				

<210> 615

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-RON mAb 11H09 heavy chain CDR1

<400> 615

Gly	Tyr	Thr	Phe	Thr	Ser	Tyr	Trp
1				5			

<210> 616

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-RON mAb 11H09 heavy chain CDR2

<400> 616

Ile	Tyr	Pro	Thr	Thr	Gly	Tyr	Thr
1				5			

<210> 617

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-RON mAb 11H09 heavy chain CDR3

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Phe	Leu	Leu	Arg	Pro	Trp	Tyr	Phe	Asp	Val
1				5					10

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 <223> Made in a lab

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 Asn Ser
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 <223> Made in a lab

<400> 619
 Ser Cys Pro Pro Cys Pro
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 Gly Gly Gly Gly Ser Gly Asn Ser
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 <223> Made in a lab

<400> 621
 Gly Cys Pro Pro Cys Pro Asn Ser
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<220>
 <223> Made in a lab

<400> 622
 Gly Ser Pro Pro Ser Pro Asn Ser
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<210> 623
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 <223> Made in a lab

<400> 623

Gly Ser Pro Pro Ser Pro Asn Ser
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<210> 624

<211> 8

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<213> Artificial Sequence

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<223> Made in a lab

<400> 624

Gly Cys Pro Pro Cys Pro Asn Ser
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<210> 625

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<223> Made in a lab

<400> 625

Gly Cys Pro Pro Cys Pro Asn Ser
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<211> 9

<212> PRT

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<223> Made in a lab

<400> 626

Gly Cys Pro Pro Cys Pro Gly Asn Ser
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<212> PRT

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<223> Made in a lab

<400> 627

Gly Cys Pro Pro Cys Pro Ala Asn Ser
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<400> 628

Gly Cys Pro Pro Cys Pro Ala Asn Ser
 1 5

<210> 629

<211> 9

<212> PRT

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<220>

<223> Made in a lab

<400> 629

Glu Glu Glu Glu Asp Glu Gly Asn Ser
1 5

<210> 630

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 630

Asn Tyr Gly Gly Gly Gly Ser Gly Asn Ser
1 5 10

<210> 631

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Made in a lab

<400> 631

Val Ser Glu Arg Pro Phe Pro Pro Asn Ser
1 5 10

<210> 632

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 632

Glu Pro Lys Ser Cys Asp Lys Thr Cys Cys Pro
1 5 10

<210> 633

<211> 11

<212> PRT

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<220>

<223> Made in a lab

<400> 633

Ser Gln Pro Glu Ile Val Pro Ile Ser Asn Ser
1 5 10

<210> 634

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 634

Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro Asn Ser
1 5 10

<210> 635

<211> 12

<212> PRT

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<220>

<223> Made in a lab

<400> 635

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

<210> 636

<211> 12

<212> PRT

<213> Artificial Sequence

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<223> Made in a lab

<400> 636

Gln	Met	Asn	Ser	Glu	Leu	Ser	Val	Leu	Ala	Asn	Ser
1				5					10		

<210> 637

<211> 13

<212> PRT

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<223> Made in a lab

<400> 637

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Cys	Pro
1				5					10			

<210> 638

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 638

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10			

<210> 639

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 639

Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Asn	Ser
1				5					10			

<210> 640

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 640
 Gly Cys Pro Pro Cys Pro Gly Gly Gly Gly Ser Asn Ser
 1 5 10

<210> 641

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 641
 Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro Gly Asn Ser
 1 5 10

<210> 642

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 642
 Gly Cys Pro Pro Cys Pro Gly Gly Gly Gly Ser Asn Ser
 1 5 10

<210> 643

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 643
 Gly Gly Gly Ala Ser Cys Pro Pro Cys Pro Gly Asn Ser
 1 5 10

<210> 644

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 644
 Gly Gly Gly Ala Ser Cys Pro Pro Cys Ala Gly Asn Ser
 1 5 10

<210> 645

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 645
 Gly Gly Gly Ala Ser Cys Pro Pro Cys Ala Gly Asn Ser
 1 5 10

<210> 646

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 646

Asn	Tyr	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Asn	Ser
1			5				10					15	

<210> 647

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 647

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

<210> 648

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 648

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

<210> 649

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 649

Leu	Lys	Ile	Gln	Glu	Arg	Val	Ser	Lys	Pro	Lys	Ile	Ser	Asn	Ser
1			5					10					15	

<210> 650

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 650

Leu	Asp	Val	Ser	Glu	Arg	Pro	Phe	Pro	Pro	His	Ile	Gln	Asn	Ser
1			5					10					15	

<210> 651

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 651

Arg	Glu	Gln	Leu	Ala	Glu	Val	Thr	Leu	Ser	Leu	Lys	Ala	Asn	Ser
1			5					10					15	

<210> 652

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 652

Arg	Ile	His	Gln	Met	Asn	Ser	Glu	Leu	Ser	Val	Leu	Ala	Asn	Ser
1				5					10					15

<210> 653

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 653

Asp	Thr	Lys	Gly	Lys	Asn	Val	Leu	Glu	Lys	Ile	Phe	Ser	Asn	Ser
1				5					10					15

<210> 654

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 654

Leu	Pro	Pro	Glu	Thr	Gln	Glu	Ser	Gln	Glu	Val	Thr	Leu	Asn	Ser
1				5					10					15

<210> 655

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 655

Arg	Ile	His	Leu	Asn	Val	Ser	Glu	Arg	Pro	Phe	Pro	Pro	Asn	Ser
1				5					10					15

<210> 656

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 656

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

<210> 657

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 657

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

<210> 658

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 658

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

<210> 659

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 659

Arg	Ile	His	Gln	Met	Asn	Ser	Glu	Leu	Ser	Val	Leu	Ala	Asn	Ser
1				5				10					15	

<210> 660

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 660

Lys	Pro	Phe	Phe	Thr	Cys	Gly	Ser	Ala	Asp	Thr	Cys	Pro	Asn	Ser
1				5				10					15	

<210> 661

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 661

Lys	Pro	Phe	Phe	Thr	Cys	Gly	Ser	Ala	Asp	Thr	Cys	Pro	Asn	Ser

1				5				10					15	

<210> 662

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 662

Gln	Tyr	Asn	Cys	Pro	Gly	Gln	Tyr	Thr	Phe	Ser	Met	Pro	Asn	Ser
1				5				10					15	

<210> 663

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 663

Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
1				5					10					15

<210> 664

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 664

Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 665

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 665

Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Ser
1				5					10					15

<210> 666

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 666

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Ser
1				5					10					15

<210> 667

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 667

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 668

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 668

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Ser
1				5					10					15

<210> 669

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 669

Pro	Arg	Gly	Pro	Thr	Ile	Lys	Pro	Cys	Pro	Pro	Cys	Lys	Cys	Pro
1				5					10					15

<210> 670

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 670

Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Ser
1				5					10					15

<210> 671

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 671

Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Ser
1				5					10					15

<210> 672

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 672

Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Ser
1				5					10					15

<210> 673

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 673

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro
1				5					10					15

<210> 674

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 674

Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Pro
1				5					10					15

<210> 675

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 675

Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Cys	Pro
1				5					10					15

<210> 676

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 676

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Pro
1				5					10					15

<210> 677

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 677

Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Pro
1				5					10					15

<210> 678

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 678

Gly	Gly	Gly	Gly	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1					5					10					15

<210> 679

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 679

Glu	Pro	Lys	Ser	Cys	Gly	Gly	Gly	Gly	Gly	Cys	Pro	Pro	Cys	Pro
1					5					10				15

<210> 680

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 680

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

<210> 681

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 681

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

<210> 682

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 682

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Ser	Pro
1				5					10					15

<210> 683

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 683

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Cys	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 684

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 684

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	Cys	Cys	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 685

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 685

Glu	Pro	Lys	Ser	Cys	Pro	Pro	Pro	Pro	Pro	Cys	Pro	Pro	Cys	Pro
1				5					10				15	

<210> 686

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 686

Pro	Pro	Pro	Pro	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10				15	

<210> 687

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 687

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Trp	Trp	Cys	Pro
1				5					10				15	

<210> 688

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 688

Glu	Pro	Lys	Ser	Cys	Asp	Trp	Trp	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10				15	

<210> 689

<211> 15

<212> PRT

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<220>

<223> Made in a lab

<400> 689

Glu	Pro	Lys	Cys	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10				15	

<210> 690

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 690

Glu	Pro	Lys	Ser	Asp	Cys	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10				15	

<210> 691

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 691

Glu	Pro	Lys	Ser	Asp	Cys	Trp	Trp	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 692

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 692

Glu	Pro	Lys	Ser	Cys	Asp	Phe	Phe	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 693

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 693

Glu	Pro	Lys	Ser	Cys	Asp	Trp	Trp	Trp	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 694

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 694

Glu	Pro	Lys	Ser	Cys	Trp	Trp	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 695

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 695

Glu	Pro	Trp	Trp	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15

<210> 696

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 696

Ser Gln Pro Glu Ile Val Pro Ile Ser Cys Pro Pro Cys Pro Asn Ser
 1 5 10 15

<210> 697

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 697

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

<210> 698

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 698

Glu Pro Lys Ser Thr Asp Lys Thr His Thr Cys Pro Pro Cys Pro Asn
 1 5 10 15
 Ser

<210> 699

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 699

Glu Pro Lys Ser Thr Asp Lys Thr His Thr Ser Pro Pro Ser Pro Asn
 1 5 10 15
 Ser

<210> 700

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 700

Glu Pro Lys Ser Thr Asp Lys Thr His Thr Cys Pro Pro Cys Pro Asn
 1 5 10 15
 Ser

<210> 701

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 701

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Asn
 1 5 10 15
 Ser

<210> 702

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 702

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

<210> 703

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 703

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

<210> 704

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 704

Glu	Pro	Lys	Ser	Cys	Asp	Pro	Pro	Pro	Lys	Thr	His	Thr	Cys	Pro	Pro
1				5					10					15	
Cys	Pro														

<210> 705

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 705

Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Pro	Pro	Pro
1				5					10					15	
Cys	Pro														

<210> 706

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 706

Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly
1				5					10					15	
Asn	Ser														

<210> 707

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 707

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Asn Tyr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 1          5          10          15
Ser Asn Ser

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<210> 708

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 708

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Leu Ser Val Lys Ala Asp Phe Leu Thr Pro Ser Ile Ser Pro Pro Cys
 1          5          10          15
Pro Asn Ser

```

<210> 709

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 709

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Ser Val Leu Ala Asn Phe Ser Gln Pro Glu Ile Ser Cys Pro Pro Cys
 1          5          10          15
Pro Asn Ser

```

<210> 710

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 710

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Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Lys Ala
 1          5          10          15
Arg His Ser Pro
          20

```

<210> 711

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 711

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Leu Ser Val Leu Ala Asn Phe Ser Gln Pro Glu Ile Ser Cys Pro Pro
 1          5          10          15
Cys Pro Asn Ser
          20

```

<210> 712

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 712

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Leu Lys Ile Gln Glu Arg Val Ser Lys Pro Lys Ile Ser Cys Pro Pro
1           5           10           15
Cys Pro Asn Ser
                20

```

<210> 713

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 713

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Arg Glu Gln Leu Ala Glu Val Thr Leu Ser Leu Lys Ala Cys Pro Pro
1           5           10           15
Cys Pro Asn Ser
                20

```

<210> 714

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 714

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Arg Ile His Gln Met Asn Ser Glu Leu Ser Val Leu Ala Cys Pro Pro
1           5           10           15
Cys Pro Asn Ser
                20

```

<210> 715

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 715

```

Arg Ile His Leu Asn Val Ser Glu Arg Pro Phe Pro Pro Cys Pro Pro
1           5           10           15
Cys Pro Asn Ser
                20

```

<210> 716

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 716

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Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1           5           10           15
Cys Pro Asn Ser
                20

```

<210> 717

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 717

Glu Glu Glu Glu Asp Glu Glu Asp Glu Glu Asp Glu Glu Glu Glu Glu
 1 5 10 15
 Asp Gly Asn Ser
 20

<210> 718

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 718

Leu Asp Val Ser Glu Arg Pro Phe Pro Pro His Ile Gln Ser Cys Pro
 1 5 10 15
 Pro Cys Pro Asn Ser
 20

<210> 719

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 719

Asp Thr Lys Gly Lys Asn Val Leu Glu Lys Ile Phe Asp Ser Cys Pro
 1 5 10 15
 Pro Cys Pro Asn Ser
 20

<210> 720

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 720

Leu Pro Pro Glu Thr Gln Glu Ser Gln Glu Val Thr Leu Ser Cys Pro
 1 5 10 15
 Pro Cys Pro Asn Ser
 20

<210> 721

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 721

Glu Pro Ala Phe Thr Pro Gly Pro Asn Ile Glu Leu Gln Lys Asp Ser
 1 5 10 15
 Asp Cys Pro Asn Ser
 20

<210> 722

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 722

Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Lys Ala Arg
 1 5 10 15
 His Cys Pro Asn Ser
 20

<210> 723

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 723

Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Lys Ala Arg
 1 5 10 15
 His Ser Pro Asn Ser
 20

<210> 724

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 724

Asn Tyr Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 1 5 10 15
 Ser Asn Tyr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 20 25 30
 Gly Ser Asn Ser
 35

<210> 725

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 725

Arg Thr Arg Tyr Leu Gln Val Ser Gln Gln Leu Gln Gln Thr Asn Arg
 1 5 10 15
 Val Leu Glu Val Thr Asn Ser Ser Leu Arg Gln Gln Leu Arg Leu Lys
 20 25 30
 Ile Thr Gln Leu Gly Gln Ser Ala Glu Asp Leu Gln Gly Ser Arg Arg
 35 40 45
 Glu Leu Ala Gln Ser Gln Glu Ala Leu Gln Val Glu Gln Arg Ala His
 50 55 60
 Gln Ala Ala Glu Gly Gln Leu Gln Ala Cys Gln Ala Asp Arg Gln Lys
 65 70 75 80
 Thr Lys Glu Thr Leu Gln Ser Glu Glu Gln Gln Arg Arg Ala Leu Glu
 85 90 95
 Gln Lys Leu Ser Asn Met Glu Asn Arg Leu Lys Pro Phe Phe Thr Cys
 100 105 110
 Gly Ser Ala Asp Thr Cys Cys Pro Asn Ser
 115 120

<210> 726

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 726

Gly Gly Gly Ala Ser Cys Pro Pro Cys Ala Gly Asn Ser
 1 5 10

<210> 727

<211> 39

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 727

```

Asn Asn Tyr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 1          5          10          15
Gly Ser Gly Asn Tyr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 20          25          30
Gly Gly Gly Ser Gly Asn Ser
 35

```

<210> 728

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 728

```

Asn Tyr Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 1          5          10          15
Ser Gly Asn Ser
 20

```

<210> 729

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 729

```

Ser Pro Pro Ser Pro Asn Ser
 1          5

```

<210> 730

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 730

```

Glu Pro Thr Ser Thr Asp Lys Thr His Thr Ser Pro Pro Ser Pro Asn
 1          5          10          15
Ser

```

<210> 731

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 731

```

Glu Pro Thr Ser Thr Asp Lys Thr His Thr Cys Pro Pro Cys Pro Asn
 1          5          10          15
Ser

```

<210> 732

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 732

```

Leu Ser Val Lys Ala Asp Phe Leu Thr Pro Ser Ile Ser Pro Pro Cys
 1          5          10          15
Pro Asn Ser

```

<210> 733

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 733

```

Gly Gly Gly Ala Ser Cys Pro Pro Cys Ala Asn Ser
 1          5          10

```

<210> 734

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 734

```

Arg Thr Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Lys
 1          5          10          15
Ala Arg His Ser Gly His
                20

```

<210> 735

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 735

```

Arg Thr Arg Tyr Leu Gln Val Ser Gln Gln Leu Gln Gln Thr Asn Arg
 1          5          10          15

Val Leu Glu Val Thr Asn Ser Ser Leu Arg Gln Gln Leu Arg Leu Lys
          20          25          30
Ile Thr Gln Leu Gly Gln Ser Ala Glu Asp Leu Gln Gly Ser Arg Arg
          35          40          45
Glu Leu Ala Gln Ser Gln Glu Ala Leu Gln Val Glu Gln Arg Ala His
          50          55          60
Gln Ala Ala Glu Gly Gln Leu Gln Ala Cys Gln Ala Asp Arg Gln Lys
65          70          75          80
Thr Lys Glu Thr Leu Gln Ser Glu Glu Gln Gln Arg Arg Ala Leu Glu
          85          90          95
Gln Lys Leu Ser Asn Met Glu Asn Arg Leu Lys Pro Phe Phe Thr Cys
          100          105          110
Gly Ser Ala Asp Thr Cys
          115

```

<210> 736

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 736

```

Arg Thr Gln Ser Glu Glu Gln Gln Arg Arg Ala Leu Glu Gln Lys Leu
 1          5          10          15
Ser Asn Met Glu Asn Arg Leu Lys Pro Phe Phe Thr Cys Gly Ser Ala
 20          25          30
Asp Thr Cys
 35

```

<210> 737

<211> 25

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 737

```

Arg Thr Glu Gln Lys Leu Ser Asn Met Glu Asn Arg Leu Lys Pro Phe
 1          5          10          15
Phe Thr Cys Gly Ser Ala Asp Thr Cys
 20          25

```

<210> 738

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 738

```

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 1          5          10          15
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 20          25

