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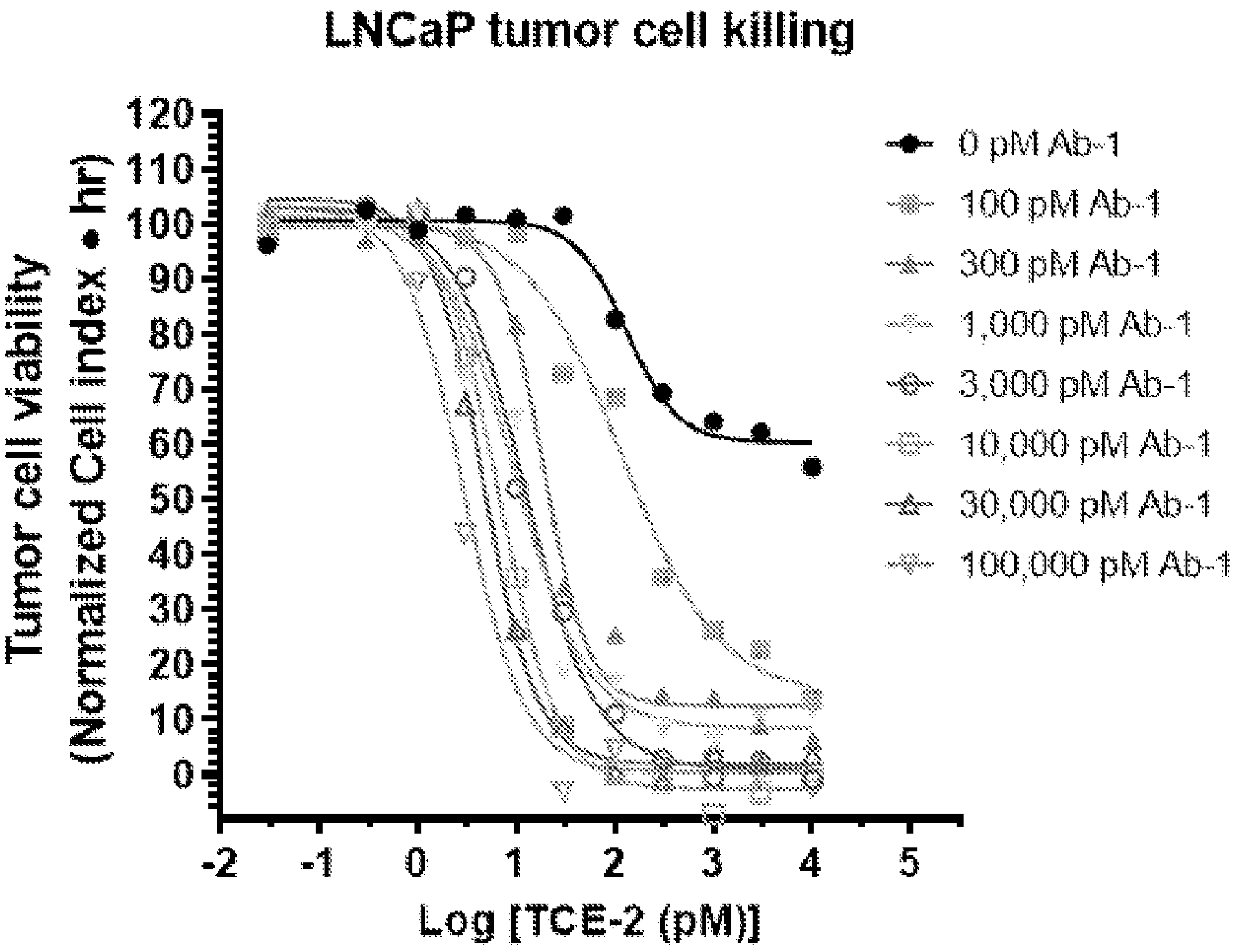

Fig. 10A

(57) **Abstract:** Provided herein are antibodies that selectively bind to CD28 and PD-L1, pharmaceutical compositions thereof, as well as nucleic acids, and methods of use, and methods for making and discovering the same.

[Continued on next page]

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MULTISPECIFIC ANTIBODIES FOR TARGETING CD28 AND PD-L1 AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/107,942, filed October 30, 2020, U.S. Provisional Application No. 63/141,268, filed January 25, 2021, U.S. Provisional Application No. 63/189,843, filed May 18, 2021, U.S. Provisional Application No. 63/123,327, filed December 9, 2020, U.S. Provisional Application No. 63/187,719, filed May 12, 2021, U.S. Provisional Application No. 63/123,329, filed December 9, 2020, U.S. Provisional Application No. 63/187,699, filed May 12, 2021, U.S. Provisional Application No. 63/187,690, filed May 12, 2021, each of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 27, 2021, is named 52426-726_601_SL.txt and is 483,304 bytes in size.

SUMMARY

[0003] Disclosed herein, in certain embodiments, are multispecific antibodies comprising a CD28 binding domain and a PD-L1 binding domain, wherein when the CD28 binding domain is a single chain variable fragment (scFv), then the PD-L1 binding domain is not a scFv. In some instances, the multispecific antibody is according to the following formula:

A-L-B (Formula I)

wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; and L comprises a linker that connects A to B. In some instances, the CD28 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′. In some instances, the CD28 binding domain comprises the single chain variable fragment. In some instances, the CD28 binding domain comprises the single domain antibody. In some instances, the CD28 binding domain comprises the Fab or the Fab′. In some instances, the PD-L1 binding domain comprises a single domain antibody, a Fab, or a Fab′. In some instances, the PD-L1 binding domain comprises the Fab or the Fab′. In some instances, the PD-L1 binding domain comprises the Fab or the Fab′ and the CD28 binding domain comprises the single chain variable fragment. In some instances, the PD-L1 binding domain that comprises the Fab or the Fab′ comprises a Fab heavy chain polypeptide comprising a Fab heavy chain variable domain and a Fab light chain polypeptide comprising a Fab light chain variable domain. In some instances, the CD28 binding domain that comprises the single chain variable fragment comprises a scFv heavy chain variable domain and a scFv light chain variable domain. In some instances, the linker connects the C-terminus of A to an N-terminus of B. In some instances, the linker connects the N-terminus of A to a C-terminus of B. In some instances, the linker connects the C-terminus of A to the N-terminus of the Fab heavy chain polypeptide. In some instances, the linker connects the N-terminus of A to the C-terminus of the Fab heavy chain polypeptide. In some instances, the linker connects the C-terminus of A to the N-terminus of the Fab light chain polypeptide. In some instances, the linker connects the N-terminus of A to the C-terminus of the Fab light chain polypeptide. In some instances, the linker connects the Fab light chain polypeptide to the scFv light chain variable domain. In some instances, the linker connects the Fab light chain polypeptide to the scFv heavy chain variable domain. In some instances, the linker connects the Fab heavy chain polypeptide to the scFv light chain variable domain. In some instances, the linker connects the Fab heavy chain polypeptide to the scFv heavy chain variable domain. In some instances, the linker connects the Fab light chain polypeptide to the N-terminus of the scFv light chain variable domain. In some instances, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain. In some instances, the linker connects the Fab light chain polypeptide to the N-terminus of the scFv heavy chain variable domain. In some instances, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv heavy chain variable domain. In some instances, the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv light chain variable domain. In some instances, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain. In some instances, the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv heavy chain variable domain. In some instances, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv heavy chain variable domain. In some instances, the linker is at least 5 amino acids in length. In some instances, the linker is no more than 30 amino acids in length. In some instances, the linker is at least 5 amino acids and no more than 30 amino acids in length. In some instances, the linker is 5 amino acids in length. In some instances, the linker is 15 amino acids in length. In some instances, the linker is selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1. In some instances, L has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3. In some instances, the linker comprises an amino acid sequence of SEQ ID NO: 18 (GGGGSGGGGSGGGGS) or SEQ ID NO: 19 (GGGGS). In some instances, the scFv heavy chain variable domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the scFv heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some instances, the scFv light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the scFv light chain variable domain comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some instances, the Fab heavy chain variable domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the Fab heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12; HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; or HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32 and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some instances, the Fab light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the Fab light chain variable domain comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15; LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35; LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38; or LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41 and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some instances, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some instances, the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7 In some instances, the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some instances, the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7 and has at least 80% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some instances, the scFv heavy chain variable domain comprises an amino acid sequence according to SEQ ID NO: 7. In some instances, the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some instances, the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some instances, the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some instances, the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8 and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some instances, the scFv light chain variable domain comprises an amino acid sequence according to SEQ ID NO: 8. In some instances, the scFv comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some instances, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some instances, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some instances, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9 and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some instances, the scFv comprises an amino acid sequence according to SEQ ID NO: 9. In some instances, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47. In some instances, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47. In some instances, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47. In some instances, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17 and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47. In some instances, the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47. In some instances, the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46. In some instances, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46. In some instances, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46. In some instances, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46. In some instances, the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46. In some instances, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 21. In some instances, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21. In some instances, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21. In some instances, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21. In some instances, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 22. In some instances, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22. In some instances, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22. In some instances, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 22.

[0004] Disclosed herein, in certain embodiments, are pharmaceutical compositions comprising: the multispecific antibody described herein; and a pharmaceutically acceptable excipient.

[0005] Disclosed herein, in certain embodiments, are isolated recombinant nucleic acid molecules encoding a polypeptide of the multispecific antibody described herein.

[0006] Disclosed herein, in certain embodiments, are methods of treating cancer in a subject in need thereof comprising administering to the subject the multispecific antibody described herein or the pharmaceutical composition described herein. In some instances, the multispecific antibody is administered to the subject as a single agent therapy. In some instances, the multispecific antibody is not administered as a part of a treatment regimen with a second therapeutic agent. In some instances, the multispecific antibody is not administered as a part of a treatment regimen with a second therapeutic agent comprising a tumor binding domain. In some instances, the multispecific antibody is not administered as a part of a treatment regimen with a second therapeutic agent comprising an anti-CD19 antibody. In some instances, the multispecific antibody is not administered as a part of a treatment regimen with a second therapeutic agent comprising an antibody that has an anti-CD19 binding domain and an anti-CD3 binding domain. In some instances, the multispecific antibody induces T cell mediated cytotoxicity of tumor cells. In some instances, the administering to the subject of the multispecific antibody is sufficient to reduce or eliminate the cancer as compared to a baseline measurement of the cancer taken from the subject prior to the administering of the multispecific antibody. In some instances, the reduction is at least about 1-fold, 5-fold, 10-fold, 20-fold, 40-fold, 60-fold, 80-fold, or up to about 100-fold. In some instances, the cancer is a hematological malignancy. In some instances, the cancer is leukemia or lymphoma. In some instances, the cancer is lymphoma, and wherein the lymphoma is B-cell lymphoma. In some instances, the cancer is a solid tumor. In some instances, the solid tumor expresses PD-L1. In some instances, the solid tumor is sarcoma, breast cancer, lung cancer, or carcinoma. In some instances, the solid tumor is lung cancer, and wherein the lung cancer is non-small cell lung cancer.Disclosed herein are methods of treating cancer in a subject in need thereof comprising administering to the subject a multispecific antibody that comprises a CD28 binding domain and a PD-L1 binding domain wherein the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain is not administered as part of a treatment regimen with another multispecific antibody that targets a cancer antigen different from PD-L1 or CD28. In some embodiments, the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain is administered to the subject as a single agent therapy. In some embodiments, the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain comprises an IgG framework, an IgA framework, an IgE framework, or an IgM framework. In some embodiments, the CD28 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′. In some embodiments, the PD-L1 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′. In some embodiments, the PD-L1 binding domain comprises a single chain variable fragment and the CD28 binding domain comprises a single chain variable fragment. In some embodiments, the CD28 binding domain comprises an anti-CD28 light chain polypeptide. In some embodiments, the anti-CD28 light chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 light chain. In some embodiments, the CD28 binding domain comprises an anti-CD28 heavy chain polypeptide. In some embodiments, the anti-CD28 heavy chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 heavy chain. In some embodiments, the PD-L1 binding domain comprises an anti-PD-L1 light chain polypeptide. In some embodiments, the anti-PD-L1 light chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 light chain. In some embodiments, the PD-L1 binding domain comprises an anti-PD-L1 heavy chain polypeptide. In some embodiments, the anti- PD-L1 heavy chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 heavy chain. In some embodiments, the multispecific antibody further comprises a fragment crystallizable (Fc) region. In some embodiments, the Fc region comprises an IgG CH2 domain and an IgG CH3 domain. In some embodiments, the Fc region comprises a heterodimeric Fc region. In some embodiments, the Fc region comprises at least one amino acid modification that increases the half-life of the multispecific antibody. In some embodiments, the Fc region comprises at least one amino acid modification that modulates its interaction with an Fc receptor. In some embodiments, the Fc region comprises at least one amino acid modification that increases binding of the Fc region to an Fc receptor. In some embodiments, the Fc region comprises at least one amino acid modification that decreases glycosylation of the Fc region. In some embodiments, the modification is an amino acid substitution, deletion, or addition. In some embodiments, the modification is an amino acid substitution. In some embodiments, the at least one amino acid modification that decreases glycosylation of the Fc region comprises an amino acid substitution at a position corresponding to position N297 of human IgG1, wherein the numbering is according to the EU index of Kabat. In some embodiments, the Fc region is afucosylated. In some embodiments, the anti-CD28 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 the anti-CD28 light chain polypeptide: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6 and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-CD28 heavy chain polypeptide comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-CD28 heavy chain polypeptide comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15; LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35; LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38; or LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41;and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-PD-L1 heavy chain polypeptide the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12; HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; or HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32 and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the multispecific antibody induces T cell mediated cytotoxicity of tumor cells. In some embodiments, the administering to the subject of the multispecific antibody is sufficient to reduce or eliminate the cancer as compared to a baseline measurement of the cancer taken from the subject prior to the administering of the multispecific antibody. In some embodiments, the reduction is at least about 1-fold, 5-fold, 10-fold, 20-fold, 40-fold, 60-fold, 80-fold, or up to about 100-fold. In some embodiments, the cancer is a hematological malignancy. In some embodiments, the cancer is leukemia or lymphoma. In some embodiments, the cancer is lymphoma, and wherein the lymphoma is B-cell lymphoma. In some embodiments, the cancer is a solid tumor. In some embodiments, the solid tumor expresses PD-L1.

In some embodiments, the solid tumor is sarcoma, breast cancer, lung cancer, or carcinoma. In some embodiments, the solid tumor is lung cancer, and wherein the lung cancer is non-small cell lung cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0008] **Figs. 1A-1B** illustrate exemplary schemas of PDL1 x CD28 multispecific antibodies.

[0009] **Fig. 2** illustrates an exemplary schema of the in vitro immune cell activation assays using target coated beads.

[0010] **Fig. 3A** illustrates a graph of IFNγ cytokine release from PBMCs cultured with single agent PDL1 x CD28 multispecific Ab-1.

[0011] **Fig. 3B** illustrates a graph of TNFα cytokine release from PBMCs cultured with single agent PDL1 x CD28 multispecific Ab-1.

[0012] **Fig. 3C** illustrates a graph of IL-2 cytokine release from PBMCs cultured with single agent PDL1 x CD28 multispecific Ab-1.

[0013] **Fig. 4A** illustrates a graph of the number of live immune cells over time in response to PBMC co-cultured with PDL1 target coated beads and Ab-1.

[0014] **Fig. 4B** illustrates a graph of the number of live CD3+ cells over time in response to PBMC co-cultured with PDL1 target coated beads and Ab-1.

[0015] **Fig. 4C** illustrates a graph of the number of live CD4+ cells over time in response to PBMC co-cultured with PDL1 target coated beads and Ab-1.

[0016] **Fig. 4D** illustrates a graph of the number of live CD8+ cells over time in response to PBMC co-culture with PDL1 target coated beads and Ab-1.

[0017] **Fig. 5A** illustrates binding kinetics of Ab-1 to biotinylated human PD-L1.

[0018] **Fig. 5B** illustrates binding kinetics of anti-PD-L1 Fab 1 to biotinylated human PD-L1.

[0019] **Fig. 6A** illustrates binding kinetics of Ab-1 to biotinylated human CD28.

[0020] **Fig. 6B** illustrates binding kinetics of Ab-2 to biotinylated human CD28.

[0021] **Fig. 7A** illustrates binding kinetics of Ab-1 to human PD-L1 Fc.

[0022] **Fig. 7B** illustrates binding kinetics of Ab-1 to cynomolgus monkey PD-L1 Fc.

[0023] **Fig. 8A** illustrates binding of Ab-1 to Ab-6 to PD-L1 as measured by ELISA.

[0024] **Fig. 8B** illustrates binding of Ab-1 to Ab-6 to CD28 as measured by ELISA.

[0025] **Fig. 9A** illustrates a cartoon configuration of a multispecific antibody that targets CD28 and PD-L1 that is administered in combination with a T cell engager that targets a tumor associated antigen such as TROP2 and CD3 of T cell.

[0026] Figs. 9B – 9D illustrate immune cell activation as measured by cytokine release after co-culture of target coated beads and PBMCs and administration of Ab-1 and the combination of Ab-1 and TCE-1 an anti-TROP2 x CD3 T cell engager.

[0027] Figs. 9E – 9H illustrate immune cell proliferation after co-culture of target coated beads and PBMCs and administration of Ab-1 and the combination of Ab-1 and TCE-1 an anti-TROP2 x CD3 T cell engager.

[0028] Figs. 9I – 9K illustrate polypeptide complexes of different orientation harboring different PD-L1 binding domains (Ab-1 through Ab-8) activate PBMCs as measured by cytokine release in combination with a T cell engager (TCE-3) against non-immunogenic beads coated with tumor associated antigen and PD-L1.

[0029] Fig. 9L illustrates polypeptide complex mediated activation of PBMCs in combination with a T cell engager.

[0030] Fig. 9M – 9S illustrate polypeptide complex mediated activation of PBMCs in combination with a T cell engager is PDL1 density dependent.

[0031] Figs. 10A -10C illustrate results of an in vitro tumor cell killing assay using the LNCaP PDL1 positive tumor cell line in which Ab-1 and TCE-2 are co-administered in the presence of human PBMCs. In vitro tumor cell killing and PBMC activation measured by cytokine release is synergized when Ab-1 is combined with an anti-PSMA x CD3 T cell engager, TCE-2.

[0032] Fig. 10D illustrates a graph of PBMC mediated in vitro killing of H292 tumor cells using Ab-1 and TCE-4.