```

<210> 739

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 739

```

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser
 1          5          10          15

```

<210> 740

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 740

```

Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 1          5          10          15

```

<210> 741

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 741

```

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

```

<210> 742

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 742

Gln	Arg	His	Asn	Asn	Ser	Ser	Leu	Asn	Thr	Gly	Thr	Gln	Met	Ala	Gly
1				5					10					15	
His	Ser	Pro	Asn	Ser											
			20												

<210> 743

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 743

Gln	Arg	His	Asn	Asn	Ser	Ser	Leu	Asn	Thr	Gly	Thr	Gln	Lys	Ala	Arg
1				5					10					15	
His	Ser	Pro	Asn	Ser											
			20												

<210> 744

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 744

Gln	Arg	His	Asn	Asn	Ser	Ser	Leu	Asn	Thr	Gly	Thr	Gln	Met	Ala	Arg
1				5					10					15	
His	Ser	Pro	Asn	Ser											
			20												

<210> 745

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 745

Gln	Arg	His	Asn	Asn	Ser	Ser	Leu	Asn	Thr	Arg	Thr	Gln	Lys	Ala	Gly
1				5					10					15	
His	Ser	Pro	Asn	Ser											
			20												

<210> 746

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 746

Gln	Arg	His	Asn	Asn	Ser	Ser	Leu	Asn	Thr	Arg	Thr	Gln	Met	Ala	Gly
1				5					10					15	
His	Ser	Pro	Asn	Ser											
			20												

<210> 747

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 747

Gln	Arg	His	Asn	Asn	Ser	Ser	Leu	Asn	Thr	Arg	Thr	Gln	Met	Ala	Arg
1				5					10					15	
His	Ser	Pro	Asn	Ser											
			20												

<210> 748

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 748

Pro	Pro	Pro	Pro	Pro	Cys	Pro	Pro	Cys	Pro
1				5				10	

<210> 749

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 749

Thr	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro
1				5					10					15	

<210> 750

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 750

Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Pro	Cys
1				5					10					15	
Pro	Pro	Cys	Pro												
			20												

<210> 751

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 751

Glu	Pro	Lys	Ser	Ser	Asp	Thr	Pro	Pro	Pro	Ser	Pro	Arg	Ser	Pro	Cys
1				5					10					15	
Pro	Pro	Cys	Pro												
			20												

<210> 752

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 752

```

Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro Ser
 1           5           10           15
Pro Ser Cys Pro Pro Cys Pro
                20

```

<210> 753

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 753

```

Arg Thr Glu Pro Arg Val Pro Ile Thr Gln Asn Pro Cys Pro Pro Leu
 1           5           10           15
Lys Glu Cys Pro Pro Cys Ala
                20

```

<210> 754

<211> 39

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 754

```

Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala Gln Pro Gln
 1           5           10           15
Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala Thr Thr Arg
                20           25           30
Asn Thr Cys Pro Pro Cys Pro
                35

```

<210> 755

<211> 50

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 755

```

Gln Glu Lys Glu Ala Ile Glu Arg Leu Lys Ala Ala Gly Ala Pro Glu
 1           5           10           15
Ser Leu Val Ile Gln Ala Tyr Phe Ala Ser Glu Lys Asn Glu Asn Leu
                20           25           30
Ala Ala Asn Phe Leu Leu Ser Gln Asn Phe Asp Asp Glu Cys Pro Pro
                35           40           45
Cys Pro
                50

```

<210> 756

<211> 52

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 756

```

Gln Glu Lys Glu Ala Ile Glu Arg Leu Lys Ala Ala Gly Ala Pro Glu
1      5      10      15
Ser Leu Val Ile Gln Ala Tyr Phe Ala Ser Glu Lys Asn Glu Asn Leu
20      25      30
Ala Ala Asn Phe Leu Leu Ser Gln Asn Phe Asp Asp Glu Cys Pro Pro
35      40      45
Cys Pro Ser Gly
50

```

<210> 757

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 757

```

Ser Arg Asp Phe Thr Pro Pro Thr Val Lys Ile Leu Gln Ser Ser Ser
1      5      10      15
Asp Gly Gly Gly His Phe Pro Pro Thr Ile Gln Leu Leu Cys Leu Val
20      25      30
Ser Gly Tyr Thr Pro Gly Thr Ile Asn Ile Thr Trp Leu Glu Asp Gly
35      40      45
Gln Val Met Asp Val Asp Leu Ser Thr Ala Ser Thr Thr Gln Glu Gly
50      55      60
Glu Leu Ala Ser Thr Gln Ser Glu Leu Thr Leu Ser Gln Lys His Trp
65      70      75      80
Leu Ser Asp Arg Thr Tyr Thr Cys Gln Val Thr Tyr Gln Gly His Thr
85      90      95
Phe Glu Asp Ser Thr Lys Lys Ser Ala Cys Pro Pro Cys Pro
100      105      110

```

<210> 758

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 758

```

Ser Arg Asp Phe Thr Pro Pro Thr Val Lys Ile Leu Gln Ser Ser Ser
1      5      10      15
Asp Gly Gly Gly His Phe Pro Pro Thr Ile Gln Leu Leu Cys Leu Val
20      25      30
Ser Gly Tyr Thr Pro Gly Thr Ile Asn Ile Thr Trp Leu Glu Asp Gly
35      40      45
Gln Val Met Asp Val Asp Leu Ser Thr Ala Ser Thr Thr Gln Glu Gly
50      55      60
Glu Leu Ala Ser Thr Gln Ser Glu Leu Thr Leu Ser Gln Lys His Trp
65      70      75      80
Leu Ser Asp Arg Thr Tyr Thr Cys Gln Val Thr Tyr Gln Gly His Thr
85      90      95
Phe Glu Asp Ser Thr Lys Lys Ser Ala Cys Pro Pro Cys Ser Gly
100      105      110

```

<210> 759

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge sequence

<400> 759

```

Ile Ala Glu Leu Pro Pro Lys Val Ser Val Phe Val Pro Pro Arg Asp
1      5      10      15
Gly Phe Phe Gly Asn Pro Arg Lys Ser Lys Leu Ile Cys Gln Ala Thr
20      25      30
Gly Phe Ser Pro Arg Gln Ile Gln Val Ser Trp Leu Arg Glu Gly Lys
35      40      45
Gln Val Gly Ser Gly Val Thr Thr Asp Gln Val Gln Ala Glu Ala Lys
50      55      60
Glu Ser Gly Pro Thr Thr Tyr Lys Val Thr Ser Thr Leu Thr Ile Lys

```

```

65          70          75          80
Glu Ser Asp Trp Leu Gly Gln Ser Met Phe Thr Cys Arg Val Asp His
      85          90          95
Arg Gly Leu Thr Phe Gln Gln Asn Ala Ser Ser Met Ser Val Pro Cys
      100          105          110
Pro Pro Cys Pro
      115

```

<210> 760

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> linker sequence of monolL-10

<400> 760

```

Gly Gly Gly Ser Gly Gly
1          5

```

<210> 761

<211> 106

<212> PRT

<213> Homo sapiens

<400> 761

```

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
1          5          10          15
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
      20          25          30
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
      35          40          45
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
      50          55          60
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65          70          75          80
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
      85          90          95
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
      100          105

```

<210> 762

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> IgG1 CH2 CH3 Null2 desLys

<400> 762

```

Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
1          5          10          15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
      20          25          30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
      35          40          45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
      50          55          60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65          70          75          80
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
      85          90          95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
      100          105          110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
      115          120          125
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
      130          135          140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
      145          150          155          160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
      165          170          175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
      180          185          190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
      195          200          205
Lys Ser Leu Ser Leu Ser Pro Gly
      210          215

```

<210> 763

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 763

Ser	Pro	Pro	Ser	Pro	Asn	Ser
1				5		

<210> 764

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 764

Glu	Pro	Thr	Ser	Thr	Asp	Lys	Thr	His	Thr	Ser	Pro	Pro	Ser	Pro	Asn
1				5					10					15	
Ser															

<210> 765

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 765

Glu	Pro	Thr	Ser	Thr	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Asn
1				5					10					15	
Ser															

<210> 766

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 766

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

<210> 767

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 767

Asn	Ser	Gly	Ala	Asn	Gln	Glu	Val	Gln	Ile	Pro	Leu	Thr	Glu	Ser	Tyr
1				5					10					15	
Ser	Pro	Asn	Ser												
				20											

<210> 768

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 768

Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser
1 5 10

<210> 769

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 769

Asn Ser Gly Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1 5 10 15
Ser Pro Asn Ser
20

<210> 770

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 770

Asn Ser Leu Ala Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1 5 10 15
Ser Pro Asn Ser
20

<210> 771

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 771

Asn Ser Leu Phe Ser Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1 5 10 15
Ser Pro Asn Ser
20

<210> 772

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 772

Asn Ser Leu Ala Ser Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1 5 10 15
Ser Pro Asn Ser
20

<210> 773

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 773

Glu Gln Lys Leu Ser Asn Met Glu Asn Arg Leu Lys Pro Phe Phe Thr
 1 5 10 15
 Ser Gly Ser Ala Asp Thr Ser Pro Asn Ser
 20 25

<210> 774

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 774

Gln Arg His Ala Asn Ser Ala Leu Asn Thr Gly Thr Gln Met Ala Gly
 1 5 10 15
 His Ser Pro Asn Ser
 20

<210> 775

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 775

Gln Arg His Asn Ala Ala Ser Leu Asn Thr Gly Thr Gln Met Ala Gly
 1 5 10 15
 His Ser Pro Asn Ser
 20

<210> 776

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 776

Gln Arg His Ala Ala Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly
 1 5 10 15
 His Ser Pro Asn Ser
 20

<210> 777

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 777

Gln Arg His Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser
 1 5 10 15
 Pro Asn Ser

<210> 778

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 778

Gln Arg His Gly Gly Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly
 1 5 10 15
 His Ser Pro Asn Ser
 20

<210> 779

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 779

His Asp Gly Ser Ser Leu Asn Thr Pro Asn Ser

1 5 10

<210> 780

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 780

Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn Ser
 1 5 10 15

<210> 781

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 781

Ser Ser Leu Asn Thr Arg Thr Gln Met Ala Gly His Ser Pro Asn Ser
 1 5 10 15

<210> 782

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 782

Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Arg His Ser Pro Asn Ser
 1 5 10 15

<210> 783

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 783

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

<210> 784

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 784

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

1 5 10 15

<210> 785

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 785

Ser Ser Leu Asn Thr Arg Thr Gln Met Ala Arg His Ser Pro Asn Ser
1 5 10 15

<210> 786

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 786

Ser Ser Leu Asn Thr Arg Thr Gln Lys Ala Gly His Ser Pro Asn Ser
1 5 10 15

<210> 787

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 787

Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Pro Asn
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Ser

<210> 788

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 788

Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Pro Asn Ser
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<210> 789

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 789

Asn Ser Leu Phe Asn Gln Glu Val Pro Asn Ser
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<210> 790

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 790

Gln Arg His Asn Asn Ser Ser Leu Asn Thr Pro Asn Ser
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<210> 791

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Peptide linker

<400> 791

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
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 Pro Asn Ser

<210> 792

<211> 2730

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC038 comprises: G19-4 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, human Ck(YAE), H75 linker and 3D1 (anti-CD86) scFv

<400> 792

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<210> 793

<211> 1821

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC039 comprises: BMA031 (anti-TCR) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 793

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<210> 794

<211> 1821

<212> DNA

<213> Artificial Sequence

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<223> TSC041 comprises: CRIS7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 794

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<210> 795

<211> 1773

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC043 comprises: OKT3-M (Micromet variant anti-CD3, see also US 7,635,472) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 795

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<210> 796

<211> 2088

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC049 comprises: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1

<400> 796

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<210> 797

<211> 2067

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC050 comprises: 2H7 (anti-CD20) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1

<400> 797

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ggaaggtgcc actccactg tccttctcta ataaatgag gaaattgcat cgcattgtct 2040
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```

<210> 798

<211> 2055

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC051 comprises: P2C2 (anti-CD79) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1

<400> 798

```

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ttctattctg gggggg 2055

```

<210> 799

<211> 1870

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC052 comprises: 5D5 (anti-cMet) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1

<400> 799

```

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tgcaacgtga atcacaggcc cagcaacacc aagggtggaca agaaagtgtg ataccactac 1860
atatcgcggc 1870

```

<210> 800

<211> 1827

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC053 comprises: G19-4 (anti CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 800

```

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tacgagaaac acaaagtcta cgccctgcga gtacacccatc agggcctgag ctgcgccgtc 1800
acaaagagct tcaacagggg agagtga 1827

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<210> 801

<211> 2707

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC064 comprises: G19-4 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, human Ck(YAE), H75 linker, and Met021 (anti-c-Met) scFv

<400> 801

```

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<210> 802

<211> 1812

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC076 comprises: OKT3 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 802

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aggggagagt ga 1812

```

<210> 803

<211> 1821

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC077 comprises: HuM291 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 803

```

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aacaactaca agaccacgac tcccgctgct gactccgagc gctccttctt cctctacagc 1380

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```

<210> 804

<211> 1821

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC093 comprises from its amino to carboxy terminus: CRIS7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 804

```

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agcttcaaca ggggagagtg a 1821

```

<210> 805

<211> 1773

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC094 comprises: OKT3-M (Micromet variant anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, human Ck(YAE)

<400> 805

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cccgtcacia agagcttcaa caggggagag tga 1773

```

<210> 806

<211> 1821

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC095 comprises: BMA031 (anti-TCR) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, human Ck(YAE)

<400> 806

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<210> 807

<211> 1836

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC096 comprises: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, human Ck(YAE)

<400> 807

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<210> 808

<211> 1812

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC097 comprises: 4C04 (anti-RON) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 808

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<210> 809

<211> 1608

<212> DNA

<213> Artificial Sequence

<220>

<223> Bispecific T-Cell Engaging molecule (BiTE) known as bsc19x3

<400> 809

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<210> 810

<211> 859

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC038 comprises: G19-4 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, human Ck(YAE), H75 linker and 3D1 (anti-CD86) scFv

<400> 810

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Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35      40      45
Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
50      55      60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Ala Tyr
65      70      75      80
Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
100      105      110
Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
115      120      125
Gly Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
130      135      140
Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
145      150      155      160
Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
165      170      175
Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
180      185      190
Leu His Ser Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
195      200      205
Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
210      215      220
Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
225      230      235      240
Thr Lys Leu Val Thr Lys Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys
245      250      255
Thr His Thr Cys Pro Pro Cys Pro Ser Gly Ala Pro Glu Leu Leu Gly
260      265      270
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
275      280      285
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
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Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
305      310      315      320
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
325      330      335
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
340      345      350
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
355      360      365
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
370      375      380
Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
385      390      395      400
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
405      410      415

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Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
450 455 460
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
465 470 475 480
Pro Gly Lys Ser Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
485 490 495
Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
500 505 510
Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
515 520 525
Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp
530 535 540
Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys
545 550 555 560
Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
565 570 575
Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Gln Arg
580 585 590
His Asn Asn Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser
595 600 605
Pro Asn Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg
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Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe
625 630 635 640
Thr Asp Tyr Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu
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Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Ser
740 745 750
Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly Glu Lys Val Thr Met
755 760 765
Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn
770 775 780
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
785 790 795 800
Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr
805 810 815
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln
820 825 830
Ala Glu Asp Leu Ala Val Tyr Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr
835 840 845
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
850 855

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<210> 811

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC039 comprises from its amino to carboxyl terminus: BMA031 (anti-TCR) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 811

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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 Lys Phe Thr Ser Tyr
20      25      30
Val Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Tyr Asn Asp Val Thr Lys Tyr Asn Glu Lys Phe
50      55      60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65      70      75      80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val His Tyr Cys
85      90      95
Ala Arg Gly Ser Tyr Asp Tyr Asp Gly Phe Val Tyr Trp Gly Gln
100      105      110
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly
115      120      125
Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln Ser
130      135      140
Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr Cys
145      150      155      160
Ser Ala Thr Ser Ser Val Ser Tyr Met His Trp Tyr Gln Gln Lys Pro
165      170      175
Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser
180      185      190
Gly Val Pro Ala Arg Phe Ile Gly Ser Gly Ser Gly Thr Glu Phe Thr
195      200      205
Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys
210      215      220
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225      230      235      240
Glu Ile Lys Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr
245      250      255
Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
260      265      270
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
275      280      285
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
290      295      300
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
305      310      315      320
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
325      330      335
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
340      345      350
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
355      360      365
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
370      375      380
Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
385      390      395      400
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
405      410      415
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
420      425      430
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
435      440      445
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
450      455      460      465
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg
465      470      475      480

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
485      490      495
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr
500      505      510
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
515      520      525
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
530      535      540
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
545      550      555      560
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
565      570      575
Val Thr Lys Ser Phe Asn Arg Gly Glu
580      585

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<210> 812

<211> 586

<212> PRT

<213> Artificial Sequence

<220>

<223> polypeptide TSC041 comprises from its amino to carboxy terminus: CRIS7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 812

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20 25 30
 Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Trp Ile
 35 40 45
 Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50 55 60
 Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65 70 75 80
 Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85 90 95
 Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
 100 105 110
 Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
 130 135 140
 Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
 145 150 155 160
 Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
 165 170 175
 Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
 180 185 190
 Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr
 195 200 205
 Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
 210 215 220
 Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
 225 230 235 240
 Leu Gln Ile Thr Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
 245 250 255
 Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Gly Gly Pro Ser Val
 260 265 270
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 275 280 285
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu

290 295 300
 Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 305 310 315 320
 Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 325 330 335
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 340 345 350
 Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
 355 360 365
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 370 375 380
 Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 385 390 395 400
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 405 410 415
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 420 425 430
 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 435 440 445
 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 450 455 460
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
 465 470 475 480
 Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 485 490 495
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe
 500 505 510
 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 515 520 525
 Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser
 530 535 540
 Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 545 550 555 560
 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 565 570 575
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
 580 585

<210> 813

<211> 570

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC043 comprises from its amino to carboxy terminus: OKT3-M (Micromet variant anti-CD3, see also US 7,635,472) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, and human Ck(YAE)

<400> 813

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Asp Ile Lys Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1      5      10      15
Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Arg Tyr
20      25      30
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Thr Ala Tyr
65      70      75      80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100      105      110

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Thr Thr Leu Thr Val Ser Ser Val Glu Gly Gly Ser Gly Gly Ser Gly
115      120      125
Gly Ser Gly Gly Ser Gly Gly Val Asp Asp Ile Gln Leu Thr Gln Ser
130      135      140
Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys
145      150      155      160
Arg Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Ser
165      170      175
Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
180      185      190
Gly Val Pro Tyr Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser
195      200      205
Leu Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
210      215      220
Gln Gln Trp Ser Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
225      230      235      240
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
245      250      255
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
260      265      270
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
275      280      285
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
290      295      300
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
305      310      315      320
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
325      330      335
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
340      345      350
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
355      360      365
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
370      375      380
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
385      390      395      400
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
405      410      415
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
420      425      430
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
435      440      445
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
450      455      460
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
465      470      475      480
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe
485      490      495
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
500      505      510
Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser
515      520      525
Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu
530      535      540
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
545      550      555      560
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
565      570

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<210> 814

<211> 584

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC049 comprises from its amino to carboxy terminus: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1

<400> 814

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
245      250      255
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
260      265      270
Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
275      280      285
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
290      295      300
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305      310      315      320
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
325      330      335
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340      345      350
Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
355      360      365
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370      375      380
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
385      390      395      400
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405      410      415
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420      425      430
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435      440      445
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450      455      460

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465      470      475      480
Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
485      490      495
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
500      505      510
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
515      520      525
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
530      535      540
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
545      550      555      560
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
565      570      575
Asn Thr Lys Val Asp Lys Lys Val
580

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<210> 815

<211> 577

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC050 comprises from its amino to carboxy terminus: 2H7 (anti-CD20) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1

<400> 815

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
 1 5 10 15
 Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Val Ser Tyr Met
 20 25 30
 His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
 35 40 45
 Ala Pro Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
 50 55 60
 Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
 65 70 75 80
 Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
 85 90 95
 Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Asp Gly Gly Gly Ser Gly
 100 105 110
 Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln Ala Tyr Leu Gln Gln
 115 120 125
 Ser Gly Ala Glu Ser Val Arg Pro Gly Ala Ser Val Lys Met Ser Cys
 130 135 140
 Lys Ala Ser Gly Tyr Phe Thr Ser Tyr Asn Met His Trp Val Lys
 145 150 155 160
 Gln Thr Pro Arg Gln Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly
 165 170 175
 Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu
 180 185 190
 Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
 195 200 205
 Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Val Val Tyr Tyr
 210 215 220
 Ser Asn Ser Tyr Trp Tyr Phe Asp Val Trp Gly Thr Gly Thr Thr Val
 225 230 235 240
 Thr Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys
 245 250 255
 Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu
 260 265 270
 Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu

275 280 285
 Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 290 295 300
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 305 310 315 320
 Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
 325 330 335
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala
 340 345 350
 Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 355 360 365
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 370 375 380
 Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 385 390 395 400
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 405 410 415
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 420 425 430
 Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
 435 440 445
 Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 450 455 460
 His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Ala
 465 470 475 480
 Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
 485 490 495
 Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
 500 505 510
 Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
 515 520 525
 Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
 530 535 540
 Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
 545 550 555 560
 Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
 565 570 575

Val

<210> 816

<211> 573

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC051 comprises from its amino to carboxy terminus: P2C2 (anti-CD79) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1

<400> 816