[0033] Fig. 10E illustrates a graph of PBMC mediated in vitro killing of H292 tumor cells using Ab-1 and TRACTr-1.

[0034] Fig. 10F illustrates a graph of PBMC mediated in vitro killing of H292 tumor cells using Ab-1 and TRACTr-pre-treated with MTSP1.

[0035] Fig. 10G illustrates a graph of IL-2 cytokine release from PBMCs co-cultured with H292 cells, Ab-1, and TCE-4.

[0036] Fig. 10H illustrates a graph of IL-2 cytokine release from PBMCs co-cultured with H292 cells, Ab-1 and TRACTr-1.

[0037] Fig. 10I illustrates a graph of IL-2 cytokine release from PBMCs co-cultured with H292 cells Ab-1, and TRACTr-1 pre-treated with MTSP1.

[0038] Fig. 11 illustrates pharmacokinetics of Ab-1 in cynomolgus monkey after a single IV bolus injection.

[0039] Fig. 12A – 12F illustrate cytokine release in cynomolgus monkey after a single IV bolus injection of Ab-1.

[0040] Fig. 13A – 13B illustrate serum liver enzymes in cynomolgus monkey after a single IV bolus injection of Ab-1.

[0041] Fig. 14 illustrates a schematic for identifying P1 or P2 peptides that can be attached to the PD-L1 and CD28 multispecific antibodies for selective activation in tumor microenvironments. The schematic illustrates a directed evolution and phage display technology to identify peptides that block antigen recognition by antigen binding domains.

[0042] **Figs. 15A-15C** exemplify schematics for the multispecific antibodies comprising a CD28 binding domain and a PD-L1 binding domain described herein can increase activation as a monotherapy. Fig. 15A shows a T cell attacking a tumor cell, and the potential secondary signals are the PD-1 (stop) and CD28 (go). Fig. 15B shows how a tumor deactivates T cells through PD-L1. The PD-L1/PD-1 triggers the stop signal while the CD28 (go) signaling is not activated. Fig. 15C shows a reactivated T cell in which the multispecific antibody with a PD-L1 binding domain and CD28 binding domain reactivate the T cell by converting the PD-L1/PD-1 stop signal to a CD28 go signal.

[0043] **Fig. 16** exemplifies a schematic of a multispecific antibody comprising a CD28 binding domain and a PD-L1 binding domain in combination with a T cell engager.

DETAILED DESCRIPTION

[0044] Bispecific antibodies for redirecting T cells for mediating cancer cell killing have shown promise in both pre-clinical and in clinical studies. Efficient T cell activation has been obtained with single chain variable fragments (scFv), notably the Bispecific T-cell Engagers (BiTEs) format, in which one scFv targets a tumor cell antigen, and the other scFv targets an epitope such as CD3 that is involved in T cell activation. One such example of a BiTE is blinatumomab that targets CD19 and CD3 which has been approved in Europe and the United States for treatment of chemotherapy-resistant CD19+ B cell acute lymphoblastic leukemia. Despite advances with T cell engagers such as blinatumomab some patients respond poorly to treatment even if the patient expresses the tumor antigen for reasons that are not entirely understood.

[0045] Strategies for increasing T cell cytotoxicity of T cell engagers have been explored through co-administration with a second antibody that targets the co-inhibitory immune checkpoint programmed death-ligand 1 (PD-L1) and/or CD28. CD28 is a protein expressed on T cells that provide co-stimulatory signals required for T cell activation and survival. It is known that stimulatory signaling through CD28 in combinations with BiTEs increase T cell-induced tumor cell cytotoxicity. However, central to obtaining T cell mediated cytotoxicity of tumor cells in prior studies required the presence of a BiTE that has a tumor binding domain, such as an anti-CD19 antibody, and a CD3 binding domain, while single agent administration of an anti-CD28 and anti-PD-L1 in a scFv-scFv format was found to not induce T cell mediated cytotoxicity against tumor cells.

[0046] Activation of T cells is a highly regulated process that typically requires two signaling events for full functionality: the first signal is initiated upon binding of the MHC-antigen complex, which helps distinguish “self” from “non-self” to the T cell receptor (TCR) and the second signal through activation of a costimulatory receptor. While the first recognition signal activates a T cell and triggers T cell mediated toxicity of the recognized cell, if the T cell does not receive a second costimulatory signal it can lead to T cell tolerance whereby the T cells continue to recognize the tumor antigen but do not mount an immune response against the tumor cell. The second costimulatory signal prevents T cell tolerance, and further activates the T cell to enhance T cell cytotoxicity towards the targeted cell.

[0047] Multispecific antibodies comprising a CD28 binding domain and PD-L1 binding domain as described herein are designed to act both as an antagonist of PD-L1 and a conditional agonist of C28. While CD28 agonism has shown some clinical promise, the efficacy seen with this approach has been limited due to dose-limiting toxicities that result from systemic activation of CD28. The multispecific antibodies comprising a CD28 binding domain and PD-L1 binding domain, described herein, are designed to conditionally agonize CD28 only in the presence of PD-L1, which is often overexpressed by tumors to avoid T cell mediated killing. In addition, engagement of PD-L1 is designed to block PD-1 binding and provide checkpoint inhibiton. This combination provides a mechanism of action that enhances anti-tumor responses and limits the systemic toxicity of CD28 agonism. As shown in **Fig. 11**, studies of multispecific antibodies described herein demonstrate a lack of systemic immune system activation, as evidenced by the lack of cytokine release. Despite unprecedented clinical response rates, most patients fail to respond to therapies targeting PD-1 and PD-L1, which is due in part because T cells require costimulation for full functionality. As such, checkpoint inhibition alone is likely insufficient to fully enable the immune system to attack a tumor. Further benefit can be derived by the addition of the multispecific antibodies as described herein.

[0048] Disclosed herein are antibodies that bind specifically to PD-L1 and CD28 which are able to induce T cell mediated cytotoxicity of tumor cells as a single agent **(Fig. 15C)** or in combination with a T cell engager **(Fig. 16)**. Significantly, such antibodies that target PD-L1 and CD28 are able to induce T cell mediated cytotoxicity of tumor cells as a single agent, even when not administered with a second agent that specifically targets a tumor cell antigen as exemplified in the schematics of **Figs. 15A-15C**. Such antibodies that bind specifically to PD-L1 and CD28 are not in a scFv-scFv format.

[0049] Disclosed herein are multispecific antibodies that comprise a CD28 binding domain and a PD-L1 binding domain, wherein when the CD28 binding domain is a single chain variable fragment (scFv), then the PD-L1 binding domain is not a scFv. In some embodiments, the multispecific antibody is according to the formula:

A-L-B (Formula I)

wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; and L comprises a linker that connects A to B. In some embodiments, the multispecific antibody comprises the formula:

A-L-B (Formula I)

wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; and L comprises a linker that connects A to B. In some embodiments, the multispecific antibody comprises the formula:

A-L-B (Formula I)

wherein A is the CD28 binding domain; B is the PD-L1 binding domain; and L is the linker that connects A to B. In some embodiments, the multispecific antibody is according to the formula:

A-L-B (Formula I)

wherein A is the CD28 binding domain; B is the PD-L1 binding domain; and L is the linker that connects A to B.

[0050] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Definitions

[0051] The terminology used herein is for the purpose of describing particular cases only and is not intended to be limiting. As used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Furthermore, to the extent that the terms "including", "includes", "having", "has", "with", or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term "comprising."

[0052] The term "antibody" is used in the broadest sense and covers fully assembled antibodies, antibody fragments that can bind antigen, for example, Fab, F(ab')2, Fv, single chain antibodies (scFv), diabodies, antibody chimeras, hybrid antibodies, bispecific antibodies, and the like.

[0053] The term "complementarity determining region" or "CDR" is a segment of the variable region of an antibody that is complementary in structure to the epitope to which the antibody binds and is more variable than the rest of the variable region. Accordingly, a CDR is sometimes referred to as hypervariable region. A variable region comprises three CDRs. CDR peptides can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells. See, for example, Larrick et al., *Methods: A Companion to Methods in Enzymology* 2: 106 (1991); Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in *Monoclonal Antibodies: Production, Engineering and Clinical Application*, Ritter et al. (eds.), pages 166-179 (Cambridge University Press 1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in *Monoclonal Antibodies: Principles and Applications*, Birch et al., (eds.), pages 137-185 (Wiley-Liss, Inc. 1995).

[0054] In some instances, the CDRs of an antibody are determined according to (i) the Kabat numbering system (Kabat et al. (197) Ann. NY Acad. Sci. 190:382-391 and, Kabat et al. (1991) Sequences of Proteins of Immunological Interest Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242); or (ii) the Chothia numbering scheme, which will be referred to herein as the "Chothia CDRs" (see, e.g., Chothia and Lesk, 1987, J. Mol. Biol., 196:901-917; Al-Lazikani et al., 1997, J. Mol. Biol., 273 :927-948; Chothia et al., 1992, J. Mol. Biol., 227:799-817; Tramontano A et al. , 1990, J. Mol. Biol. 215(1): 175-82; and U.S. Patent No. 7,709,226); or (iii) the ImMunoGeneTics (IMGT) numbering system, for example, as described in Lefranc, M.-P., 1999, The Immunologist, 7: 132-136 and Lefranc, M.-P. et al, 1999, Nucleic Acids Res., 27:209-212 ("IMGT CDRs"); or (iv) MacCallum et al, 1996, J. Mol. Biol., 262:732-745. See also, e.g., Martin, A., "Protein Sequence and Structure Analysis of Antibody Variable Domains," in

Antibody Engineering, Kontermann and Diibel, eds., Chapter 31, pp. 422-439, Springer- Verlag, Berlin (2001).

[0055] With respect to the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35 A and 35B) (CDRl), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDRl), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). As is well known to those of skill in the art, using the Kabat numbering system, the actual linear amino acid sequence of the antibody variable domain can contain fewer or additional amino acids due to a shortening or lengthening of a FR and/or CDR and, as such, an amino acid's Kabat number is not necessarily the same as its linear amino acid number.

[0056] The term "Fab" refers to a protein that contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab′ fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab′ in which the cysteine residue(s) of the constant domains bear a free thiol group. Fab′ fragments are produced by reducing the F(ab')2 fragment's heavy chain disulfide bridge. Other chemical couplings of antibody fragments are also known.

[0057] A "single-chain variable fragment (scFv)" is a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of an antibody, connected with a short linker peptide of ten to about 25 amino acids. The linker is usually rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the VH with the C-terminus of the VL, or vice versa. This protein retains the specificity of the original antibody, despite removal of the constant regions and the introduction of the linker. scFv antibodies are, e.g. described in Houston, J. S., Methods in Enzymol. 203 (1991) 46-96). In addition, antibody fragments comprise single chain polypeptides having the characteristics of a VH domain, namely being able to assemble together with a VL domain, or of a VL domain, namely being able to assemble together with a VH domain to a functional antigen binding site and thereby providing the antigen binding property of full length antibodies.

[0058] The term "multispecific" means that the antibody is able to specifically bind to two or more distinct antigenic determinants for example two or more binding sites each formed by a pair of an antibody heavy chain variable domain (VH) and an antibody light chain variable domain (VL), or in the case of a single domain antibody a single variable domain, binding to different antigens.

[0059] As used herein, the term "percent (%) amino acid sequence identity" with respect to a sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific 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. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as EMBOSS MATCHER, EMBOSS WATER, EMBOSS STRETCHER, EMBOSS NEEDLE, EMBOSS LALIGN, BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[0060] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y, where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0061] The terms “individual(s)”, “subject(s)” and “patient(s)” are used interchangeably herein and refer to any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g. constant or intermittent) of a health care worker (e.g. a doctor, a registered nurse, a nurse practitioner, a physician’s assistant, an orderly or a hospice worker).

CD28 Binding Domains

[0062] Disclosed herein are multispecific antibodies that comprise a CD28 binding domain. In some embodiments, the CD28 binding domain comprises an antibody or antigen binding fragment. In some embodiments, the antibody or antigen binding fragment is a monoclonal antibody. In some embodiments, the antibody or antigen binding fragment is a human antibody, a murine antibody, a humanized antibody, or a chimeric antibody. In some embodiments, antibody or antigen binding fragment that binds specifically to CD28 comprises an anti-CD28 heavy chain polypeptide and an anti-CD28 light chain polypeptide.

[0063] In some embodiments, the anti-CD28 heavy chain polypeptide comprises an anti-CD28 heavy chain variable domain. In some embodiments, the anti-CD28 heavy chain variable domain comprises an IgG framework, an IgA framework, an IgE framework, or an IgM framework. In some embodiments, the anti-CD28 heavy chain variable domain comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 heavy chain. In some embodiments, the anti-CD28 light chain polypeptide comprises an anti-CD28 light chain variable domain. In some embodiments, the anti-CD28 light chain variable domain comprises an IgG framework, an IgA framework, an IgE framework, or an IgM framework. In some embodiments, the anti-CD28 light chain variable domain comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 light chain.

[0064] In some embodiments the CD28 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′. In some embodiments, the CD28 binding domain comprises the single chain variable fragment. In some embodiments, the CD28 binding domain comprises the single domain antibody. In some embodiments, the CD28 binding domain comprises the Fab or the Fab′. In some embodiments, the CD28 binding domain that comprises the single chain variable fragment comprises a scFv heavy chain variable domain and a scFv light chain variable domain. In some embodiments, the anti-CD28 heavy chain polypeptide comprises the scFv heavy chain variable domain. In some embodiments, the anti-CD28 light chain polypeptide comprises the scFv light chain variable domain.

[0065] In some embodiments, the anti-CD28 heavy chain polypeptide comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-CD28 heavy chain polypeptide comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the anti-CD28 heavy chain polypeptide comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-CD28 heavy chain polypeptide comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3.

[0066] In some embodiments, the anti-CD28 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 the anti-CD28 light chain polypeptide: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-CD28 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-CD28 light chain polypeptide: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6.

[0067] In some embodiments, anti-CD28 heavy chain polypeptide comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-CD28 heavy chain polypeptide comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the anti-CD28 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-CD28 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0068] In some embodiments, the anti-CD28 heavy chain polypeptide comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-CD28 heavy chain polypeptide comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3; and the anti-CD28 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-CD28 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6.

Table 1. anti-CD28 heavy chain polypeptide complementarity determining regions (CDR)s as determined by IMGT definition.

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
anti-CD28: HC: CDR1	GYTFTSYY	1
anti-CD28: HC: CDR2	IYPGNVNT	2
anti-CD28: HC: CDR3	TRSHYGLDWNFDV	3

Table 2. anti-CD28 light chain polypeptide complementarity determining regions (CDR)s as determined by IMGT definition.

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
anti-CD28: LC: CDR1	QNIYVW	4
anti-CD28: LC: CDR2	KA	5
anti-CD28: LC: CDR3	QQGQTYPYT	6

[0069] In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence according to SEQ ID NO: 7.

[0070] In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7 In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7 In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0071] In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0072] In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0073] In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0074] In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0075] In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 98%

sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence according to SEQ ID NO: 8.

[0076] In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0077] In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0078] In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0079] In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0080] In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0081] In some embodiments, the scFv comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 91% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 92% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 93% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 94% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence according to SEQ ID NO: 9.

[0082] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9.In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9.

[0083] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 9.

[0084] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 9.

[0085] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 9.

[0086] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 9.

Table 3. anti-CD28 light chain variable domain, heavy chain variable domain sequences, and full length sequence. CDR sequences are underlined and were determined using IMGT definition.

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
anti-CD28: HC	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSS	7
anti-CD28: LC	DIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIK	8
Anti-CD28 scFv (VH – linker 1 – VL)	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIK	9

[0087] In some embodiments, the CD28 binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the CD28 binding domain comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the CD28 binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the CD28 binding domain comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3.

[0088] In some embodiments, the CD28 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 the anti-CD28 light chain polypeptide: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the CD28 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-CD28 light chain polypeptide: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6.

[0089] In some embodiments, CD28 binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the CD28 binding domain comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the CD28 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the CD28 binding domain comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0090] In some embodiments, the CD28 binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the CD28 binding domain comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3; and the CD28 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the CD28 binding domain comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6.

[0091] In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 85%

sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence according to SEQ ID NO: 7.

[0092] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7 In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7 In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0093] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7, and has at least 80% sequence identity to the at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0094] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7, and has at least 90% sequence identity to the at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0095] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7, and has at least 95% sequence identity to the at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0096] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 115 consecutive amino acid residues of SEQ ID NO: 7, and has at least 99% sequence identity to the at least 115 consecutive amino acid residues of SEQ ID NO: 7.

[0097] In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence according to SEQ ID NO: 8.

[0098] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0099] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8, and has at least 80% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0100] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8, and has at least 90% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0101] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8, and has at least 95% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0102] In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 80 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 80 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 90 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 90 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 95 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 95 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the CD28 binding domain comprises an amino acid sequence of at least 105 consecutive amino acid residues of SEQ ID NO: 8, and has at least 99% sequence identity to the at least 105 consecutive amino acid residues of SEQ ID NO: 8.

[0103] In some embodiments, the scFv comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 91% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 92% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 93% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 94% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence according to SEQ ID NO: 9.

[0104] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9.In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO:

9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9.

[0105] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9, and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 9.

[0106] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9, and has at least 90% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 9.

[0107] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 9.

[0108] In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 9, and has at least 99% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 9.

PD-L1 Binding Domains

[0109] Disclosed here are multispecific antibodies that comprise a PD-L1 binding domain. In some embodiments, the PD-L1 binding domain comprises an antibody or antigen binding fragment. In some embodiments, the antibody or antigen binding fragment is a monoclonal antibody. In some embodiments, the antibody or antigen binding fragment is a human antibody, a murine antibody, a humanized antibody, or a chimeric antibody. In some embodiments, antibody or antigen binding fragment that binds specifically to PD-L1 comprises an anti-PD-L1 heavy chain polypeptide and an anti-PD-L1 light chain polypeptide.

[0110] In some embodiments, the PD-L1 binding domain is derived from BMS-936559. In some embodiments, the PD-L1 binding domain is derived from atezolizumab, durvalumab, and avelumab, CK-301, CS-1001, SHR-1316, CBT-502, envafolimab, or BGB-A333.In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises an anti-PD-L1 heavy chain variable domain. In some embodiments, the anti-PD-L1 heavy chain variable domain comprises an IgG framework, an IgA framework, an IgE framework, or an IgM framework. In some embodiments, the anti-PD-L1 heavy chain variable domain comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 heavy chain. In some embodiments, the anti-PD-L1 light chain polypeptide comprises an anti-PD-L1 light chain variable domain. In some embodiments, the anti-PD-L1 light chain variable domain comprises an IgG framework, an IgA framework, an IgE framework, or an IgM framework. In some embodiments, the anti-PD-L1 light chain variable domain comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 light chain.