```

Asp Ile Val Met Ile Gln Asp Glu Leu Ser Asn Pro Val Ser Ser Gly
1      5      10      15
Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu Asp Lys
20      25      30
Glu Gly Lys Thr Tyr Leu Asn Trp Phe Leu Gln Arg Pro Gly Gln Ser
35      40      45
Pro Gln Leu Leu Ile Tyr Leu Met Ser Met Arg Glu Ser Gly Val Ser
50      55      60
Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Glu Ile
65      70      75      80
Ser Arg Val Lys Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Leu
85      90      95

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Val Glu Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100      105      110
Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln
115      120      125
Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Phe Ser
145      150      155      160
Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly
165      170      175
Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Arg
180      185      190
Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu
195      200      205
Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Thr
210      215      220
Trp Ser Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ser
225      230      235      240
Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
245      250      255
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
260      265      270
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275      280      285
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290      295      300
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305      310      315      320
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325      330      335
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
340      345      350
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355      360      365
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
370      375      380
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385      390      395      400
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405      410      415
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420      425      430
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435      440      445
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450      455      460
Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly
465      470      475      480
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
485      490      495
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
500      505      510
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
515      520      525
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
530      535      540
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
545      550      555      560
Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
565      570

```

<210> 817

<211> 580

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC052 comprises from its amino to carboxy terminus: 5D5 (anti-cMet) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human IgG1 CH1

<400> 817

```

Asp Phe Met Met Ser Gln Ser Pro Ser Ser Leu Thr Val Ser Val Gly
1      5      10      15
Glu Lys Val Thr Val Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Thr
20      25      30
Ser Ser Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35      40      45
Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50      55      60
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65      70      75      80
Ile Thr Ser Val Lys Ala Asp Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85      90      95
Tyr Tyr Ala Tyr Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu
100      105      110
Lys Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115      120      125
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Ala
130      135      140
Ser Val Lys Met Ser Cys Arg Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
145      150      155      160
Trp Leu His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
165      170      175
Gly Met Ile Asp Pro Ser Asn Ser Asp Thr Arg Phe Asn Pro Asn Phe
180      185      190
Lys Asp Lys Ala Thr Leu Asn Val Asp Arg Ser Ser Asn Thr Ala Tyr
195      200      205
Met Leu Leu Ser Ser Leu Thr Ser Ala Asp Ser Ala Val Tyr Tyr Cys
210      215      220
Ala Thr Tyr Gly Ser Tyr Val Ser Pro Leu Asp Tyr Trp Gly Gln Gly
225      230      235      240
Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr
245      250      255
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser
260      265      270
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
275      280      285
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
290      295      300
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
305      310      315      320
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
325      330      335
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr
340      345      350
Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
355      360      365
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
370      375      380
Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
385      390      395      400
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
405      410      415
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
420      425      430
Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
435      440      445

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
450      455      460
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465      470      475      480
Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
485      490      495
Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
500      505      510
Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
515      520      525
Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
530      535      540
Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
545      550      555      560
Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
565      570      575
Asp Lys Lys Val
580

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<210> 818

<211> 588

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC053 comprises from its amino to carboxy terminus: G19-4 (anti CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 818

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30
 Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
 35 40 45
 Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
 100 105 110
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
 115 120 125
 Gly Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
 130 135 140
 Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
 145 150 155 160
 Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
 165 170 175
 Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
 180 185 190
 Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Thr
 195 200 205
 Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
 210 215 220
 Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
 225 230 235 240
 Thr Lys Leu Val Thr Lys Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys
 245 250 255
 Thr His Thr Cys Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 260 265 270
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 275 280 285
 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 290 295 300
 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
 305 310 315 320
 Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala
 325 330 335
 Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 340 345 350
 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 355 360 365
 Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
 370 375 380
 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 385 390 395 400
 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 405 410 415
 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 420 425 430
 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 435 440 445
 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 450 455 460
 Lys Ser Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
 465 470 475 480
 Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
 485 490 495
 Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala
 500 505 510
 Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys
 515 520 525
 Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp
 530 535 540
 Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
 545 550 555 560
 Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
 565 570 575
 580 585

<210> 819

<211> 853

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC064 comprises from its amino to carboxy terminus: G19-4 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2, human IgG1 CH3, human Ck(YAE), H75 linker, and Met021 (anti-c-Met) scFv

<400> 819

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30
 Ile Val Asn Trp Leu Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
 35 40 45
 Gly Leu Ile Asn Pro Tyr Lys Gly Leu Thr Thr Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp
 100 105 110
 Gly Ala Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
 115 120 125
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr
 130 135 140
 Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile
 145 150 155 160
 Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln
 165 170 175
 Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile Tyr Tyr Thr Ser Arg
 180 185 190
 Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
 195 200 205
 Asp Tyr Ser Leu Thr Ile Ala Asn Leu Gln Pro Glu Asp Ile Ala Thr
 210 215 220
 Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gly Gly
 225 230 235 240
 Thr Lys Leu Val Thr Lys Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys
 245 250 255
 Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
 260 265 270
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 275 280 285
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 290 295 300
 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 305 310 315 320
 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
 325 330 335
 Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 340 345 350
 Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 355 360 365
 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 370 375 380
 Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
 385 390 395 400
 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 405 410 415
 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 420 425 430
 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 435 440 445
 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 450 455 460
 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 465 470 475 480
 Lys Ser Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
 485 490 495
 Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
 500 505 510
 Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala
 515 520 525
 Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys
 530 535 540
 Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp
 545 550 555 560
 Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
 565 570 575
 Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Gln Arg His Asn
 580 585 590
 Asn Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn

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      595              600              605
Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
610
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Asn
625              630              635              640
Tyr Leu Asn Trp Tyr Gln Gln Glu Pro Gly Lys Ala Pro Lys Leu Leu
645              650              655
Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
660              665              670
Gly Ser Gly Ser Gly Thr Asp Phe Ile Leu Thr Ile Ser Ser Leu Gln
675              680              685
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Val Thr Pro
690              695              700
Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly
705              710              715              720
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
725              730              735
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
740              745              750
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Tyr
755              760              765
Asp Met Leu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
770              775              780
Ser Tyr Ile Tyr Pro Ser Gly Gly Leu Thr Glu Tyr Ala Asp Ser Val
785              790              795              800
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
805              810              815
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
820              825              830
Ala Arg Arg Ala Pro Arg Ser Leu Ser Phe Asp Ile Trp Gly Gln Gly
835              840              845
Thr Met Val Thr Val
850

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<210> 820

<211> 583

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC076 comprises from its amino to carboxy terminus: OKT3 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 820

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Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1              5              10              15
Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20              25              30
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35              40              45
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50              55              60
Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
65              70              75              80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85              90              95
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100              105              110
Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115              120              125
Ser Gly Gly Gly Gly Ser Ala Gln Gln Ile Val Leu Thr Gln Ser Pro
130              135              140

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Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys Ser
145                               150           155           160
Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Ser Gly
                               165           170           175
Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly
                               180           185           190
Val Pro Ala His Phe Arg Gly Ser Gly Thr Ser Tyr Ser Leu
                               195           200           205
Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln
210                               215           220
Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu
225                               230           235
Ile Asn Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
                               245           250           255
Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe
260                               265           270
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
275                               280           285
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
290                               295           300
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
305                               310           315
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
325                               330           335
Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val
340                               345           350
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
355                               360           365
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
370                               375           380
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
385                               390           395
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
405                               410           415
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
420                               425           430
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
435                               440           445
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
450                               455           460
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr Val
465                               470           475
Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
485                               490           495
Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg
500                               505           510
Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
515                               520           525
Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
530                               535           540
Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
545                               550           555
Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
565                               570           575
Lys Ser Phe Asn Arg Gly Glu
580

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<210> 821

<211> 586

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC077 comprises: HuM291 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 821

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 Ile Ser Tyr
 20 25 30
 Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr His Tyr Asn Gln Lys Leu
 50 55 60
 Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ala Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ala Tyr Tyr Asp Tyr Asp Gly Phe Ala Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly
 115 120 125
 Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln Ser
 130 135 140
 Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
 145 150 155 160
 Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
 165 170 175
 Gly Lys Ala Pro Lys Arg Leu Ile Tyr Asp Thr Ser Lys Leu Ala Ser
 180 185 190
 Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 195 200 205
 Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
 210 215 220
 Gln Gln Trp Ser Ser Asn Pro Pro Thr Phe Gly Gly Thr Lys Val
 225 230 235 240
 Glu Ile Lys Arg Thr Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
 245 250 255
 Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
 260 265 270
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 275 280 285
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
 290 295 300
 Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 305 310 315 320
 Thr Lys Pro Arg Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 325 330 335
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
 340 345 350
 Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
 355 360 365
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 370 375 380
 Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 385 390 395 400
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 405 410 415
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 420 425 430
 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 435 440 445
 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 450 455 460
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
 465 470 475 480
 Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu

485 490 495
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe
 500 505 510
 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 515 520 525
 Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser
 530 535 540
 Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 545 550 555 560
 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 565 570 575
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
 580 585

<210> 822

<211> 586

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC093 comprises from its amino to carboxy terminus: CRIS7 (anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 822

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20 25 30
 Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Trp Ile
 35 40 45
 Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50 55 60
 Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65 70 75 80
 Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85 90 95
 Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
 100 105 110
 Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
 130 135 140
 Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
 145 150 155 160
 Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
 165 170 175
 Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
 180 185 190
 Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr
 195 200 205
 Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
 210 215 220
 Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
 225 230 235 240
 Leu Gln Ile Thr Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
 245 250 255
 Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
 260 265 270
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 275 280 285
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
 290 295 300

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 305 310 315 320
 Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 325 330 335
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
 340 345 350
 Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
 355 360 365
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 370 375 380
 Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 385 390 395 400
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 405 410 415
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 420 425 430
 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 435 440 445
 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 450 455 460
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
 465 470 475 480
 Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 485 490 495
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe
 500 505 510
 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 515 520 525
 Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser
 530 535 540
 Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 545 550 555 560
 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 565 570 575
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
 580 585

<210> 823

<211> 570

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC094 comprises from its amino to carboxy terminus: OKT3-M (Micromet variant anti-CD3) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, human Ck(YAE)

<400> 823

Asp Ile Lys Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
 1 5 10 15
 Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Arg Tyr
 20 25 30
 Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Trp Ile
 35 40 45
 Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
 50 55 60
 Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Thr Leu Thr Val Ser Ser Val Glu Gly Gly Ser Gly Gly Ser Gly

115 120 125
 Gly Ser Gly Gly Ser Gly Gly Val Asp Asp Ile Gln Leu Thr Gln Ser
 130 135 140
 Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr Cys
 145 150 155 160
 Arg Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Ser
 165 170 175
 Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Val Ala Ser
 180 185 190
 Gly Val Pro Tyr Arg Phe Ser Gly Ser Gly Thr Ser Tyr Ser
 195 200 205
 Leu Thr Ile Ser Ser Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys
 210 215 220
 Gln Gln Trp Ser Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
 225 230 235 240
 Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
 245 250 255
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 260 265 270
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
 275 280 285
 Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 290 295 300
 Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 305 310 315 320
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
 325 330 335
 Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
 340 345 350
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 355 360 365
 Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 370 375 380
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 385 390 395 400
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 405 410 415
 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 420 425 430
 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 435 440 445
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
 450 455 460
 Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 465 470 475 480
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe
 485 490 495
 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 500 505 510
 Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser
 515 520 525
 Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 530 535 540
 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 545 550 555 560
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
 565 570

<210> 824

<211> 586

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC095 comprises from its amino to carboxy terminus: BMA031 (anti-TCR) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, human Ck(YAE)

<400> 824

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Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly
1      5      10      15
Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Lys Phe Thr Ser
20      25      30
Tyr Val Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp
35      40      45
Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Val Thr Lys Tyr Asn Glu Lys
50      55      60
Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Gly Ser Thr Asn Thr Ala
65      70      75      80
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val His Tyr
85      90      95
Cys Ala Arg Gly Ser Tyr Tyr Asp Tyr Asp Gly Phe Val Tyr Trp Gly
100      105      110
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
115      120      125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130      135      140
Ser Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
145      150      155      160
Cys Ser Ala Thr Ser Ser Val Ser Tyr Met His Trp Tyr Gln Gln Lys
165      170      175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala
180      185      190
Ser Gly Val Pro Ala Arg Phe Ile Gly Ser Gly Ser Gly Thr Glu Phe
195      200      205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr
210      215      220
Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys
225      230      235      240
Val Glu Ile Lys Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
245      250      255
Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
260      265      270
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
275      280      285
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
290      295      300
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
305      310      315      320
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
325      330      335
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
340      345      350
Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
355      360      365
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
370      375      380
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
385      390      395      400
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
405      410      415
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
420      425      430
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
435      440      445
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
450      455      460
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
465      470      475      480
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
485      490      495
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe
500      505      510
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
515      520      525
Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser
530      535      540
Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu
545      550      555      560
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
565      570      575
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
580      585

```

<210> 825

<211> 591

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC096 comprises: HD37 (anti-CD19) scFv, human IgG1 SCC-P hinge, human IgG1 CH2 (ADCC/CDC null), human IgG1 CH3, human Ck(YAE)

<400> 825


```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
245      250      255
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
260      265      270
Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
275      280      285
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

290      295      300
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305      310      315
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
320      325      330      335
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340      345      350
Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
355      360      365
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370      375      380
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
385      390      395      400
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405      410      415
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420      425      430
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435      440      445
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450      455      460
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465      470      475      480
Ser Pro Gly Lys Ser Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
485      490      495
Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
500      505      510
Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
515      520      525
Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln
530      535      540
Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser
545      550      555      560
Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
565      570      575
Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
580      585      590

```

<210> 826

<211> 583

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC097 comprises from its amino to carboxy terminus: 4C04 (anti-RON) scFv, human IgG1 SCC-P hinge, human IgG1 CH2(ADCC/CDC null), human IgG1 CH3, and human Ck(YAE)

<400> 826

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly
 1 5 10 15
 Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Ile
 35 40 45
 Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Ala
 50 55 60
 Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Asp Ser Leu Gln Ser
 65 70 75 80
 Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Asn Thr Pro Trp
 85 90 95
 Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
 100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Gln Leu Gln Gln
 115 120 125
 Ser Gly Pro Glu Leu Val Lys Pro Gly Thr Ser Val Lys Ile Ser Cys
 130 135 140
 Lys Ala Ser Asp Tyr Thr Leu Thr Asp Phe Tyr Met Asn Trp Val Arg
 145 150 155 160
 Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly
 165 170 175
 Thr Asp Lys Thr Arg Tyr Asn Glu Lys Phe Arg Asp Lys Ala Ile Leu
 180 185 190
 Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
 195 200 205
 Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Ser Ala Tyr Tyr
 210 215 220
 Gly Asn Tyr Val Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
 225 230 235 240
 Val Ser Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
 245 250 255
 Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe
 260 265 270
 Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 275 280 285
 Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 290 295 300
 Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 305 310 315 320
 Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 325 330 335
 Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val
 340 345 350
 Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
 355 360 365
 Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
 370 375 380
 Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 385 390 395 400
 Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
 405 410 415
 Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
 420 425 430
 Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 435 440 445
 Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 450 455 460
 Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr Val
 465 470 475 480
 Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
 485 490 495
 Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg
 500 505 510
 Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
 515 520 525
 Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
 530 535 540
 Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
 545 550 555 560
 Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
 565 570 575
 Lys Ser Phe Asn Arg Gly Glu
 580

<210> 827

<211> 512

<212> PRT

<213> Artificial Sequence

<220>

<223> Bispecific T-Cell Engaging molecule (BiTE) known as bsc19x3

<400> 827

```

Asp Tyr Lys Asp Asp Asp Asp Lys Asp Ile Gln Leu Thr Gln Ser Pro
1      5      10      15
Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys
20      25      30
Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr
35      40      45
Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser
50      55      60
Asn Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly
65      70      75      80
Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala
85      90      95
Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly
100      105      110
Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly Gly Gly
115      120      125
Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
130      135      140
Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
145      150      155      160
Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
165      170      175
Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr
180      185      190
Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu
195      200      205
Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp
210      215      220
Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr Val Gly Arg
225      230      235      240
Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
245      250      255
Ser Ser Gly Gly Gly Gly Ser Asp Ile Lys Leu Gln Gln Ser Gly Ala
260      265      270
Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Thr Ser
275      280      285
Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Lys Gln Arg Pro
290      295      300
Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr
305      310      315      320
Thr Asn Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Thr Asp
325      330      335
Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu
340      345      350
Asp Ser Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys
355      360      365
Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Val Glu
370      375      380
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Ser Gly Gly Val Asp
385      390      395      400
Asp Ile Gln Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
405      410      415
Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
420      425      430
Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
435      440      445
Asp Thr Ser Lys Val Ala Ser Gly Val Pro Tyr Arg Phe Ser Gly Ser
450      455      460

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
465      470      475      480
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
485      490      495
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys His His His His His His
500      505      510

```

<210> 828

<211> 120

<212> PRT

<213> Homo sapiens

<220>

<223> VH region of BMA031 (anti-TCR) scFv

<400> 828

```

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 Lys Phe Thr Ser Tyr
20      25      30
Val Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Tyr Asn Asp Val Thr Lys Tyr Asn Glu Lys Phe
50      55      60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65      70      75      80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val His Tyr Cys
85      90      95
Ala Arg Gly Ser Tyr Tyr Asp Tyr Asp Gly Phe Val Tyr Trp Gly Gln
100      105      110
Gly Thr Leu Val Thr Val Ser Ser
115      120

```

<210> 829

<211> 111

<212> PRT

<213> Homo sapiens

<220>

<223> VL region of BMA031 (anti-TCR) scFv

<400> 829

```

Ala Gln Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser
1      5      10      15
Val Gly Asp Arg Val Thr Met Thr Cys Ser Ala Thr Ser Ser Val Ser
20      25      30
Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp
35      40      45
Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ile
50      55      60
Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65      70      75      80
Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro
85      90      95
Leu Thr Phe Gly Gly Thr Lys Val Glu Ile Lys Ser Ser Ser
100      105      110

```

<210> 830

<211> 246

<212> PRT

<213> Homo sapiens

<220>

<223> BMA031 scFv

<400> 830

```

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 Lys Phe Thr Ser Tyr
20      25      30
Val Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Tyr Asn Asp Val Thr Lys Tyr Asn Glu Lys Phe
50      55      60
Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65      70      75      80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val His Tyr Cys
85      90      95
Ala Arg Gly Ser Tyr Tyr Asp Tyr Asp Gly Phe Val Tyr Trp Gly Gln
100      105      110
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115      120      125
Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln Ser
130      135      140
Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr Cys
145      150      155      160
Ser Ala Thr Ser Ser Val Ser Tyr Met His Trp Tyr Gln Gln Lys Pro
165      170      175
Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser
180      185      190
Gly Val Pro Ala Arg Phe Ile Gly Ser Gly Ser Gly Thr Glu Phe Thr
195      200      205
Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys
210      215      220
Gln Gln Trp Ser Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
225      230      235      240
Glu Ile Lys Ser Ser
245

```

<210> 831

<211> 119

<212> PRT

<213> Homo sapiens

<220>

<223> VH region of OKT3-M (anti-CD3) scFv

<400> 831

```

Asp Ile Lys Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
 1          5          10          15
Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Arg Tyr
          20          25          30
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
          35          40          45
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
          50          55          60
Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
          65          70          75          80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
          85          90          95
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
          100          105          110
Thr Thr Leu Thr Val Ser Ser
          115

```

<210> 832

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> OKT3-M Linker

<400> 832

```

Val Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
 1          5          10          15
Val Asp

```

<210> 833

<211> 94

<212> PRT

<213> Homo sapiens

<220>

<223> VL region of OKT3-M (anti-CD3) scFv

<400> 833

```

Asp Ile Gln Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
 1          5          10          15
Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
          20          25          30
Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
          35          40          45
Asp Thr Ser Lys Val Ala Ser Gly Val Pro Tyr Arg Phe Ser Gly Ser
          50          55          60
Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
          65          70          75          80
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Ser Ser
          85          90

```

<210> 834

<211> 231

<212> PRT

<213> Homo sapiens

<220>

<223> OKT3-M scFv

<400> 834

```

Asp Ile Lys Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1      5      10      15
Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Arg Tyr
20      25      30
Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
65      70      75      80
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100     105     110
Thr Thr Leu Thr Val Ser Ser Val Glu Gly Gly Ser Gly Gly Ser Gly
115     120     125
Gly Ser Gly Gly Ser Gly Gly Val Asp Asp Ile Gln Leu Thr Gln Ser
130     135     140

```

```

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

```

<210> 835

<211> 120

<212> PRT

<213> Homo sapiens

<220>

<223> VH region of HuM291 (anti-CD3) scFv

<400> 835

```

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 Ile Ser Tyr
20      25      30
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35      40      45
Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr His Tyr Asn Gln Lys Leu
50      55      60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ala Ser Thr Ala Tyr
65      70      75      80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85      90      95
Ala Arg Ser Ala Tyr Tyr Asp Tyr Asp Gly Phe Ala Tyr Trp Gly Gln
100     105     110
Gly Thr Leu Val Thr Val Ser Ser
115     120

```

<210> 836

<211> 112

<212> PRT

<213> Homo sapiens

<220>

<223> VL region of HuM291 (anti-CD3) scFv

<400> 836

```

Ala Gln Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1      5      10      15
Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser
20      25      30
Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu
35      40      45
Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50      55      60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65      70      75      80
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro
85      90      95
Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Ser Ser
100     105     110

```

<210> 837

<211> 247

<212> PRT

<213> Homo sapiens

<220>

<223> HuM291 scFv

<400> 837

```

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 Ile Ser Tyr
 20          25          30
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35          40          45
Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr His Tyr Asn Gln Lys Leu
 50          55          60
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ala Ser Thr Ala Tyr
 65          70          75          80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85          90          95
Ala Arg Ser Ala Tyr Tyr Asp Tyr Asp Gly Phe Ala Tyr Trp Gly Gln
100          105          110
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly
115          120          125
Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln Ser
130          135          140
Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145          150          155          160
Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
165          170          175
Gly Lys Ala Pro Lys Arg Leu Ile Tyr Asp Thr Ser Lys Leu Ala Ser
180          185          190
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr
195          200          205
Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210          215          220
Gln Gln Trp Ser Ser Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys Val
225          230          235          240
Glu Ile Lys Arg Thr Ser Ser
245

```

<210> 838

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated human Ck DAE

<400> 838

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1          5          10          15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asp Phe Tyr
 20          25          30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35          40          45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50          55          60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65          70          75          80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85          90          95
Val Thr Lys Ser Phe Asn Arg Gly Glu

```

100

105

<210> 839

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated human Ck MAE

<400> 839

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Met Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50      55      60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100      105

```

<210> 840

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated human Ck SAE

<400> 840

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Ser Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45
Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50      55      60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100      105

```

<210> 841

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated human FAE

<400> 841

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Phe Phe Tyr
 20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 35      40      45

Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr
 50      55      60
Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
 100      105

```

<210> 842

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated Ck L29E

<400> 842


```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Glu Leu Asn Asn Phe Tyr
20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35      40      45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50      55      60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100      105

```

<210> 843

<211> 105

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated Ck L29K

<400> 843

```

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1      5      10      15
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Lys Leu Asn Asn Phe Tyr
20      25      30
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35      40      45
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50      55      60
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65      70      75      80
His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85      90      95
Val Thr Lys Ser Phe Asn Arg Gly Glu
100      105

```

<210> 844

<211> 98

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated CH1 V68E

<400> 844

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1      5      10      15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20      25      30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35      40      45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50      55      60
Leu Ser Ser Glu Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65      70      75      80
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85      90      95
Lys Val

```

<210> 845

<211> 98

<212> PRT

<213> Artificial Sequence

<220>

<223> mutated CH1 V68K

<400> 845

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1      5      10      15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20      25      30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35      40      45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50      55      60
Leu Ser Ser Lys Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65      70      75      80
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85      90      95
Lys Val

```

<210> 846

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> CH3-CH1 linker or CH3-Ck linker

<400> 846

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Lys Ser Arg
1

```

<210> 847

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CH3-CH1 linker

<400> 847

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Gly Gly Gly Ser Ser
1      5

```

<210> 848

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> CH3-CH1 linker

<400> 848

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Ser Tyr Ser Pro Asn Ser
1      5

```

<210> 849

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> CH3-CH1 linker

<400> 849

```

Ser Ser Leu Asn Thr Pro Asn Ser
1      5

```

<210> 850

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CH3-Ck linker

<400> 850
Gly Gly Gly Ser Arg
1 5

<210> 851

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CH3-Ck linker

<400> 851

Ser Tyr Ser Pro Asn Ser Arg
1 5

<210> 852

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CH3-Ck linker

<400> 852

Ser Ser Leu Asn Thr Pro Asn Ser Arg
1 5

<210> 853

<211> 1806

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC145 (Cris7 scFv-hinge-CH2-CH3-GGGSS linker-CH1)

<400> 853

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caggtccagc	tgggtcagtc	tgggggcgga	gtgggtgcagc	ctgggcccgtc	actgaggctg	120
tcctgcgaag	ctctggcta	cacctttact	agatctacga	tgcaactgggt	aaggcaggcc	180
cctggaaagg	gtctggaatg	gattggatac	attaatccta	gcagtgccta	tactaattac	240
aatcagaaat	tcaaggacag	gttcacaatc	agcgagagca	aatccaagag	cacagccttc	300
ctgcagatgg	acagccctgag	gccccaggac	acggcgctct	atttctgtgc	acggccccaa	360
gtccactatg	attacaacgg	gtttccttac	tggggccaag	ggactcccgt	cactgtctct	420
agcgggtggcg	gagggtctgg	gggtggcgga	tcgggaggtg	gtggctctgc	acaagacatc	480
cagatgacc	agctccaag	cagcctgtct	gcaagcgtgg	gggacagggt	caccatgacc	540
tgcaagtcca	gctcaagtg	aagttacatg	aactggtacc	agcagaagcc	cggaaggcc	600
cccaaaagat	ggatttatga	ctcatccaaa	ctggctctcg	gagtcacctg	tcgcttcagt	660
ggcagtggtg	ctggggaccga	ctataccctc	acaatcagca	gcctgcagcc	cgaagatttc	720
gccacttatt	actgccagca	gtggagtcgt	aaaccaccca	cgttcggagg	ggggaccaaag	780
ctacaaatta	cacgctcgag	tgagcccaaa	tcttctgaca	aaactcacac	atgccaccgc	840
tgcccagcac	ctgaagccgc	gggtgcaccg	tcagtcttcc	tcttcccccc	aaaacccaag	900
gacaccctca	tgatctcccg	gacccctgag	gtcacatcgc	tgggtgtgga	cgtgagccac	960
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cagtcctcag	gactctactc	cctcagcagc	gtggtgacgc	tgccctccag	cagcttgggc	1740
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gtttga						1806

<210> 854

<211> 1809

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC146 (Cris7 scFv-hinge-CH2-CH3-SYSPNS linker-CH1)

<400> 854

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tcttgcaagg	cttctggcta	caaccttact	agatctacga	tgcactgggt	aaggcaggcc	180
cctggaaagg	gtctggaatg	gattggatac	attaatccta	gcagtgtcta	tactaattac	240
aatcagaaat	tcaaggacag	gttcacaatc	agcgcagaca	aatccaagag	cacagccttc	300
ctgcagatgg	acagcctgag	gccccaggac	acggcggtct	atttctgtgc	acggccccaa	360
gtccactatg	attacaacgg	gtttccttac	tggggccaag	ggactcccg	cactgtctct	420
agcgggtggc	gagggtctgg	gggtggcgga	tccggaggtg	gtggctctgc	acaagacatc	480
cagatgaccc	agtctccaag	cagcctgtct	gcaagcgtgg	gggacagggt	caccatgacc	540
tgcaagtcca	gctcaagtgt	aagttacatg	aactggtagc	agcagaagcc	cggaaggcc	600
cccaaaagat	ggatttatga	ctcatccaaa	ctggctttctg	gagtcctctg	tgccttcagt	660
ggcagtggtg	ctgggaccga	ctataccctc	acaatcagca	gcctgcagcc	cgaagatttc	720
gccacttatt	actgccagca	gtggagtcgt	aacccaccca	cgttcggagg	ggggaccagg	780
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tacacctgc	ccccatccc	ggatgagctg	accaagaacc	aggtcagcct	gacctgcctg	1260
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aaagtttga						1809

<210> 855

<211> 1815

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC147 (Cris7 scFv-hinge-CH2-CH3-SSLNTPNS linker-CH1)

<400> 855

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caggtccagc	tgggtgcagtc	tgggggcgga	gtgggtgcagc	ctgggcggtc	actgaggctg	120
tcttgcaagg	cttctggcta	caaccttact	agatctacga	tgcactgggt	aaggcaggcc	180
cctggaaagg	gtctggaatg	gattggatac	attaatccta	gcagtgtcta	tactaattac	240
aatcagaaat	tcaaggacag	gttcacaatc	agcgcagaca	aatccaagag	cacagccttc	300
ctgcagatgg	acagcctgag	gccccaggac	acggcggtct	atttctgtgc	acggccccaa	360
gtccactatg	attacaacgg	gtttccttac	tggggccaag	ggactcccg	cactgtctct	420
agcgggtggc	gagggtctgg	gggtggcgga	tccggaggtg	gtggctctgc	acaagacatc	480
cagatgaccc	agtctccaag	cagcctgtct	gcaagcgtgg	gggacagggt	caccatgacc	540
tgcaagtcca	gctcaagtgt	aagttacatg	aactggtagc	agcagaagcc	cggaaggcc	600
cccaaaagat	ggatttatga	ctcatccaaa	ctggctttctg	gagtcctctg	tgccttcagt	660
ggcagtggtg	ctgggaccga	ctataccctc	acaatcagca	gcctgcagcc	cgaagatttc	720
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agcttgggca	cccagacctc	catctgcaac	gtgaatcaca	agcccagcaa	caccaaggtg	1800
gacaagaaag	tttga					1815

<210> 856

<211> 1842

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC148 (HD37 scFv-hinge-CH2-CH3-GGGS linker-Ck)

<400> 856

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gacattgtgc	tgacccaatc	tccagcttct	ttggctgtgt	ctctagggca	gagggccacc	120

atctcctgca	aggccagcca	aagtgttgat	tatgatggg	atagttat	gaactggtac	180
caacagattc	caggacagcc	acccaaactc	ctcatctatg	atgcattcaa	tctagtttct	240
gggataccac	ccaggtttag	tggcagtggt	tctgggacag	acttcaccct	caacatccat	300
cctgtggaga	aggtggatgc	tgcaacctat	cactgccagc	aaagtactga	ggatccgtgg	360
acgttcggtg	gaggcaccac	gctggaaatc	aaaggtggcg	gtggttcggg	cgtggtggg	420
tcgggtggcg	gcggagctag	ccaggttcag	ctgcagcagt	ctggggctga	gctggtgagg	480
cctgggtcct	cagtgaagat	ttcctgcaag	gcttctggct	atgcattcag	tagctactgg	540
atgaactggg	tgaagcagag	gcctggacag	ggtcttgagt	ggattggaca	gatttgccct	600
ggagatgggt	atactaaacta	caatggaaag	ttcaagggtg	aagccactct	gactgcagac	660
gaatcctcca	gcacagccta	catgcaactc	agcagcctag	catctgagga	ctctgcggtc	720
tatttctgtg	caagacggga	gactacgacg	gtaggccgtt	attactatgc	tatggactac	780
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gtggacgtga	gccacgaaga	ccctgaggtc	aagttcaact	ggtacgtgga	cggcgtggag	1020
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ctgagcaaa	cagactacga	gaacacacaa	gtctacgcct	gcgaagtcac	ccatcagggc	1800
ctgagctcgc	ccgtcacaaa	gagcttcaac	aggggagagt	ga		1842