[0111] In some embodiments, the PD-L1 binding domain comprises a single domain antibody, a Fab, or a Fab′. In some embodiments, the PD-L1 binding domain comprises the Fab or the Fab′. In some embodiments, the PD-L1 binding domain comprises the Fab or the Fab′. In some embodiments, the PD-L1 binding domain that comprises the Fab or the Fab′ comprises a Fab heavy chain polypeptide comprising a Fab heavy chain variable domain and a Fab light chain polypeptide comprising a Fab light chain variable domain. In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises the Fab heavy chain polypeptide comprising the Fab heavy chain variable domain. In some embodiments, the anti-PD-L1 light chain polypeptide comprises the Fab light chain polypeptide comprising the Fab light chain variable domain. In some embodiments, the PD-L1 binding domain comprises the single chain variable fragment. In some embodiments, the PD-L1 binding domain that comprises the single chain variable fragment comprises a scFv heavy chain variable domain and a scFv light chain variable domain. In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises the scFv heavy chain variable domain. In some embodiments, the anti- PD-L1 light chain polypeptide comprises the scFv light chain variable domain.

[0112] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-

CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12.

[0113] In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15.

[0114] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0115] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15.

[0116] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26.

[0117] In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35.

[0118] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0119] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35.

[0120] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29.

[0121] In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38.

[0122] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0123] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38.

[0124] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32.

[0125] In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41.

[0126] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0127] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41.

Table 4. anti-PD-L1 heavy chain polypeptide complementarity determining regions (CDR)s as determined by IMGT definition.

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
anti-PD-L1 Fab 1: HC: CDR1	GDTFSTYA	10
anti-PD-L1 Fab 1: HC: CDR2	IIPIFGKA	11
anti-PD-L1 Fab 1: HC: CDR3	ARKFHFVSGSPFGMDV	12
anti-PD-L1 Fab 2: HC: CDR1	GFTFSDSW	24
anti-PD-L1 Fab 2: HC: CDR2	ISPYGGST	25
anti-PD-L1 Fab 2: HC: CDR3	ARRHWPGGFDY	26
anti-PD-L1 Fab 3: HC: CDR1	GFTFSSYI	27

anti-PD-L1 Fab 3: HC: CDR2	IYPSGGIT	28
anti-PD-L1 Fab 3: HC: CDR3	ARIKLGTVTTVDY	29
anti-PD-L1 Fab 4: HC: CDR1	GFTFSRYW	30
anti-PD-L1 Fab 4: HC: CDR2	IKQDGSEK	31
anti-PD-L1 Fab 4: HC: CDR3	AREGGWFGELAFDY	32

Table 5. anti-PD-L1 light chain polypeptide complementarity determining regions (CDR)s as determined by IMGT definition.

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
anti-PD-L1 Fab 1: LC: CDR1	QSVSSY	13
anti-PD-L1 Fab 1: LC: CDR2	DA	14
anti-PD-L1 Fab 1: LC: CDR3	QQRSNWPT	15
anti-PD-L1 Fab 2: LC: CDR1	QDVSTA	33
anti-PD-L1 Fab 2: LC: CDR2	SA	34
anti-PD-L1 Fab 2: LC: CDR3	QQYLYHPAT	35
anti-PD-L1 Fab 3: LC: CDR1	SSDVGGYNY	36
anti-PD-L1 Fab 3: LC: CDR2	DV	37
anti-PD-L1 Fab 3: LC: CDR3	FGTGTKVTVLGQP	38
anti-PD-L1 Fab 4: LC: CDR1	QRVSSSY	39
anti-PD-L1 Fab 4: LC: CDR2	DA	40
anti-PD-L1 Fab 4: LC: CDR3	QQYGSLPWT	41

[0128] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO:

17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 17.

[0129] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0130] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0131] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0132] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0133] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0134] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 16.

[0135] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0136] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0137] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0138] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0139] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0140] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 16.

[0141] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 43.

[0142] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 43.

[0143] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 42.

[0144] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 42. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 42.

[0145] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 42.

[0146] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 45.

[0147] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 45.

[0148] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 44.

[0149] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 44. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 44.

[0150] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO:

44. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 44.

[0151] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 47.

[0152] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ

ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 47. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 47.

[0153] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 46.

[0154] In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 46. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 46.

[0155] In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 46.

Table 6. anti-PD-L1 Fab light chain polypeptide and Fab heavy chain polypeptide sequences. CDR sequences are underlined and were determined using IMGT definition

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
anti-PD-L1 Fab 1: LC	EIVLTQSPATLSLSPGERATLSCRAS**QSVSSY**LAWYQQKPGQAPRLLIY**DA**SNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQRSNWPT**FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	16
anti-PD-L1 Fab 1: HC	QVQLVQSGAEVKKPGSSVKVSCKTS**GDTFSTYA**ISWVRQAPGQGLEWMGG**IIPIFGKA**HYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYFC**ARKFHFVSGSPFGMDV**WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	17
anti-PD-L1 Fab 2: LC	DIQMTQSPSSLSASVGDRVTITCRAS**QDVSTA**VAWYQQKPGKAPKLLIY**SA**SFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQYLYHPAT**FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	42
anti-PD-L1 Fab 2: HC	EVQLVESGGGLVQPGGSLRLSCAAS**GFTFSDSW**IHWVRQAPGKGLEWVAW**ISPYGGST**YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC**ARRHWPGGFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	43
anti-PD-L1 Fab 3: LC	QSALTQPASVSGSPGQSITISCTGT**SSDVGGYNY**VSWYQQHPGKAPKLMIY**DV**SNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRV**FGTGTKVTVLGQP**KANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTV	44

	AWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	
anti-PD-L1 Fab 3: HC	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSYI**MMWVRQAPGKGLEWVSS**IYPSGGIT**FYADTVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARIKLGTVTTVDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	45
anti-PD-L1 Fab 4: LC	EIVLTQSPGTLSLSPGERATLSCRAS**QRVSSSY**LAWYQQKPGQAPRLLIY**DA**SSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYGSLPWT**FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	46
anti-PD-L1 Fab 4: HC	EVQLVESGGGLVQPGGSLRLSCAAS**GFTFSRYW**MSWVRQAPGKGLEWVAN**IKQDGSEK**YYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**AREGGWFGELAFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC	47

[0156] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12.

[0157] In some embodiments, the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15.

[0158] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise: LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0159] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12; and the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise: LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15.

[0160] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26.

[0161] In some embodiments, the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise:LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise:LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35.

[0162] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise: LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0163] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; and the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise: LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35.

[0164] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29.

[0165] In some embodiments, the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise:LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise:LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38.

[0166] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise: LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0167] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; and the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise: LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38.

[0168] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32.

[0169] In some embodiments, the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise:LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise:LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41.

[0170] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise: LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0171] In some embodiments, the PD-L1 binding domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the PD-L1 binding domain comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32; and the PD-L1 binding domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the PD-L1 binding domain comprise: LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41.

[0172] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 17.

[0173] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0174] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17, and has at least 80% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0175] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17, and has at least 90% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0176] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17, and has at least 95% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0177] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 17, and has at least 99% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 17.

[0178] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 16.

[0179] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0180] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16, and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0181] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16, and has at least 90% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0182] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0183] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 16, and has at least 99% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 16.

[0184] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 17; and the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 16.

[0185] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 43.

[0186] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 43. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 43, and has at least 95% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 43.

[0187] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 42.

[0188] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 42, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 42.

[0189] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 42. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 43; and the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 42.

[0190] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 45.

[0191] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 45. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 45, and has at least 95% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 45.

[0192] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 44.

[0193] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 44, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 44.

[0194] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 45;

and the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 44. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 45; and the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 44.

[0195] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 47.

[0196] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 47. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 47, and has at least 95% sequence identity to the at least 220 consecutive amino acid residues of SEQ ID NO: 47.

[0197] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 46.

[0198] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 175 consecutive amino acid residues of SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 190 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 190 consecutive amino acid residues of SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 205 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 205 consecutive amino acid residues of SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 46, and has at least 95% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 46.

[0199] In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the PD-L1 binding domain comprises an amino acid sequence that has at least 70% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the PD-L1 binding domain comprises an amino acid sequence that has at least 85% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the PD-L1 binding domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the PD-L1 binding domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the PD-L1 binding domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the PD-L1 binding domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the PD-L1 binding domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 46. In some embodiments, the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 47; and the PD-L1 binding domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 46.