<210> 857

<211> 1848

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC149 (HD37 scFv-hinge-CH2-CH3-SYSPNSR linker-Ck)

<400> 857

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atctcctgca	aggccagcca	aagtgttgat	tatgatggg	atagttat	gaactggtac	180
caacagattc	caggacagcc	acccaaactc	ctcatctatg	atgcattcaa	tctagtttct	240
gggataccac	ccaggtttag	tggcagtggt	tctgggacag	acttcaccct	caacatccat	300
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ggagatgggt	atactaaacta	caatggaaag	ttcaagggtg	aagccactct	gactgcagac	660
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tcccaggaga	gtgccacaga	caggacagc	aaggacagca	cctacagcct	cagcagcgag	1740
ctgacgctga	gcacaaagc	ctacgagaaa	cacaaagtct	acgcctgcga	agtcacccat	1800
cagggcctga	gctgcgccgt	cacaaagagc	ttcaacaggg	gagagtga		1848

<210> 858

<211> 1854

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC150 (HD37 scFv-hinge-CH2-CH3-SSLNTPNSR linker-Ck)

<400> 858

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atctcctgca agggccagcca aagtgttgat tatgatgggt atagttattt gaactggtac      180
caacagattc caggacagcc acccaaatc ctcatctatg atgcattcaa tctagtttct      240
gggatccccc caaggttttag tggcagtggt tctgggacag acttcaccct caacatccat      300
cctgtggaga aggtggatgc tgcaacctat cactgccagc aaagtactga ggatccgtgg      360
acgttcggtg gaggcaccaa gctggaaatc aaagtggtgg gtggttcggg cgggtggtgg      420
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cctgggtcct cagtgaagat ttccctgcaag gcttctggct atgcattcag tagctactgg      540
atgaactggg tgaagcagag gcctggacag ggtcttgagt ggattggaca gatttgccct      600
ggagatgggt atactaacta caatggaag ttcaagggtta aagccactct gactgcagac      660
gaatcctcca gcacagccta catgcaactc agcagcctag catctgagga ctctgcggtc      720
tatttctgtg caagacggga gactacgacg gtaggccgtt attactatgc tatggactac      780
tggggtcaag gaacctcagt cccgtctctc tcgagtgagc ccaaatcttc tgacaaaact      840
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gtggacgtga gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag      1020
gtgcataatg ccaagacaaa gccgcgggag gagcagta caagcacgta ccgtgtggtc      1080
agcgtctcta ccgtcctgca ccaggactgg ctgaatggca aggcgtacgc gtgcgcggtc      1140
tccaaacaaag ccctccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc      1200
cgagaaccac aggtgtacac cctgccccca tcccgggatg agctgaccaa gaaccaggtc      1260
agcctgacct gcctgggtcaa aggtcttctat ccaagcgaca tcgccgtgga gtgggagagc      1320
aatgggcagc cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc      1380
ttcttctctc acagcaagct caccgtggac aagagcaggt ggagcaggg gaacgtcttc      1440
tcatgtcccg tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg      1500
tctccgggtt cttccctgaa tacaccgaac tctaggactg ttgctgcacc atctgtcttc      1560
atcttccccc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg      1620
aattacttct atcccagaga ggccaaagta cagtgggaagg tggataacgc cctccaatcg      1680
ggtaactccc agggagatgc cacagagcag gacagcaagg acagcaccta cagcctcagc      1740
agcgagctga cgtgagcaca agcagactac gagaacaca aagtctacgc ctgcgaagtc      1800
accatcaggt gcctgagctc gcccgtcaca aagagcttca acaggggaga gtga      1854

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<210> 859

<211> 581

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC145 (Cris7 scFv-hinge-CH2-CH3-GGGSS linker-CH1)

<400> 859

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Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1              5              10              15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20              25              30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35              40              45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50              55              60

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Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
65      70      75      80
Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
      85      90      95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100      105      110
Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115      120      125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130      135      140
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
145      150      155
Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
165      170      175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180      185      190
Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr
195      200      205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
210      215      220
Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
225      230      235
Leu Gln Ile Thr Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
245      250      255
Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
260      265      270
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
275      280      285
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
290      295      300
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
305      310      315
Thr Lys Pro Arg Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
325      330      335
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
340      345      350
Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
355      360      365
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
370      375      380
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
385      390      395
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
405      410      415
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
420      425      430
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
435      440      445
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
450      455      460
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly
465      470      475
Gly Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
485      490      495
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
500      505      510
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
515      520      525
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
530      535      540
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
545      550      555
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
565      570      575
Val Asp Lys Lys Val

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580

<210> 860

<211> 582

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC146 (Cris7 scFv-hinge-CH2-CH3-SYSPNS linker-CH1)

<400> 860

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20 25 30
 Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Trp Ile
 35 40 45
 Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50 55 60
 Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65 70 75 80
 Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85 90 95
 Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
 100 105 110
 Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
 130 135 140
 Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
 145 150 155 160
 Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
 165 170 175
 Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
 180 185 190
 Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr
 195 200 205
 Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
 210 215 220
 Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
 225 230 235 240
 Leu Gln Ile Thr Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
 245 250 255
 Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
 260 265 270
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 275 280 285
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
 290 295 300
 Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 305 310 315 320
 Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 325 330 335
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
 340 345 350
 Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
 355 360 365
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 370 375 380
 Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 385 390 395 400
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 405 410 415
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 420 425 430
 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 435 440 445
 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 450 455 460
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ser Tyr
 465 470 475 480
 Ser Pro Asn Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 485 490 495
 Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 500 505 510
 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 515 520 525
 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 530 535 540
 Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 545 550 555 560
 Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 565 570 575
 Lys Val Asp Lys Lys Val
 580

<210> 861

<211> 584

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC147 (Cris7 scFv-hinge-CH2-CH3-SSLNTPNS linker-CH1)

<400> 861

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20 25 30
 Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Trp Ile
 35 40 45
 Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50 55 60
 Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65 70 75 80
 Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85 90 95
 Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
 100 105 110
 Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
 130 135 140
 Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
 145 150 155 160
 Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
 165 170 175
 Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
 180 185 190
 Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr
 195 200 205
 Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
 210 215 220
 Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
 225 230 235 240
 Leu Gln Ile Thr Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
 245 250 255
 Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val

260 265 270
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 275 280 285
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
 290 295 300
 Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 305 310 315 320
 Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 325 330 335
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
 340 345 350
 Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
 355 360 365
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 370 375 380
 Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 385 390 395 400
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 405 410 415
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 420 425 430
 Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 435 440 445
 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 450 455 460
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ser Ser
 465 470 475 480
 Leu Asn Thr Pro Asn Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 485 490 495
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 500 505 510
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 515 520 525
 Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 530 535 540
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 545 550 555 560
 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 565 570 575
 Asn Thr Lys Val Asp Lys Lys Val
 580

<210> 862

<211> 593

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC148 (HD37 scFv-hinge-CH2-CH3-GGGSR linker-Ck)

<400> 862

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
 20 25 30
 Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
 35 40 45
 Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
 50 55 60
 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65 70 75 80
 Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
 85 90 95
 Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
 100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Gln
 115 120 125
 Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
 130 135 140
 Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
 145 150 155 160
 Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
 165 170 175
 Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
 180 185 190
 Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
 195 200 205
 Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
 210 215 220
 Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
 225 230 235 240
 Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
 245 250 255
 Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
 260 265 270
 Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 275 280 285
 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 290 295 300
 His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
 305 310 315 320
 Val His Asn Ala Lys Thr Lys Pro Arg Glu Gln Tyr Asn Ser Thr
 325 330 335
 Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 340 345 350
 Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
 355 360 365
 Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 370 375 380
 Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
 385 390 395 400
 Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 405 410 415
 Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 420 425 430
 Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 435 440 445
 Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 450 455 460
 Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 465 470 475 480
 Ser Pro Gly Gly Gly Ser Arg Thr Val Ala Ala Pro Ser Val Phe
 485 490 495
 Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
 500 505 510
 Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
 515 520 525
 Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Ala Thr
 530 535 540
 Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Glu Leu Thr
 545 550 555 560
 Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
 565 570 575
 Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
 580 585 590
 Glu

<210> 863

<211> 595

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC149 (HD37 scFv-hinge-CH2-CH3-SYSPNSR linker-Ck)

<400> 863

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Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
245      250      255
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
260      265      270
Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
275      280      285
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
290      295      300
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305      310      315      320
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
325      330      335
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340      345      350
Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
355      360      365
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370      375      380
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
385      390      395      400
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405      410      415
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420      425      430
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435      440      445
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450      455      460

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465      470      475      480
Ser Pro Gly Ser Tyr Ser Pro Asn Ser Arg Thr Val Ala Ala Pro Ser
485      490      495
Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
500      505      510
Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys Val
515      520      525
Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
530      535      540
Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Glu
545      550      555      560
Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
565      570      575
Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
580      585      590
Arg Gly Glu
595

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<210> 864

<211> 597

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC150 (HD37 scFv-hinge-CH2-CH3-SSLNTPNSR linker-Ck)

<400> 864

```

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
245      250      255
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
260      265      270
Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
275      280      285

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Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
290      295      300
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305      310      315      320
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
325      330      335
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340      345      350
Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
355      360      365
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370      375      380
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
385      390      395      400
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405      410      415
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420      425      430
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435      440      445
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450      455      460
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465      470      475      480
Ser Pro Gly Ser Ser Leu Asn Thr Pro Asn Ser Arg Thr Val Ala Ala
485      490      495
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
500      505      510
Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala
515      520      525
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
530      535      540
Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
545      550      555      560
Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
565      570      575
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
580      585      590
Phe Asn Arg Gly Glu
595

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<210> 865

<211> 1800

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC125 (Cris7 scFv-CH2-CH3-CH1)

<400> 865

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atggaagcac cagcgcagct tctcttctc ctgctactct ggctcccaga taccaccggt 60
caggtccagc tgggtgcagtc tggggggcga gtgggtgcagc ctgggcggtc actgagggtg 120
tctgtcaagg ctcttggtcta cacttttact agatctacga tgcactgggt aaggcaggcc 180
cctggaaagg gtctggaatg gattggatcac attaatccta gcagtgttta tactaattac 240
aatcagaat tcaaggacag gttcacaatc agcgcagaca aatccaagag cacagccttc 300
ctgcagatgg acagcctgag gcccgaggac accggcgtct atttctgtgc acggcccaa 360
gtccactatg attacaacgg gtttccttac tggggccaa ggactccgt cactgtctct 420
agcgggtggc gagggtctgg ggggtggcga tccggaggtg gtggctctgc acaagacatc 480
cagatgaccc agtctccaag cagcctgtct gcaagcgtgg gggacagggt caccatgacc 540
tgcagtgcc gctcaagtgt aagttacatg aactggtacc agcagaagcc cggcaaggcc 600
cccaaaagat ggatttatga ctcatccaaa ctggcttctg gactccctgc tcgcttcagt 660
ggcagtggtg ctgggaccga ctataccctc acaatcagca gcctgcagcc cgaagatttc 720
gccacttatt actgccagca gtggagtcgt aaccaccca cgttcggagg ggggaccaag 780
ctacaaatta cagctcgag tgagcccaaa tcttctgaca aaactcacac atgccaccg 840
tgccacgac ctgaagccgc ggggtgcacc tcagtcttcc tcttcccccc aaaacccaag 900

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gacacctca tgatctccc gacctctgag gtccacatcg tgggtggtgga cgtgagccac 960
gaagaccctg aggtcaagtt caactggtac gtggagcgcg tggaggtgca taatgccaa 1020
acaaagccgc gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcacogtc 1080
ctgcaccagg actggctgaa tggcaaggcg tacgcgtgcg cgtctccaa caaagccctc 1140
ccagccccc tcgagaaaa catctccaaa gccaaaggcg agccccgaga accacagggt 1200
tacacctgc cccatcccc ggtatgagtc accaagaacc aggtcagctc gactgcctg 1260
gtcaaaaggc tctatccaag cgacatcgcc gtggagtgg agagcaatgg gcagccggag 1320
aacaactaca agccacggcc tcccgctgtg gactccgacg gctccttctt cctctacagc 1380
aagctcaccg tggacaagag caggtggcag caggggaaag tcttctcatg ctccgtgatg 1440
catgaggtc tgcacaacca ctacacgacg aagagcctct cctgtctcc gggtaaatct 1500
agagcctcca caaaggcccc atcggctctc cccctggcac cctcctccaa gacacacct 1560
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<210> 866

<211> 1785

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC157 (Cris7 scFv-IgA2UH-CH2-CH3-CH1)

<400> 866

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<210> 867

<211> 1815

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC158 (Cris7 scFv-IgG1miniUH-CH2-CH3-CH1)

<400> 867

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<210> 868

<211> 1815

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC159 (Cris7 scFv-IgG3UH-CH2-CH3-CH1)

<400> 868

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cctggaaagg gtctggaatg gattggatcac attaatccta gcagtgtcta tactaattac 240
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<210> 869

<211> 2103

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC160 (Cris7 scFv-IgMCH2UH-CH2-CH3-CH1)

<400> 869

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tga						2103

<210> 870

<211> 1821

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC161 (HD37 scFv-IgA2UH-CH2-CH3-Ck)

<400> 870

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<210> 871

<211> 1851

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC162 (HD37 scFv-IgG1miniUH-CH2-CH3-Ck)

<400> 871

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<210> 872

<211> 1851

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC163 (HD37 scFv-IgG3UH-CH2-CH3-Ck)

<400> 872

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togggtggcg	gcggagctag	ccaggttcag	ctgcagcagt	ctggggtcga	gctggtgagg	480
cctgggtcct	cagtgaagat	ttcctgcaag	gcttctggct	atgcattcag	tagctactgg	540
atgaactggg	tgaagcagag	gcctggacag	ggtcttgagt	ggattggaca	gatttggcct	600
ggagatggtg	atactaacta	caatggaaag	ttcaagggtg	aagccactct	gactgcagac	660
gaatcctcca	gcacagccta	catgcaactc	agcagcctag	catctgagga	ctctgoggtc	720
tatttctgtg	caagacggga	gactacgacg	gtaggccgtt	attactatgc	tatggactac	780
tggggtcaag	gaacctcagt	caccgtctcc	tcgagcgagc	ccaaatctag	cgacacacct	840
ccccaaagcc	cacggtcccc	atgcccaccg	tgcccagcac	ctgaagccgc	gggtgcaccg	900
tcagtctctc	tcttcccccc	aaaaccccaag	gacaccccta	tgatctcccg	gacccctgag	960
gtcacatgcg	tgggtgtgga	cgtgagccac	gaagaccctg	aggtcaagtt	caactggtac	1020
gtggagggcg	tggaggtgca	taatgccaaag	acaaagccgc	gggaggagca	gtacaacagc	1080
acgtaccgtg	tgggtcagcgt	cctcaccgtc	ctgcaccagg	actggctgaa	tggaaggcg	1140
tacgcgtgcg	cggtctccaa	caaagccctc	ccagccccc	tcgagaaaac	catctccaaa	1200
gccaaagggc	agccccgaga	accacaggtg	tacacccctg	ccccatcccg	ggatgagctg	1260
accaagaacc	aggtcagcct	gacctgcctg	gtcaaaggct	tctatccaag	cgacatcgcc	1320
gtggagtggg	agagcaatgg	gcagccggag	aacaactaca	agaccacgcc	tccgtgctg	1380
gactccgacg	gctcctctct	cctctacagc	aagctcaccg	tggaacaagag	caggtggcag	1440
caggggaacc	tcttctcatg	ctccgtgatg	catgaggctc	tgcaacaacca	ctacacgcag	1500
aagagcctct	ccctgtctcc	gggtaaatct	agaactgtgg	ctgcaccatc	tgtcttcata	1560
ttcccgccat	ctgatgagca	gttgaaatct	ggaactgcct	ctgttgtgtg	cctgctgaat	1620
tactttctatc	ccagagaggg	caaagtacag	tggaggtgg	ataacgccct	ccaatcggt	1680
aactccccag	agagtgcacc	agagcaggac	agcaaggaca	gcacctacag	cctcagcagc	1740
gagctgacgc	tgagcaaaag	agactacgag	aaacacaaag	tctacgcctg	cggaagtcacc	1800
catcagggcc	tgagctcgcc	cgtcacaaaag	agcttcaaca	ggggagagtg	a	1851

<210> 873

<211> 2139

<212> DNA

<213> Artificial Sequence

<220>

<223> TSC164 (HD37 scFv-IgMCH2UH-CH2-CH3-Ck)

<400> 873


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atggaagcac cagcgcagct tctcttctc ctgctactct ggctcccaga taccaccggt      60
gacattgtgc tgaccaaatc tccagcttct ttggctgtgt ctctagggca gagggccacc      120
atctcctgca aggccagcca aagtgttgat tatgatgtg atagttattt gaactggtag      180
caacagattc caggacagcc acccaaatc ctcatctatg atgcattcaa tctagtttct      240
gggatccacc ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat      300
cctgtggaga aggtggatgc tgcaacctat cactgccagc aaagtactga ggatccgtgg      360
acgttctggtg gaggcaccaa gctggaaatc aaagtggtgg gtggttcggg cgtggtgggg      420
tcgggtggcg ccggagctag ccaggttcag ctgcagcagt ctggggctga gctggtgagg      480
cctgggtcct cagtgaagat ttctctcaag gcttctggct atgcattcag tagctactgg      540

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atgaactggg tgaagcagag gcctggacag ggtcttgagt ggattggaca gatttggcct      600
ggagatggtg atactaacta caatgaaag ttcaagggtg aagccactct gactgcagac      660
gaatcctcca gcacagccta catgcaatc agcagcctag catctgagga ctctgcggtc      720
tatttctgtg caagacggga gactacgacg gtaggccgtt attactatgc tatggactac      780
tgggggtcaag gaacctcagt caccgtctcc tcgagcattg ccgagctgcc tcccaaagtg      840
agcgtctctcg tcccaccocg gcacggcttc ttcggaacc cccgaagtc caagctcatc      900
tgccaggcca cgggtttcag tcccggcagc attcaggtgt cctggctcgc ogaggggaag      960
caggtggggt ctggcgtcac caccgaccag gtgcaggctg aggccaaaga gtcctgggcc      1020
acgacctaca aggtgaccag cacactgacc atcaagaga gcgactggct cagccagagc      1080
atgttcacct gccgcgtgga tcacaggggc ctgaccttcc agcagaatgc gtcctccatg      1140
agtgtccctc gccaccgtg cccagcactc gaagcccgcg gtgcaccgtc agtcttctc      1200
ttcccccaa aacccaagga caccctcatg atctcccgga cccctgaggt ccatgogtg      1260
gtggtggacg tgagccacga agaccctgag gtcaagttca actggtacgt ggacggcggt      1320
gaggtgcata atgccaaagc aaagcccgcg gagagcagt acaacagcac gtaccgtgtg      1380
gtcagcgtcc tcacgtctcc gcaccaggac tgggtgaatg gcaaggcgta cgcgtgcgcg      1440
gtctccaaac aagccctccc agccccatc gagaaaacca tctccaaagc caaaggcgag      1500
ccccgagaac cacaggtgta caccctgccc ccatcccggg atgagctgac caagaaccag      1560
gtcagcctga cctgcctggt caaaggcttc tatccaagcg acatcgccgt ggagtgggag      1620
agcaatgggc agccggagaa caactacaag accacgcctc cgtgctgga ctccgacggc      1680
tccttcttcc tctacaccaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc      1740
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc      1800
ctgtctcccg gtaaatctag aactgtggtc gcaccatctg tcttcatctt ccgcctatct      1860
gatgagcagt tgaatatctg aactgcctct gttgtgtgcc tgctgaatta cttctatccc      1920
agagaggcca aagtacagtg gaaggtggat aacgcctccc aatcggttaa ctcccaggag      1980
agtgccacag agcaggacag caaggacagc acctacagcc tcagcagcga gctgacgctg      2040
agcaaaagcag actacagaaa acacaaagtc tacgcctcgc aagtcaccga tcagggcctg      2100
agctcgcccc tcacaaagag cttcaacagg ggagagtga      2139

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<210> 874

<211> 579

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC125 (Cris7 scFv-CH2-CH3-CH1)

<400> 874

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Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1          5          10          15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20          25          30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35          40          45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50          55          60
Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65          70          75          80
Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85          90          95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100          105          110
Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115          120          125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130          135          140
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
145          150          155          160
Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
165          170          175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180          185          190
Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr
195          200          205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
210          215          220

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Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
225          230          235          240
Leu Gln Ile Thr Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
245          250          255
Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
260          265          270
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
275          280          285
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
290          295          300
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
305          310          315          320
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
325          330          335
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
340          345          350
Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
355          360          365
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
370          375          380
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
385          390          395          400
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
405          410          415
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
420          425          430
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
435          440          445
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
450          455          460
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
465          470          475          480
Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
485          490          495
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
500          505          510
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
515          520          525
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
530          535          540
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
545          550          555          560
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
565          570          575
Lys Lys Val

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<210> 875

<211> 574

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC157 (Cris7 scFv-IgA2UH-CH2-CH3-CH1)

<400> 875

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Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1          5          10          15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
20          25          30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35          40          45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
50          55          60
Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe

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65      70      75      80
Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
85      90      95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100      105      110
Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
115      120      125
Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130      135      140
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
145      150      155
Cys Ser Ala Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
165      170      175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180      185      190
Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr
195      200      205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
210      215      220
Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
225      230      235
Leu Gln Ile Thr Arg Ser Ser Pro Pro Pro Pro Cys Pro Pro Cys
245      250      255
Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
260      265      270
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
275      280      285
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
290      295      300
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
305      310      315
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
325      330      335
His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn
340      345      350
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
355      360      365
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
370      375      380
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
385      390      395
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
405      410      415
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
420      425      430
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
435      440      445
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
450      455      460
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys
465      470      475
Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