Linker

[0200] In some embodiments, the linker is at least 5 amino acids in length. In some embodiments, the linker is no more than 30 amino acids in length. In some embodiments, the linker is at least 5 amino acids and no more than 30 amino acids in length. In some embodiments, the linker is 5 amino acids in length. In some embodiments, the linker is 6 amino acids in length. In some embodiments, the linker is 7 amino acids in length. In some embodiments, the linker is 8 amino acids in length. In some embodiments, the linker is 9 amino acids in length. In some embodiments, the linker is 10 amino acids in length. In some embodiments, the linker is 11 amino acids in length. In some embodiments, the linker is 12 amino acids in length. In some embodiments, the linker is 13 amino acids in length. In some embodiments, the linker is 14 amino acids in length. In some embodiments, the linker is 15 amino acids in length. In some embodiments, the linker is 16 amino acids in length. In some embodiments, the linker is 17 amino acids in length. In some embodiments, the linker is 18 amino acids in length. In some embodiments, the linker is 19 amino acids in length. In some embodiments, the linker is 20 amino acids in length. In some embodiments, the linker is 21 amino acids in length. In some embodiments, the linker is 22 amino acids in length. In some embodiments, the linker is 23 amino acids in length. In some embodiments, the linker is 24 amino acids in length. In some embodiments, the linker is 25 amino acids in length. In some embodiments, the linker is 26 amino acids in length. In some embodiments, the linker is 27 amino acids in length. In some embodiments, the linker is 28 amino acids in length. In some embodiments, the linker is 29 amino acids in length. In some embodiments, the linker is 30 amino acids in length. In some embodiments, the linker comprises an amino acid sequence of SEQ ID NO: 18 (GGGGSGGGGSGGGGS) or SEQ ID NO: 19 (GGGGS). In some embodiments, the linker comprises an amino acid sequence of SEQ ID NO: 18 (GGGGSGGGGSGGGGS). In some embodiments, the linker comprises an amino acid sequence of SEQ ID NO: 19 (GGGGS).

[0201] In some embodiments, the linker has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and (GSSGGS)n (SEQ ID NO: 61), wherein n is an integer of at least 1. In some embodiments, the linker has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 234), $(GGGS)_n$ (SEQ ID NO: 235), $(GGGGS)_n$ (SEQ ID NO: 236), and $(GSSGGS)_n$ (SEQ ID NO: 237), wherein n is an integer of 1. In some embodiments, the linker has a formula selected from the group consisting of $(G_2S)_n$ (SEQ ID NO: 233), $(GS)_n$ (SEQ ID NO: 238), $(GSGGS)_n$ (SEQ ID NO: 239), $(GGGS)_n$ (SEQ ID NO: 240), $(GGGGS)_n$ (SEQ ID NO: 241), and $(GSSGGS)_n$ (SEQ ID NO: 242), wherein n is an integer from 1 to 3. In some embodiments, the linker has a formula selected from the group consisting of $(G_2S)_n$ (SEQ ID NO: 243), $(GS)_n$ (SEQ ID NO: 244), $(GSGGS)_n$ (SEQ ID NO: 245), $(GGGS)_n$ (SEQ ID NO: 246), $(GGGGS)_n$ (SEQ ID NO: 247), and $(GSSGGS)_n$ (SEQ ID NO: 248), wherein n is an integer from 1 to 10.

[0202] In some embodiments, the linker has a formula of $(G_2S)_n$, wherein n is an integer of least 1. In some embodiments, the linker has a formula of $(GS)_n$, wherein n is an integer of least 1. In some embodiments, the linker has a formula of $(GSGGS)_n$ (SEQ ID NO: 58), wherein n is an integer of least 1. In some embodiments , the linker has a formula of $(GGGS)_n$ (SEQ ID NO: 59), wherein n is an integer of least 1. In some embodiments, the linker has a formula of $(GGGGS)_n$ (SEQ ID NO: 60), wherein n is an integer of least 1. In some embodiments, the linker has a formula of $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of least 1.

[0203] In some embodiments, the linker has a formula of $(G_2S)_n$, wherein n is an integer of 1. In some embodiments, L_1 has a formula of $(GS)_n$, wherein n is an integer of 1. In some embodiments, the linker has a formula of $(GSGGS)_n$ (SEQ ID NO: 234), wherein n is an integer of 1. In some embodiments, the linker has a formula of $(GGGS)_n$ (SEQ ID NO: 235), wherein n is an integer of 1. In some embodiments, the linker has a formula of $(GGGGS)_n$ (SEQ ID NO: 236), wherein n is an integer of 1. In some embodiments, the linker has a formula of $(GSSGGS)_n$ (SEQ ID NO: 237), wherein n is an integer of 1.

[0204] In some embodiments, the linker has a formula of $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3. In some embodiments, the linker has a formula of $(GS)_n$ (SEQ ID NO: 238), wherein n is an integer from 1 to 3. In some embodiments, the linker has a formula of $(GSGGS)_n$ (SEQ ID NO: 239), wherein n is an integer from 1 to 3. In some embodiments, the linker has a formula of $(GGGS)_n$ (SEQ ID NO: 240), wherein n is an integer from 1 to 3. In some embodiments, the linker has a formula of $(GGGGS)_n$ (SEQ ID NO: 241), wherein n is an integer from 1 to 3. In some embodiments, the linker has a formula of $(GSSGGS)_n$ (SEQ ID NO: 242), wherein n is an integer from 1 to 3.

[0205] In some embodiments, the linker has a formula of $(G_2S)_n$ (SEQ ID NO: 243), wherein n is an integer from 1 to 10. In some embodiments, the linker has a formula of $(GS)_n$ (SEQ ID NO: 244), wherein n is an integer from 1 to 10. In some embodiments, the linker has a formula of $(GSGGS)_n$ (SEQ ID NO: 245), wherein n is an integer from 1 to 10. In some embodiments, the linker has a formula of $(GGGS)_n$ (SEQ ID NO: 246), wherein n is an integer from 1 to 10. In some embodiments, the linker has a formula of $(GGGGS)_n$ (SEQ ID NO: 247), wherein n is an integer from 1 to 10. In some embodiments, the linker has a formula of $(GSSGGS)_n$ (SEQ ID NO: 248), wherein n is an integer from 1 to 10.

Table 7. Linker sequences

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
Linker 1	GGGGSGGGGSGGGGS	18
Linker 2	GGGGS	19

[0206] In some embodiments, the linker connects the C-terminus of A to an N-terminus of B. In some embodiments, the linker connects the N-terminus of A to a C-terminus of B. In some embodiments, the linker connects the C-terminus of A to the N-terminus of the Fab heavy chain polypeptide. In some embodiments, the linker connects the N-terminus of A to the C-terminus of the Fab heavy chain polypeptide. In some embodiments, the linker connects the C-terminus of A to the N-terminus of the Fab light chain polypeptide. In some embodiments, the linker connects the N-terminus of A to the C-terminus of the Fab light chain polypeptide. In some embodiments, the linker connects the Fab light chain polypeptide to the scFv light chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the scFv heavy chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the scFv light chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the scFv heavy chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the N-terminus of the scFv light chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the N-terminus of the scFv heavy chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv heavy chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv light chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv heavy chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

Multispecific Antibodies that Bind to CD28 and PD-L1

[0207] In some embodiments, the multispecific antibody comprising a CD28 binding domain and a PD-L1 binding domain comprises a variety of multispecific antibody formats. In some embodiments, the multispecific antibody comprises a CD28 binding domain and a PD-L1 binding domain, wherein when the CD28 binding domain is a single chain variable fragment (scFv), then the PD-L1 binding domain is not a scFv.

[0208] In some embodiments, the multispecific antibody further comprises a fragment crystallizable (Fc) region. In some embodiments, the Fc region comprises an IgG CH2 domain and an IgG CH3 domain. In some embodiments, the Fc region comprises a heterodimeric Fc region. In some embodiments, the Fc region comprises at least one amino acid modification that increases the half-life of the multispecific antibody. In some embodiments, the Fc region comprises at least one amino acid modification that modulates its interaction with an Fc receptor. In some embodiments, the Fc region comprises at least one amino acid modification that increases binding of the Fc region to an Fc receptor. In some embodiments, the Fc region comprises at least one amino acid modification that decreases glycosylation of the Fc region. In some embodiments, the modification is an amino acid substitution, deletion, or addition. In some embodiments, the modification is an amino acid substitution. In some embodiments, the at least one amino acid modification that decreases glycosylation of the Fc region comprises an amino acid substitution at a position corresponding to position N297 of human IgG1, wherein the numbering is according to the EU index of Kabat. In some embodiments, the Fc region is afucosylated.

[0209] In some embodiments, the multispecific antibody is assembled from at least two different heavy and light chains expressed in the same producer cell. In some embodiments, the multispecific antibody is produced using knobs-into-holes technology to force heavy-chain heterodimerization in which mutations are introduced into the two CH3 domains.

[0210] In some embodiments, the multispecific antibody lacks a fragment crystallizable (Fc) region. In some embodiments, two or more different antibodies are linked together to form the multispecific antibody. In some embodiments, two different antibodies are linked together to form the multispecific antibody. For example, the PD-L1 binding domain is a Fab or Fab′ and is linked to the CD28 binding domain that is a scFv, another Fab or Fab′, or a single domain antibody. In some embodiments, the CD28 binding domain is a scFv and is linked to the PD-L1 binding domain that is Fab or Fab′ or a single domain antibody. In some embodiments, the PD-L1 binding domain is a single domain antibody and is linked to the CD28 binding domain that is another single domain antibody. In some embodiments, the PD-L1 binding domain is a Fab or Fab′ and is linked to the CD28 binding domain that is another Fab or Fab′. In some embodiments, the PD-L1 binding domain is a Fab or Fab′ and is linked to the CD28 binding domain that is a single domain antibody. In some embodiments, the PD-L1 binding domain is a Fab or Fab′ and is linked to the CD28 binding domain that is a scFv. In some embodiments, the PD-L1 binding domain is a single domain antibody and is linked to the CD28 binding domain that is a Fab or Fab′. In some embodiments, the PD-L1 binding domain is a single domain antibody and is linked to the CD28 binding domain that is a scFv. In some embodiments, the PD-L1 binding domain is a scFv and is linked to the CD28 binding domain that is a Fab or Fab′. In some embodiments, the PD-L1 binding domain is a scFv and is linked to the CD28 binding domain that is a single domain antibody. In some embodiments, the PD-L1 binding domain is a scFv and is linked to the CD28 binding domain that is a scFv.