485      490      495
Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
500      505      510
Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
515      520      525
Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
530      535      540
Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
545      550      555
Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
565      570

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<210> 876

<211> 584

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC158 (Cris7 scFv-IgG1miniUH-CH2-CH3-CH1)

<400> 876

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Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1      5      10      15
Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
20      25      30
Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35      40      45
Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
50      55      60
Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
65      70      75      80
Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
85      90      95
Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
100     105     110
Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
115     120     125
Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
130     135     140
Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
145     150     155     160
Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
165     170     175
Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
180     185     190
Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr
195     200     205
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
210     215     220
Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
225     230     235     240
Leu Gln Ile Thr Arg Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His
245     250     255
Thr Ser Pro Pro Ser Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
260     265     270
Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
275     280     285
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
290     295     300
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305     310     315     320
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
325     330     335
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340     345     350
Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
355     360     365
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370     375     380
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
385     390     395     400
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405     410     415
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420     425     430
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435     440     445
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450     455     460
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465     470     475     480
Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
485     490     495
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
500     505     510
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
515     520     525
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
530     535     540
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
545     550     555     560
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
565     570     575
Asn Thr Lys Val Asp Lys Lys Val
580

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<210> 877

<211> 584

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC159 (Cris7 scFv-IgG3UH-CH2-CH3-CH1)

<400> 877

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20 25 30
 Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50 55 60
 Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65 70 75 80
 Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85 90 95
 Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
 100 105 110
 Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
 130 135 140
 Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr
 145 150 155 160
 Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
 165 170 175
 Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
 180 185 190
 Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr
 195 200 205
 Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
 210 215 220
 Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Gly Thr Lys
 225 230 235 240
 Leu Gln Ile Thr Arg Ser Ser Glu Pro Lys Ser Ser Asp Thr Pro Pro
 245 250 255
 Pro Ser Pro Arg Ser Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
 260 265 270
 Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 275 280 285
 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 290 295 300

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
 305 310 315 320
 Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
 325 330 335
 Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 340 345 350
 Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
 355 360 365
 Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 370 375 380
 Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
 385 390 395 400
 Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 405 410 415
 Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 420 425 430
 Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 435 440 445
 Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 450 455 460
 Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 465 470 475 480
 Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 485 490 495
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 500 505 510
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 515 520 525
 Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 530 535 540
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 545 550 555 560
 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 565 570 575
 Asn Thr Lys Val Asp Lys Lys Val
 580

<210> 878

<211> 680

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC160 (Cris7 scFv-IgMCH2UH-CH2-CH3-CH1)

<400> 878

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Ser
 20 25 30
 Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Trp Ile
 35 40 45
 Gly Tyr Ile Asn Pro Ser Ser Ala Tyr Thr Asn Tyr Asn Gln Lys Phe
 50 55 60
 Lys Asp Arg Phe Thr Ile Ser Ala Asp Lys Ser Lys Ser Thr Ala Phe
 65 70 75 80
 Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
 85 90 95
 Ala Arg Pro Gln Val His Tyr Asp Tyr Asn Gly Phe Pro Tyr Trp Gly
 100 105 110
 Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
 115 120 125
 Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Asp Ile Gln Met Thr Gln
 130 135 140
 Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr

145 150 155 160
 Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
 165 170 175
 Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Ser Ser Lys Leu Ala
 180 185 190
 Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Thr Asp Tyr
 195 200 205
 Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
 210 215 220
 Cys Gln Gln Trp Ser Arg Asn Pro Pro Thr Phe Gly Gly Thr Lys
 225 230 235 240
 Leu Gln Ile Thr Arg Ser Ser Ile Ala Glu Leu Pro Pro Lys Val Ser
 245 250 255
 Val Phe Val Pro Pro Arg Asp Gly Phe Phe Gly Asn Pro Arg Lys Ser
 260 265 270
 Lys Leu Ile Cys Gln Ala Thr Gly Phe Ser Pro Arg Gln Ile Gln Val
 275 280 285
 Ser Trp Leu Arg Glu Gly Lys Gln Val Gly Ser Gly Val Thr Thr Asp
 290 295 300
 Gln Val Gln Ala Glu Ala Lys Glu Ser Gly Pro Thr Thr Tyr Lys Val
 305 310 315 320
 Thr Ser Thr Leu Thr Ile Lys Glu Ser Asp Trp Leu Ser Gln Ser Met
 325 330 335
 Phe Thr Cys Arg Val Asp His Arg Gly Leu Thr Phe Gln Gln Asn Ala
 340 345 350
 Ser Ser Met Ser Val Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
 355 360 365
 Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 370 375 380
 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 385 390 395 400
 His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
 405 410 415
 Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
 420 425 430
 Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 435 440 445
 Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
 450 455 460
 Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 465 470 475 480
 Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
 485 490 495
 Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 500 505 510
 Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 515 520 525
 Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 530 535 540
 Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 545 550 555 560
 Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 565 570 575
 Ser Pro Gly Lys Ser Arg Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 580 585 590
 Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
 595 600 605
 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
 610 615 620
 Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
 625 630 635 640
 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
 645 650 655
 Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
 660 665 670

Asn Thr Lys Val Asp Lys Lys Val
 675 680

<210> 879

<211> 586

<212> PRT

<213> Artificial Sequence

<220>

<223> TSC161 (HD37 scFv-IgA2UH-CH2-CH3-Ck)

<400> 879

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Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1          5          10          15
Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
 20          25          30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
 35          40          45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
 50          55          60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65          70          75          80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
 85          90          95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100          105          110
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Gln
115          120          125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130          135          140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145          150          155          160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165          170          175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180          185          190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195          200          205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210          215          220
Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225          230          235          240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Pro Pro Pro Pro
245          250          255
Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
260          265          270
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
275          280          285
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
290          295          300
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
305          310          315          320
Thr Lys Pro Arg Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
325          330          335
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
340          345          350
Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
355          360          365
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
370          375          380
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
385          390          395          400
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
405          410          415
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser

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420          425          430
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
435          440          445
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
450          455          460
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser
465          470          475          480
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
485          490          495          500
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Tyr Phe
505          510          515
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
520          525          530
Ser Gly Asn Ser Gln Glu Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser
535          540          545
Thr Tyr Ser Leu Ser Ser Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu
550          555          560
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
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<210> 880

<211> 596

<212> PRT

<213> Artificial Sequence

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<223> TSC162 (HD37 scFv-IgG1miniUH-CH2-CH3-Ck)

<400> 880

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Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
245      250      255
Ser Asp Lys Thr His Thr Ser Pro Pro Ser Pro Cys Pro Pro Cys Pro
260      265      270

Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
275      280      285
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
290      295      300
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
305      310      315      320
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
325      330      335
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
340      345      350
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
355      360      365
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
370      375      380
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
385      390      395      400
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
405      410      415
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
420      425      430
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
435      440      445
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
450      455      460
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
465      470      475      480
Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr Val Ala Ala Pro
485      490      495
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
500      505      510
Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys
515      520      525
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
530      535      540
Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
545      550      555      560
Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
565      570      575
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
580      585      590
Asn Arg Gly Glu
595

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<210> 881

<211> 596

<212> PRT

<213> Artificial Sequence

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<223> TSC163 (HD37 scFv-IgG3UH-CH2-CH3-Ck)

<400> 881


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20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly

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100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Glu Pro Lys Ser
245      250      255
Ser Asp Thr Pro Pro Pro Ser Pro Arg Ser Pro Cys Pro Pro Cys Pro
260      265      270
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
275      280      285
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
290      295      300
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
305      310      315      320
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
325      330      335
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
340      345      350
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
355      360      365
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
370      375      380
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
385      390      395      400
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
405      410      415
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
420      425      430
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
435      440      445
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