[0211] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21.

[0212] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0213] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 470 consecutive amino acid residues of SEQ ID NO: 21.

[0214] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0215] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 90% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21 and has at least 90% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0216] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21 and has at least 95% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0217] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO:

21 and has at least 99% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0218] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 22.

[0219] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 220 consecutive amino acid residues of SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 460 consecutive amino acid residues of SEQ ID NO: 22.

[0220] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0221] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 90% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 90% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0222] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 95% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0223] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 96% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 96% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0224] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 97% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 97% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0225] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 98% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 98% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0226] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 99% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0227] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 48. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 42, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 48.

[0228] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 42 and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 42 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 48 and has at least 95% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 48.

[0229] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 42 and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 42 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 48 and has at least 99% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 48.

[0230] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 43, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 49. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 43, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 49. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 43, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 49. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 43, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 49. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 43, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 49. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 43, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 49. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 43, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 49. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 43, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 49.

[0231] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 43 and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 43 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 49 and has at least 95% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 49.

[0232] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 43 and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 43 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 49 and has at least 99% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 49.

[0233] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to

SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 50. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 44, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 50.

[0234] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 44 and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 44 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO:

50 and has at least 95% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 50.

[0235] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 44 and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 44 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 50 and has at least 99% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 50.

[0236] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 45, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 51. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 45, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 51. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 45, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 51. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 45, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 51. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 45, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 51. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 45, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 51. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 45, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 51. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 45, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 51.

[0237] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 45 and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 45 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 51 and has at least 95% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 51.

[0238] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 45 and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 45 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 51 and has at least 99% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 51.

[0239] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 52. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 46, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 52.

[0240] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 46 and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 46 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 52 and has at least 95% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 52.

[0241] In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 46 and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 46 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 52 and has at least 99% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 52.

[0242] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 47, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 53. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 47, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence according to SEQ ID NO: 53. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 47, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 95% sequence identity to the amino acid sequence according to SEQ ID NO: 53. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 47, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 96% sequence identity to the amino acid sequence according to SEQ ID NO: 53. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 47, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 97% sequence identity to the amino acid sequence according to SEQ ID NO: 53. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 47, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 98% sequence identity to the amino acid sequence according to SEQ ID NO: 53. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 47, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 99% sequence identity to the amino acid sequence according to SEQ ID NO: 53. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 47, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 53.

[0243] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 47 and has at least 95% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 47 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 53 and has at least 95% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 53.

[0244] In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 47 and has at least 99% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 47 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 53 and has at least 99% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 53.

Table 8. Antibody sequences that bind to CD28 and PD-L1. CDR sequences are underlined and were determined using IMGT definition

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
Ab-1 LC Anti-PDL1 Fab LC	EIVLTQSPATLSLSPGERATLSCRAS**QSVSSY**LAWYQQKPGQAPRLLIY**DA**SNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQRSNWPT**FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	20
Ab-1 HC Anti-CD28 scFv – Linker 2 – anti-PDL1 Fab HC	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIKGGGGSQVQLVQSGAEVKKPGSSVKVSCKTS**GDTFSTYA**ISWVRQAPGQGLEWMGG**IIPIFGKA**HYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYFC**ARKFHFVSGSPFGMDV**WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV	21

	TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	
Ab-2 LC Anti-CD28 scFv – Linker 2 - Anti-PDL1 Fab LC	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIKGGGGSEIVLTQSPATLSLSPGERATLSCRAS**QSVSSY**LAWYQQKPGQAPRLLIY**DA**SNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC**QQRSNWPT**FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	22
Ab-2 HC Anti-PDL1 Fab HC	QVQLVQSGAEVKKPGSSVKVSCKTS**GDTFSTYA**ISWVRQAPGQGLEWMGG**IIPIFGKA**HYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYFC**ARKFHFVSGSPFGMDV**WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	23
Ab-3 LC Anti-PDL1 Fab 2 LC	DIQMTQSPSSLSASVGDRVTITCRAS**QDVSTA**VAWYQQKPGKAPKLLIY**SA**SFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQYLYHPAT**FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	42
Ab-3 HC Anti-CD28 scFv – Linker 2 – anti-PDL1 Fab 2 HC	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTL	48

	TISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIKGGGGSEVQLVESGGGLVQPGGSLRLSCAAS**GFTFSDSW**IHWVRQAPGKGLEWVAW**ISPYGGST**YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC**ARRHWPGGFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	
Ab-4 LC Anti-CD28 scFv – Linker 2 - Anti-PDL1 Fab 2 LC	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIKGGGGSDIQMTQSPSSLSASVGDRVTITCRAS**QDVSTA**VAWYQQKPGKAPKLLIY**SA**SFLYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQYLYHPAT**FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	49
Ab-4 HC Anti-PDL1 Fab 2 HC	EVQLVESGGGLVQPGGSLRLSCAAS**GFTFSDSW**IHWVRQAPGKGLEWVAW**ISPYGGST**YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC**ARRHWPGGFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	43
Ab-5 LC Anti-PDL1 Fab 3 LC	QSALTQPASVSGSPGQSITISCTGT**SSDVGGYNY**VSWYQQHPGKAPKLMIY**DV**SNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRV**FGTGTKVTVLGQP**KANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKS	44

	HRSYSCQVTHEGSTVEKTVAPTECS	
Ab-5 HC Anti-CD28 scFv – Linker 2 – anti-PDL1 Fab 3 HC	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIKGGGGSEVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSYI**MMWVRQAPGKGLEWVSS**IYPSGGIT**FYADTVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARIKLGTVTTVDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	50
Ab-6 LC Anti-CD28 scFv – Linker 2 - Anti-PDL1 Fab 3	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIKGGGGSQSALTQPASVSGSPGQSITISCTGT**SSDVGGYNY**VSWYQQHPGKAPKLMIY**DV**SNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRV**FGTGTKVTVLGQP**KANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	51
Ab-6 HC Anti-PDL1 Fab 3 HC	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSYI**MMWVRQAPGKGLEWVSS**IYPSGGIT**FYADTVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARIKLGTVTTVDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL	45

	TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	
Ab-7 LC Anti-PDL1 Fab 4 LC	EIVLTQSPGTLSLSPGERATLSCRAS**QRVSSSY**LAWYQQKPGQAPRLLIY**DA**SSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYGSLPWT**FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	46
Ab-7 HC Anti-CD28 scFv – Linker 2 – anti-PDL1 Fab 4 HC	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIKGGGGSEVQLVESGGGLVQPGGSLRLSCAAS**GFTFSRYW**MSWVRQAPGKGLEWVAN**IKQDGSEK**YYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**AREGGWFGELAFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC	52
Ab-8 LC Anti-CD28 scFv – Linker 2 - Anti-PDL1 Fab 4 LC	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWIGS**IYPGNVNT**NYNEKFKDRATLTVDTSISTAYMELSRLRSDDTAVYFC**TRSHYGLDWNFDV**WGQGTTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHAS**QNIYVW**LNWYQQKPGKAPKLLIY**KA**SNLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGQTYPYT**FGGGTKVEIKGGGGSEIVLTQSPGTLSLSPGERATLSCRAS**QRVSSSY**LAWYQQKPGQAPRLLIY**DA**SSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYGSLPWT**FGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV	53

	DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
Ab-8 HC Anti-PDL1 Fab 4 HC	EVQLVESGGGLVQPGGSLRLSCAAS**GFTFSRYW**MSWVRQAPGKGLEWVAN**IKQDGSEK**YYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC**AREGGWFGELAFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC	47

[0245] In some embodiments, the multispecific antibodies described herein comprise improved activity in tumor cell killing. In some embodiments, the multispecific antibodies comprise an IC50 of less than about 300 picomolar (pM) in a cell killing assay. In some embodiments, the multispecific antibodies comprise an IC50 of less than about 200 picomolar (pM) in a cell killing assay. In some embodiments, the multispecific antibodies comprise an IC50 of less than about 100 picomolar (pM) in a cell killing assay. In some embodiments, the multispecific antibodies comprise an IC50 of less than about 75 picomolar (pM) in a cell killing assay. In some embodiments, the multispecific antibodies comprise an IC50 of less than about 50 picomolar (pM) in a cell killing assay. In some embodiments, the multispecific antibodies comprise an IC50 of less than about 25 picomolar (pM) in a cell killing assay. In some embodiments, the multispecific antibodies comprise an IC50 of less than about 10 picomolar (pM) in a cell killing assay.

[0246] In some embodiments, the multispecific antibodies described herein trigger little or no non-specific activation of immune cells. In some embodiments, the multispecific antibodies described herein trigger little or no cytokine release. In some embodiments, the multispecific antibodies described herein trigger little or no IFNy, TNF-alpha, or IL-2 release from immune cells. In some embodiments, the multispecific antibodies described herein trigger little or no proliferation of immune cells.