450      455      460
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
465      470      475      480
Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr Val Ala Ala Pro
485      490      495
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
500      505      510
Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys
515      520      525
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
530      535      540
Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
545      550      555      560
Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
565      570      575
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
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Asn Arg Gly Glu
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<210> 882

<211> 692

<212> PRT

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<400> 882

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20      25      30
Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35      40      45
Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50      55      60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65      70      75      80
Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85      90      95
Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100      105      110
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser Gln
115      120      125
Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser
130      135      140
Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp
145      150      155      160
Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
165      170      175
Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
180      185      190
Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met
195      200      205
Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala
210      215      220
Arg Arg Glu Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr
225      230      235      240
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ser Ile Ala Glu Leu
245      250      255
Pro Pro Lys Val Ser Val Phe Val Pro Pro Arg Asp Gly Phe Phe Gly
260      265      270
Asn Pro Arg Lys Ser Lys Leu Ile Cys Gln Ala Thr Gly Phe Ser Pro
275      280      285
Arg Gln Ile Gln Val Ser Trp Leu Arg Glu Gly Lys Gln Val Gly Ser
290      295      300
Gly Val Thr Thr Asp Gln Val Gln Ala Glu Ala Lys Glu Ser Gly Pro
305      310      315      320
Thr Thr Tyr Lys Val Thr Ser Thr Leu Thr Ile Lys Glu Ser Asp Trp
325      330      335
Leu Ser Gln Ser Met Phe Thr Cys Arg Val Asp His Arg Gly Leu Thr
340      345      350
Phe Gln Gln Asn Ala Ser Ser Met Ser Val Pro Cys Pro Pro Cys Pro
355      360      365
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
370      375      380
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
385      390      395      400
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
405      410      415
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
420      425      430
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
435      440      445
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys

450      455      460
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
465      470      475      480
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
485      490      495
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
500      505      510
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
515      520      525
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
530      535      540
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
545      550      555      560
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
565      570      575
Lys Ser Leu Ser Leu Ser Pro Gly Lys Ser Arg Thr Val Ala Ala Pro
580      585      590
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
595      600      605
Ala Ser Val Val Cys Leu Leu Asn Tyr Phe Tyr Pro Arg Glu Ala Lys
610      615      620
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
625      630      635      640
Ser Ala Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
645      650      655
Glu Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
660      665      670
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
675      680      685
Asn Arg Gly Glu
690

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PATENTKRAV

1. Polypeptidheterodimer, der omfatter:

(a) et første enkeltkædet polypeptid (SCP-I), der omfatter fra en til fire bindingsdomæner, der specifikt binder fra en til fire mål, et hængsel (H-I),
 5 et immunoglobulin-heterodimeriseringsdomæne (HD-I) og et immunoglobulin CH2- og CH3-domæne af IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD eller en hvilken som helst kombination deraf (CH2CH3-I); og

(b) et andet enkeltkædet polypeptid (SCP-II), der omfatter fra nul til fire bindingsdomæner, der specifikt binder fra nul til fire mål, et hængsel (H-II),
 10 et immunoglobulin-heterodimeriseringsdomæne (HD-II), og et immunoglobulin CH2- og CH3-domæne af IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, eller en hvilken som helst kombination deraf (CH2CH3-II);

hvor

(i) immunoglobulin-heterodimeriseringsdomænet af det første
 15 enkeltkædede polypeptid (HD-I) og immunoglobulin-heterodimeriseringsdomænet af det andet enkeltkædede polypeptid (HD-II) fortrinsvis forbundet med hinanden for at danne en polypeptidheterodimer, der er omfattet af det første enkeltkædede polypeptid (SCP-I) og det andet enkeltkædede polypeptid (SCP-II), og

(1) immunoglobulin-heterodimeriseringsdomænet af det første
 20 enkeltkædede polypeptid (HD-I) omfatter en første immunoglobulin CH1-region, og immunoglobulin-heterodimeriseringsdomænet af det andet enkeltkædede polypeptid (HD-II) omfatter en første immunoglobulin CL-region, eller

(2) immunoglobulin-heterodimeriseringsdomænet af det første
 25 enkeltkædede polypeptid (HD-I) omfatter en første immunoglobulin CL-region, og immunoglobulin-heterodimeriseringsdomænet af det andet enkeltkædede polypeptid (HD-II) omfatter en første immunoglobulin CH1-region;

(ii) hvor den første immunoglobulin CL-region er en ændret human immunoglobulin Cκ-region med én eller flere aminosyrer af en vildtype human Cκ-region substitueret ved N29, N30, Q52, V55, T56, S68 eller T70, forudsat at polypeptidheterodimeren omfatter mindst to
 30 bindingsdomæner, der specifikt binder mindst to forskellige mål.

2. Polypeptidheterodimer ifølge krav 1, hvor bindingsdomænerne er enkeltkædede Fv- (scFv) polypeptider.

3. Polypeptidheterodimer ifølge krav 1, hvor polypeptidheterodimeren omfatter to bindingsdomæner (BD1 og BD2), hvor fortrinsvis det første bindingsdomæne (BD1) er på det første enkeltkædede polypeptid (SCP-I) og det andet bindingsdomæne (BD2) er på det andet enkeltkædede polypeptid (SCP-II).
4. Polypeptidheterodimer ifølge krav 3, hvor det første bindingsdomæne (BD1) er aminoterminal for CH2CH3-I af det første enkeltkædede polypeptid, og det andet bindingsdomæne (BD2) er aminoterminal for CH2CH3-II af det andet enkeltkædede polypeptid.
5. Polypeptidheterodimer ifølge krav 1 eller 2, hvor polypeptidheterodimeren omfatter tre bindingsdomæner (BD1, BD2 og BD3).
6. Polypeptidheterodimer ifølge krav 1, hvor polypeptidheterodimeren omfatter fire bindingsdomæner (BD1, BD2, BD3, og BD4), hvor fortrinsvis HD-I og CH2CH3-I er placeret mellem BD1 og BD2, og HD-II og CH2CH3-II er placeret mellem BD3 og BD4.
7. Polypeptidheterodimer ifølge krav 1 eller 2, hvor polypeptidheterodimeren omfatter fem til otte bindingsdomæner.
8. Polypeptidheterodimer ifølge et hvilket som helst af kravene 1 til 7, hvor mindst ét af bindingsdomænerne specifikt bindes til, eller er en antagonist af, et TCR-kompleks, TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ , CD28, CD79b, hyperIL-6, monIL-10, CD86, CD20, PSMA, CD19, HLA-DR, Ron, c-Met, CEACAM-6, LIGHT, GITRL, CD40, PDL1, PDL2, HVEM, LTBR, EGFR, EGFRvIII, ErbB2, ErbB3, ErbB4, IGF1R, EphA2, PDGFR, VEGFR1-4, angiopoietin 2, CD64, CD32A, CD16, CD71, TNFR1, TNFR2, TWEAKR, TACI, BAFF-R, BCMA, FAS, CD32B, CD21, CD22, CD30, CD33, CD37, CD38, CD70, TNF α , IL-6, hyperIL-6, IL-2, IL-1, IL-7, IL-8, IL-17A/C, IP-10, IFN γ , IFN α , RANKL, FASL, TGF β , IL10, IL17A/F, CSF2, IGF1, IGF2, BLyS/APRIL, HGF, MSP, EGF (herunder epiregulin, herregulin, (β -regulin, neuregulin), HIF-1 α , VEGFA, VEGFB, VEGFC, VEGFD, TNF α , Wnt, sHH, TGF β , PDGF, TWEAK, EpCAM, CEA, PCTA-1, STEAP-1, PSCA, ALCAM (CD166), EphA2, CD151, CA-125, MUC-1, MAGE-1, TROP2, CCR5, HER-3, HER-4, EGFR, CEA, MUC2, MUC3, MUC4, MUC5_{AC}, MUC5_b, MUC7, β hCG, Lewis-Y, gangliosid GD3, 9-O-Acetyl-GD3, GM2, Globo H, fucosyl GM1, Poly SA, GD2, carboanhydrase IX (MN/CA IX), CD44v6, Sonic Hedgehog (Shh), Wue-1, Plasmacelleantigen, (membranbundet) IgE, melanom chondroitinsulfat-proteoglycan (MCSP), CCR8, TNF-alpha precursor,

- STEAP, mesothelin, A33 Antigen, prostatastamcelleantigen (PSCA), Ly-6; desmoglein 4, E-cadherinneopitop, føtal acetylcholinreceptor, CD25, CA19-9-markør, CA-125-markør og muellerianhæmmende stof (MIS) receptortype II, sTn (sialyleret Tn-antigen; TAG-72), FAP (fibroblastaktivationsantigen),
5 endosialin, EGFRvIII, LG, SAS, CD63, IGF1R, CD151, TGFBR2, GHRHR, GHR, IL-6R, gp130, TNFR2, OSMR β , Patched-1, Frizzled, Robo1, CD80, CD81, CD86, OX40, CD40, CD137, LIFR β , TLR7 eller TLR9.
9. Polypeptidheterodimer ifølge et hvilket som helst af de foregående krav, hvor
10 den ene eller flere aminosyrer af en vildtype human Ck-region er substitueret med én eller flere aminosyresubstitutioner udvalgt fra Ala (A), Arg (R), Trp (W), Tyr (Y), Glu (E), Gln (Q), Lys (K), Asp (D), Met (M), Ser (S) og Phe (F).
10. Polypeptidheterodimer ifølge et hvilket som helst af de foregående krav, hvor
15 den ændrede humane immunoglobulin Ck-region omfatter de følgende substitutioner: (i) N30Y V55A T70E; eller (ii) N30M, V55A T70E.
11. Polypeptidheterodimer ifølge et hvilket som helst af de foregående krav, hvor
20 CH1-regionen er en ændret human immunoglobulin CH1-region, der omfatter en aminosyresubstitution, ved hvilken Val (V) ved position 68 er substitueret af Lys (K), Arg (R) eller His (H), og hvor Ck-regionen er en ændret human immunoglobulin Ck-region, der omfatter en aminosyresubstitution ved hvilken Leu (L) ved position 27 er substitueret af Asp (D) eller Glu (E) eller hvor CH1-regionen er en ændret human
25 immunoglobulin CH1-region, der omfatter en aminosyresubstitution, ved hvilken Val (V) ved position 68 er substitueret af Asp (D) eller Glu (E), og hvor Ck-regionen er en ændret human immunoglobulin Ck-region, der omfatter en aminosyresubstitution ved hvilken Leu (L) ved position 27 er ændret til Lys (K), Arg (R) eller His (H).
30
12. Polypeptidheterodimer ifølge et hvilket som helst af kravene 1 til 11, hvor den
første CH1-region er en ændret human immunoglobulin CH1-region med cystein af en vildtype human immunoglobulin CH1-region, der er involveret i dannelsen af en disulfidbinding med en vildtype human immunoglobulin CL-
35 region, der er deleteret eller substitueret.
13. Polypeptidheterodimer ifølge et hvilket som helst af de foregående krav, hvor Ck-regionen er en ændret human immunoglobulin Ck-region med cysteinresten af en vildtype human Ck-region, der er involveret i dannelsen af en

disulfidbinding med en vildtype human immunoglobulin CH1-region deleteret eller substitueret.

- 5 14. Polypeptidheterodimer ifølge et hvilket som helst af kravene 1 til 13, hvor
hængslet på både første og anden enkeltkædede polypeptid er en
immunoglobulinhængselsregion.
- 10 15. Polypeptidheterodimer ifølge et hvilket som helst af kravene 1 til 14, hvor
hængselsregionen er
 - (a) ved aminoterminalen til CH₂CH₃-I eller CH₂CH₃-II,
 - (b) placeret mellem bindingsdomænet og immunoglobulin-
heterodimeriseringsdomænet af det første enkeltkædede polypeptid (HD-I)
og/eller immunoglobulin-heterodimeriseringsdomænet af det andet
enkeltkædede polypeptid (HD-II),
 - 15 (c) placeret mellem et immunoglobulin-heterodimeriseringsdomæne og
CH₂CH₃-I eller CH₂CH₃-II,
 - (d) ved aminotermius af det første eller andet enkeltkædede polypeptid,
 - (e) en C-type-lectinhængselsregion,
 - (f) et NKg2A- eller NKg2D-peptid, eller et derivat deraf,
 - 20 (g) placeret mellem CH₂CH₃-I og et bindingsdomæne, eller
(h) ved carboxylterminus af det første eller andet enkeltkædede polypeptid.
- 25 16. Heterodimer ifølge et hvilket som helst af de foregående krav, hvor det
første enkeltkædede polypeptid omfatter et bindingsdomæne, der specifikt
bindes til et TCR-kompleks eller en bestanddel deraf, og det andet
enkeltkædede polypeptid omfatter et bindingsdomæne, der specifikt bindes til
et tumor-specifikt antigen.
- 30 17. Sammensætning, der omfatter en polypeptidheterodimer ifølge et hvilket
som helst af kravene 1 til 16 og en farmaceutisk acceptabel excipiens.
- 35 18. Polypeptidheterodimer ifølge et hvilket som helst af kravene 1 til 17 til
anvendelse i:
 - a) en fremgangsmåde til dirigering af T-celleaktivering, hvor
polypeptidheterodimeren omfatter et bindingsdomæne, der specifikt binder
TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ eller en kombination deraf, og et andet
bindingsdomæne, der specifikt binder et andet mål; eller
 - 40 b) hæmning af vækst, metastaser eller metastatisk vækst af en

malignitet, hvor polypeptidheterodimeren omfatter et bindingsdomæne, der specifikt binder TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ , c-Met eller Ron,

5 c) behandling af en autoimmun eller inflammatorisk tilstand, hvor polypeptidheterodimeren omfatter et bindingsdomæne, der specifikt binder TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ eller CD28.

10 d) behandling af en B-celleassocieret lidelse eller sygdom, hvor polypeptidheterodimeren omfatter et bindingsdomæne, der specifikt binder TCR α , TCR β , CD3 γ , CD3 δ , CD3 ϵ og et andet bindingsdomæne, der specifikt bindes til CD19, CD20, CD79b eller HLA-DR.

15 19. Ekspressionsvektor i stand til at udtrykke polypeptidheterodimeren ifølge et hvilket som helst af kravene 1 til 16, hvilken vektor omfatter et første polynukleotid, der koder for det første enkeltkædede polypeptid og et andet polynukleotid, der koder for det andet enkeltkædede polypeptid.

20 20. Værtscelle, der omfatter (i) ekspressionsvektoren ifølge krav 19 eller (ii) første og anden ekspressionsvektor er i stand til at udtrykke henholdsvis de første og anden enkeltkædede polypeptider af polypeptidheterodimeren ifølge et hvilket som helst af kravene 1 til 16.

25 21. Fremgangsmåde til fremstilling af en polypeptidheterodimer, der omfatter (a) dyrkning af en værtscelle ifølge krav 20 under forhold, der er egnede til ekspression af første og andet enkeltkædede polypeptid, og (b) eventuel isolering eller oprensning af heterodimerer, der er dannet af de første og anden enkeltkædede polypeptider fra kulturen.

30

DRAWINGS

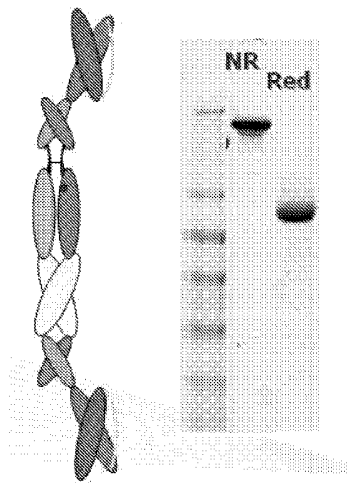


FIG. 1

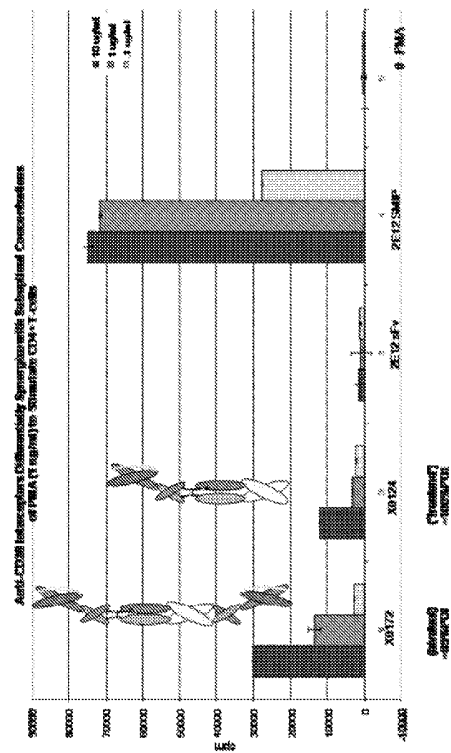


FIG. 2

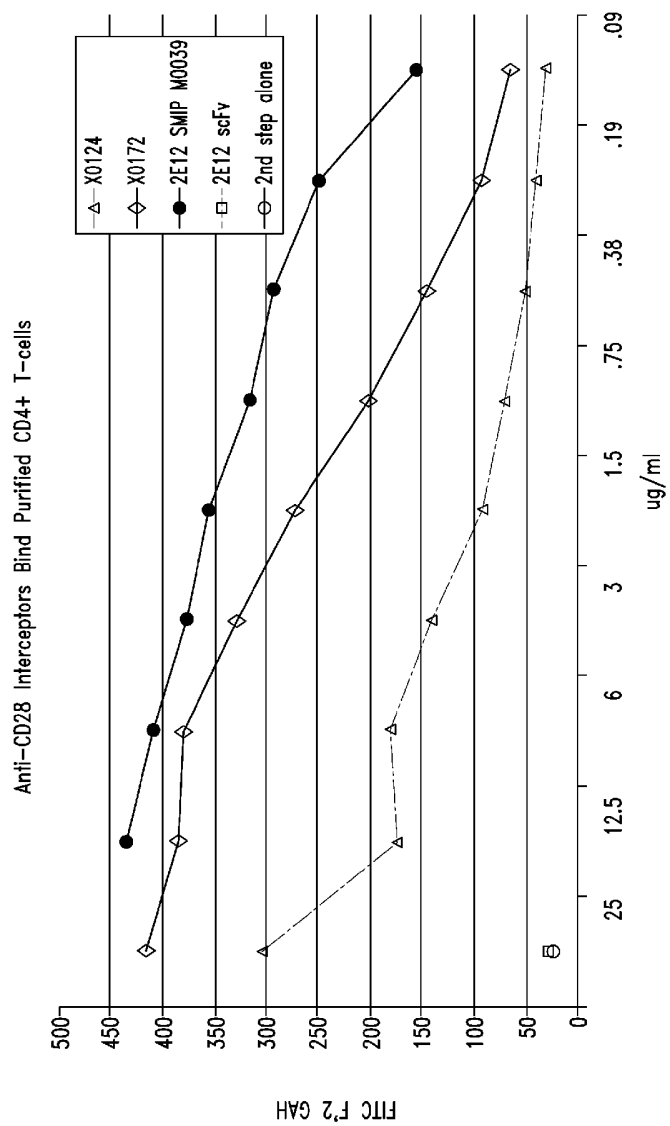


FIG. 3

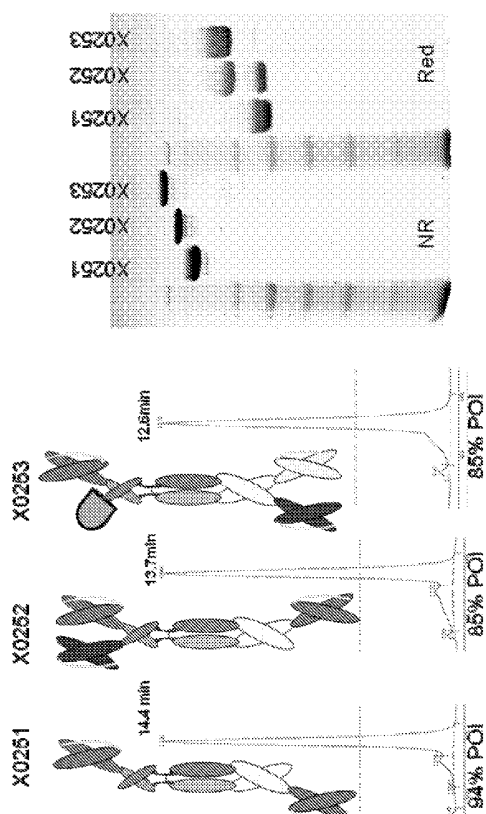


FIG. 4

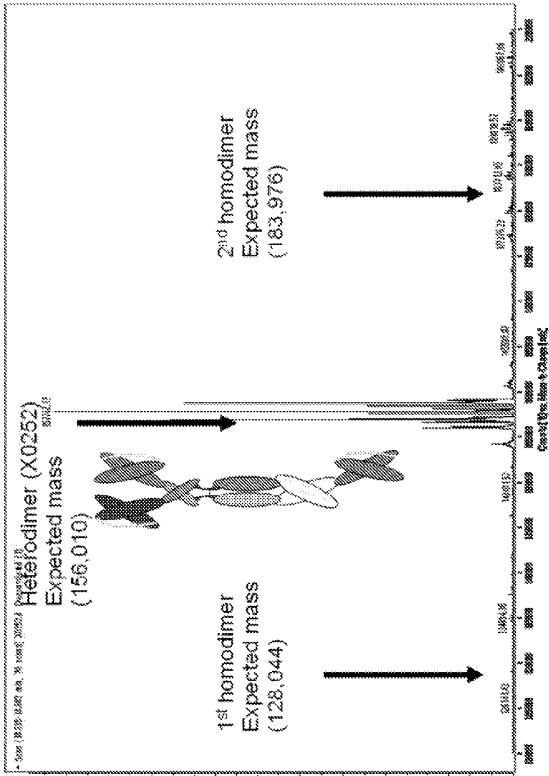


FIG. 5

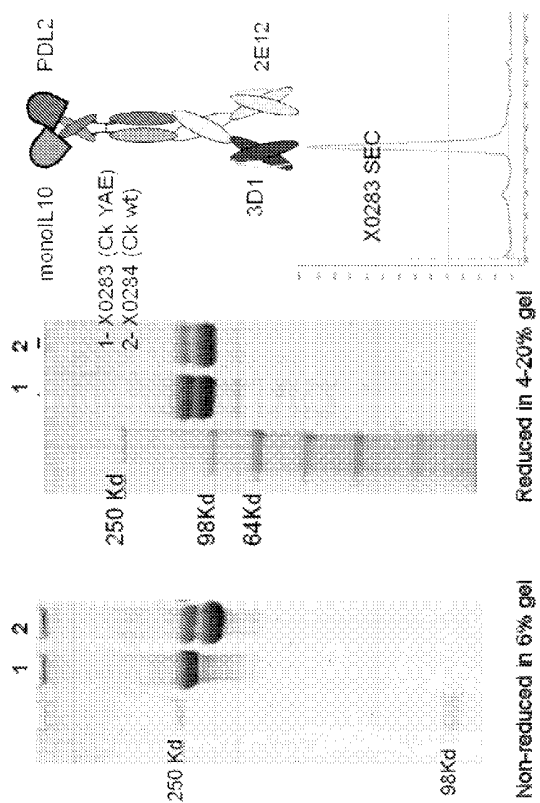


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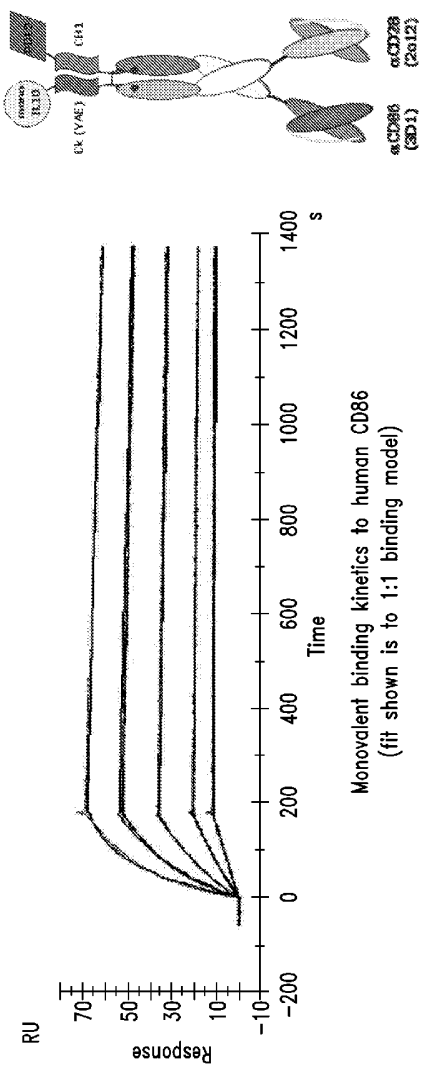
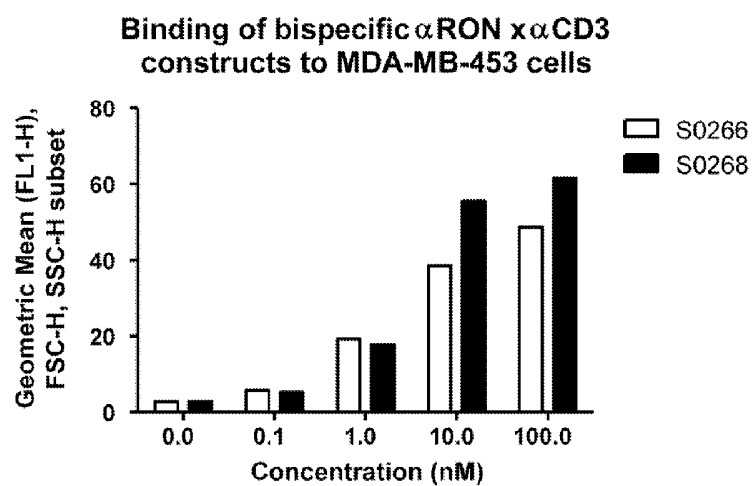
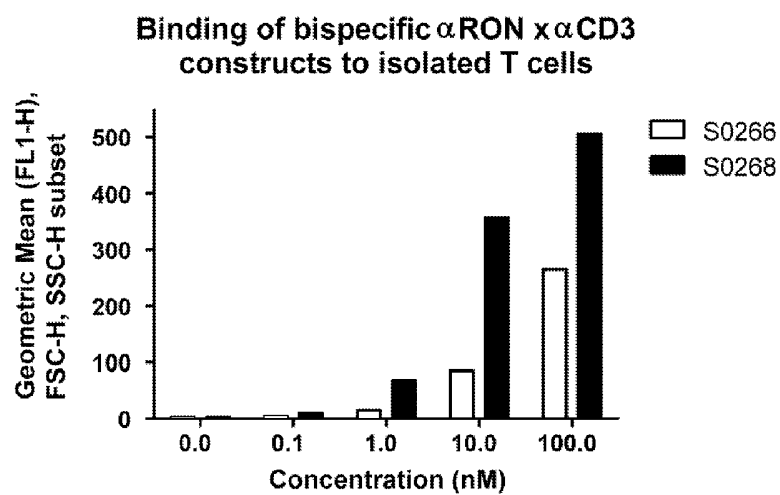


FIG. 7



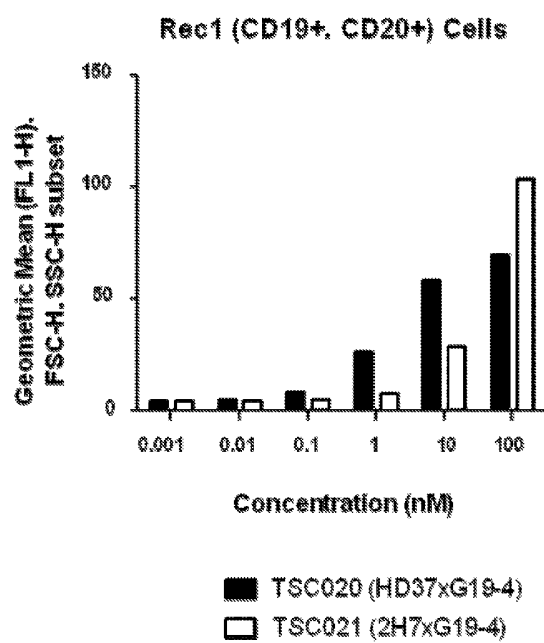
S0266 = α RON $\times$ α CD3 Scorpion
S0268 = α RON $\times$ α CD3 Interceptor

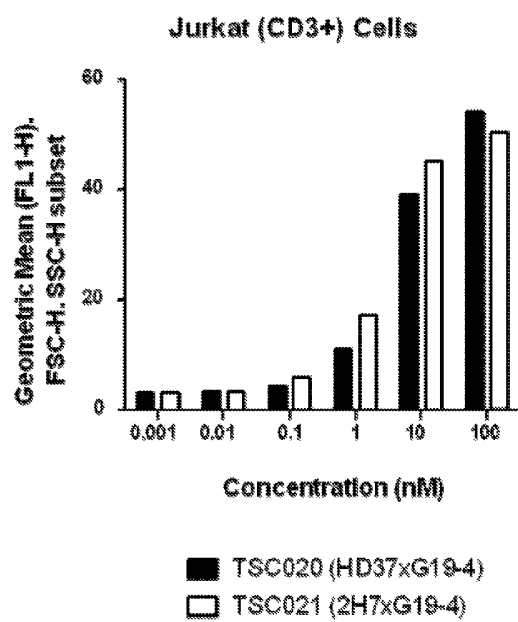
FIG. 8A



S0266 = α RON x α CD3 Scorpion
S0268 = α RON x α CD3 Interceptor

FIG. 8B

*FIG. 9A*

*FIG. 9B*

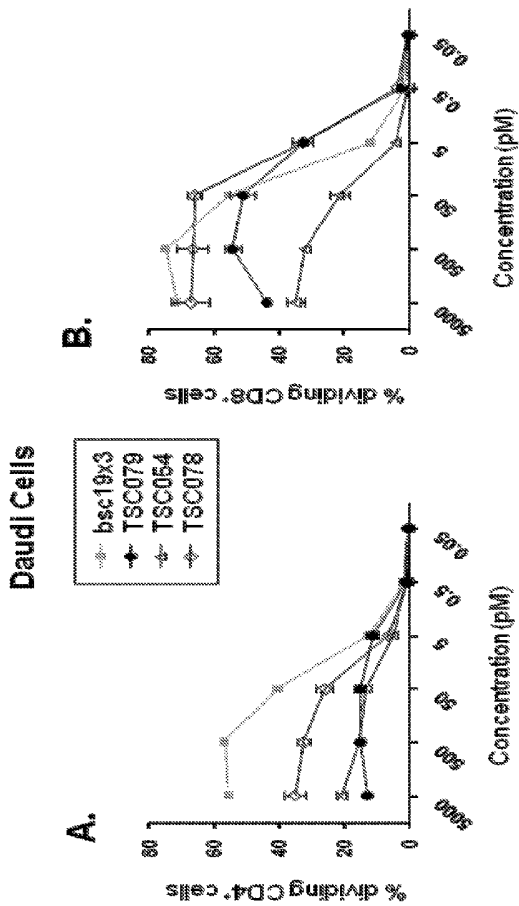


FIG. 10B

FIG. 10A

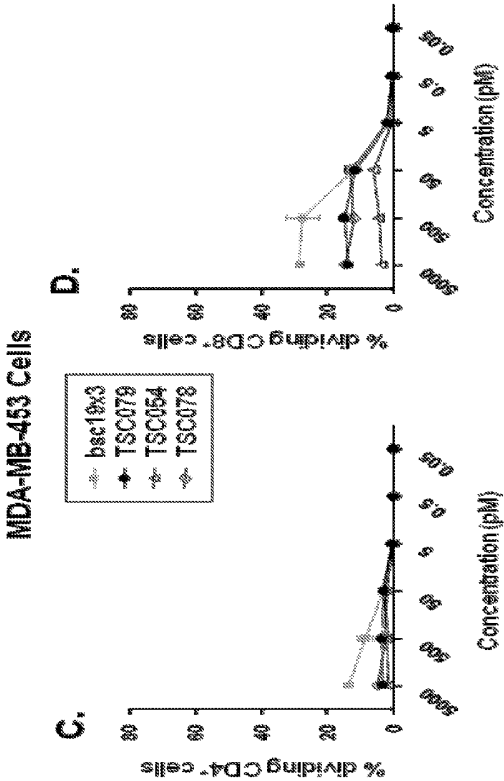
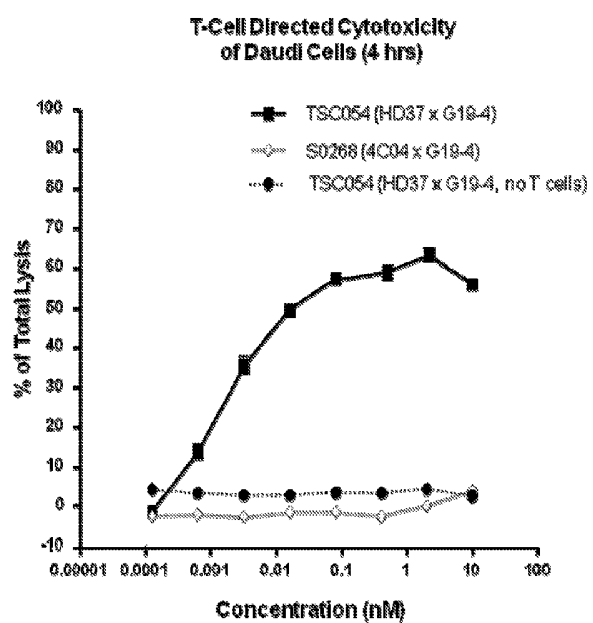


FIG. 10C

FIG. 10D

*FIG. 11A*

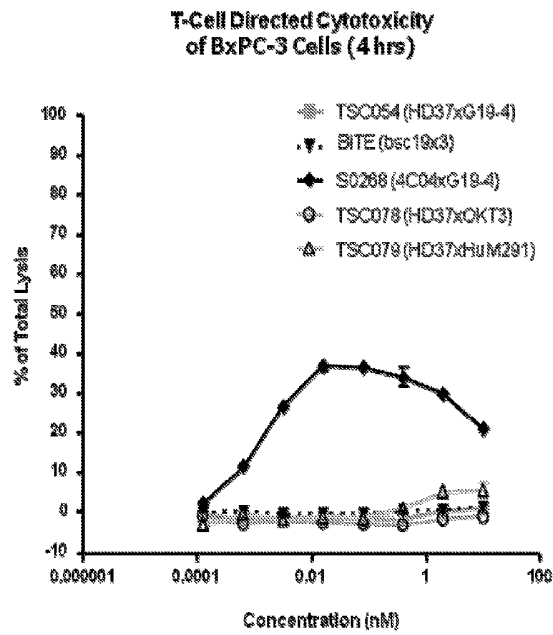


FIG. 11B

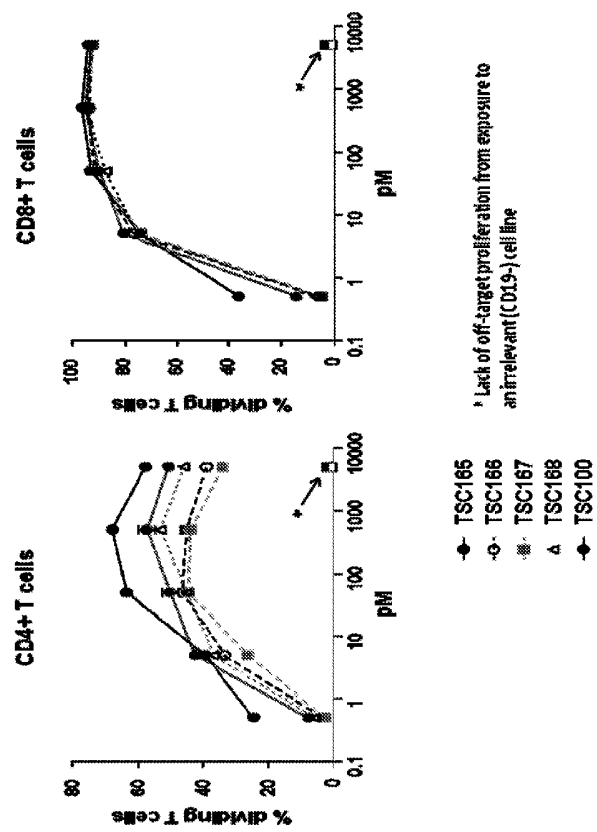


FIG. 12

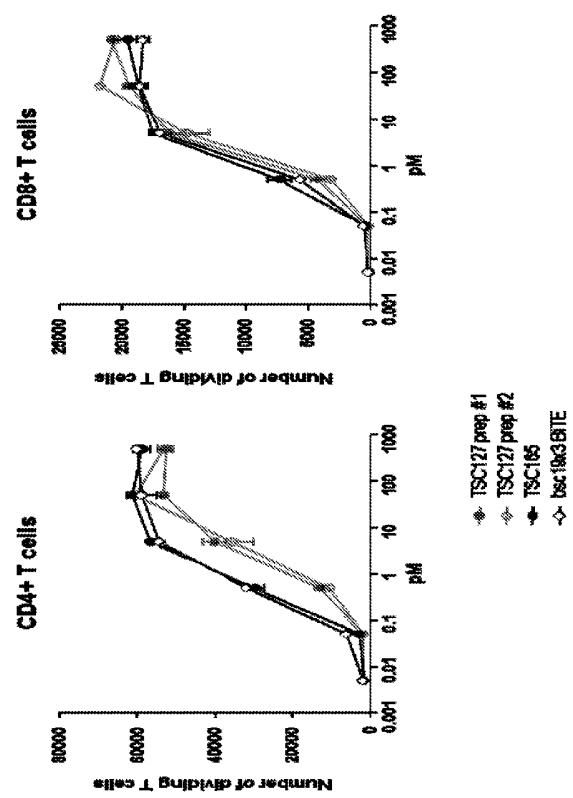


FIG. 13

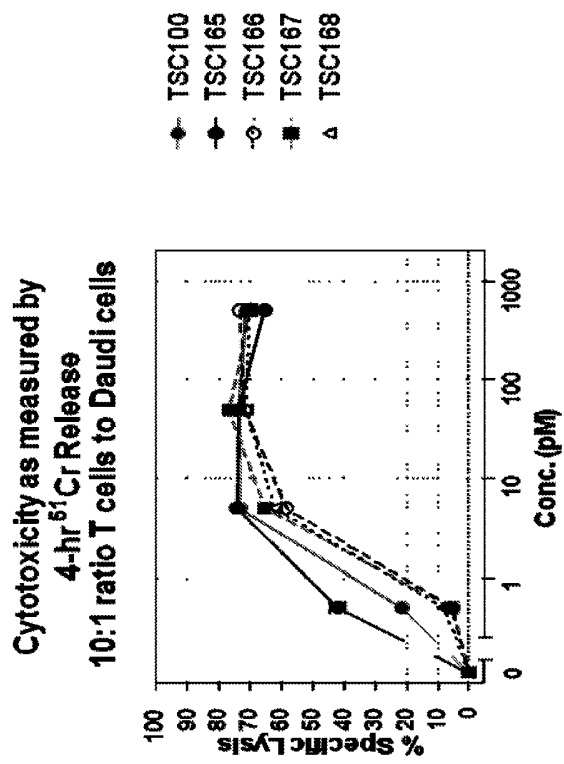


FIG. 14