Multispecific Antibodies that Bind to CD28 and PD-L1: Formats for Selective Activation in Tumor Microenvironments

[0247] In some embodiments, the multispecific antibodies described herein are selectively activated in tumor microenvironments.

[0248] In some embodiments, the multispecific antibody is according to the following subformula: **P_1-L_1-A-L-B (Formula Ia)** wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; L comprises the linker that connects A to B; P_1 comprises a peptide that binds to A and L_1 comprises a linking moiety that connects A to P_1 and is a substrate for a tumor specific protease.

[0249] In some embodiments, the multispecific antibody is according to the following subformula: **A-L-B-L_2-P_2 (Formula Ib)** wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; L comprises the linker that connects A to B; P_2 comprises a peptide that binds to B and L_2 comprises a linking moiety that connects B to P_2 and is a substrate for a tumor specific protease.

[0250] In some embodiments, the multispecific antibody is according to the following subformula: **P_1-L_1-A-L-B-L_2-P_2 (Formula Ic)** wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; L comprises the linker that connects A to B; P_1 comprises a peptide that binds to A and L_1 comprises a linking moiety that connects A to P_1 and is a substrate for a tumor specific protease; P_2 comprises a peptide that binds to B and L_2 comprises a linking moiety that connects B to P_2 and is a substrate for a tumor specific protease.

Half-life extending molecule (H_1)

[0251] In some embodiments, the multispecific antibodies of Formula Ia, Formula Ib, Formula Ic further comprise a half-life extending molecule (H_1). In some embodiments, H_1 is connected to P_1. In some embodiments, H_1 is connected to P_2. In some embodiments, H_1 does not block A binding to CD28. In some embodiments, H_1 comprises a linking moiety (L_5) that connects H_1 to P_1 or H_1 to P_2. In some embodiments, half-life extending molecule (H_1) does not have binding affinity to PD-L1. In some embodiments, the half-life extending molecule (H_1) does not have binding affinity to CD28. In some embodiments, the half-life extending molecule (H_1) does not shield the multispecific antibody from CD28.

[0252] In some embodiments, H_1 comprises a sequence as disclosed in **Table 9** or a sequence substantially identical thereto (e.g., a sequence that has at least 90%, 95%, 96%, 97%, 98%, or 99% sequence identity).

Table 9. H_1 Sequences

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
Anti-Albumin: CDR-H1	GSTFYTAV	54
Anti-Albumin: CDR-H2	IRWTALTT	55
Anti-Albumin: CDR-H3	AARGTLGLFTTADSYDY	56
Anti-albumin	EVQLVESGGGLVQPGGSLRLSCAAS**GSTFYTAV**MGWVRQAPGKGLEWVAA**IRWTALTT**SYADSVKGRFTISRDGAKTTLYLQMNSLRPEDTAVYYC**AARGTLGLFTTADSYDY**WGQGTLVTVSS	57

[0253] In some embodiments, H_1 comprises an amino acid sequence that has repetitive sequence motifs. In some embodiments, H_1 comprises an amino acid sequence that has highly ordered secondary structure. "Highly ordered secondary structure," as used in this context, means that at least about 50%, or about 70%, or about 80%, or about 90%, of amino acid residues of H_1 contribute to secondary structure, as measured or determined by means, including, but not limited to, spectrophotometry (e.g. by circular dichroism spectroscopy in the "far-UV" spectral region (190-250 nm), and computer programs or algorithms, such as the Chou-Fasman algorithm and the Garnier-Osguthorpe-Robson ("GOR") algorithm.

[0254] In some embodiments, H_1 comprises a polymer. In some embodiments, the polymer is polyethylene glycol (PEG). In some embodiments, H_1 comprises albumin. In some embodiments, H_1 comprises an Fc domain. In some embodiments, the albumin is serum albumin. In some embodiments, the albumin is human serum albumin. In some embodiments, H_1 comprises a polypeptide, a ligand, or a small molecule. In some embodiments, the polypeptide, the ligand or the small molecule binds serum protein or a fragment thereof, a circulating immunoglobulin or a fragment thereof, or CD35/CR1. In some embodiments, the serum protein comprises a thyroxine-binding protein, a transthyretin, a 1-acid glycoprotein, a transferrin, transferrin receptor or a transferrin-binding portion thereof, a fibrinogen, or an albumin. In some embodiments, the circulating immunoglobulin molecule comprises IgGl, IgG2, IgG3, IgG4, slgA, IgM or IgD. In some embodiments, the serum protein is albumin. In some embodiments, the polypeptide is an antibody. In some embodiments, the antibody comprises a single domain antibody, a single chain variable fragment or a Fab. In some embodiments, the single domain antibody comprises a single domain antibody that binds to albumin. In some embodiments, the single domain antibody is a human or humanized antibody. In some embodiments, the single domain antibody is selected from the group consisting of 645gH1gL1, 645dsgH5gL4, 23-13-A01 -sc02, A10m3 or a fragment thereof, DOM7r-31, DOM7h-11-15, Alb-1, Alb-8, Alb-23, 10G, 10E and SA21. In some embodiments, the single domain antibody comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the single domain antibody comprise: HC-CDR1: SEQ ID NO: 54, HC-CDR2: SEQ ID NO: 55, and HC-CDR3: SEQ ID NO: 56. In some embodiments, the single domain antibody comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the single domain antibody comprise: HC-CDR1: SEQ ID NO: 54, HC-CDR2: SEQ ID NO: 55, and HC-CDR3: SEQ ID NO: 56; and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of the HC-CDR1, HC-CDR2, or HC-CDR3.

[0255] In some embodiments, H_1 comprises an amino acid sequence according to SEQ ID NO: 57. In some embodiments, H_1 comprises an amino acid sequence that has at least 80% sequence identity to SEQ ID NO: 57. In some embodiments, H_1 comprises an amino acid sequence that has at least 85% sequence identity to SEQ ID NO: 57. In some embodiments, H_1 comprises an amino acid sequence that has at least 90% sequence identity to SEQ ID NO: 57. In some embodiments, H_1 comprises an amino acid sequence that has at least 95% sequence identity to SEQ ID NO: 57. In some embodiments, H_1 comprises an amino acid sequence that has at least 99% sequence identity to SEQ ID NO: 57.

[0256] In some embodiments, H_1 comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof. In some embodiments, the modified amino acid or a modified non-natural amino acid comprises a post-translational modification. In some embodiments H_1 comprise a modification including, but not limited to acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Modifications are made anywhere to H_1 including the peptide backbone, the amino acid side chains, and the terminus.

[0257] In some embodiments, H_1 comprises a linking moiety (L_5) that connects H_1 to P_1 or P_2. In some embodiments, L_5 is a peptide sequence having at least 5 to no more than 50 amino acids. In some embodiments, L_5 is a peptide sequence having at least 10 to no more than 30 amino acids. In some embodiments, L_5 is a peptide sequence having at least 10 amino acids. In some embodiments, L_5 is a peptide sequence having at least 18 amino acids. In some embodiments, L_5 is a peptide sequence having at least 26 amino acids. In some embodiments, L_5 has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

Linking Moiety (L_1 or L_2)

[0258] In some embodiments, L_1 or L_2 is a peptide sequence having at least 5 to no more than 50 amino acids. In some embodiments L_1 or L_2 is a peptide sequence having at least 10 to no more than 30 amino acids. In some embodiments, L_1 or L_2 is a peptide sequence having at least 10 amino acids. In some embodiments, L_1 or $L_2$is a peptide sequence having at least 18 amino acids. In some embodiments, L_1 or L_2 is a peptide sequence having at least 26 amino acids. In some embodiments, L_1 or L_2 has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3. In some embodiments, L_1 or L_2 has a formula comprising $(G_2S)_n$, wherein n is an integer of at least 1. In some embodiments, L_1 or L_2 has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1. In some embodiments, the tumor specific protease is selected from the group consisting of metalloprotease, serine protease, cysteine protease, threonine protease, and aspartic protease. In some embodiments L_1 or L_2 comprises a urokinase cleavable amino acid sequence, a matriptase cleavable amino acid sequence, a legumain cleavable amino acid sequence, or a matrix metalloprotease cleavable amino acid sequence.

[0259] In some embodiments, L_1 or L_2 comprises a sequence as disclosed in **Table 10** or a sequence substantially identical thereto (e.g., a sequence that has 0, 1, or 2 amino acid modifications).

Table 10. L_1 or L_2

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
Linker 1	GGGGSGGGGSGGGGS	18
Linker 2	GGGGS	19
Linker 3	GGGGSGGGS	62
Cleavable linker	GGGGSGGGLSGRSDAGSPLGLAGSGGGS	63
Linker 4	GGGGSLSGRSDNHGSSGT	64
Linker 5	GGGGSSGGSGGSGLSGRSDNHGSSGT	65

Linker 6	ASGRSDNH	66
Linker 7	LAGRSDNH	67
Linker 8	ISSGLASGRSDNH	68
Linker 9	ISSGLLAGRSDNH	69
Linker 10	LSGRSDNH	70
Linker 11	ISSGLLSGRSDNP	71
Linker 12	ISSGLLSGRSDNH	72
Linker 13	LSGRSDNHSPLGLAGS	73
Linker 14	SPLGLAGSLSGRSDNH	74
Linker 15	SPLGLSGRSDNH	75
Linker 16	LAGRSDNHSPLGLAGS	76
Linker 17	LSGRSDNHVPLSLKMG	77
Linker 18	LSGRSDNHVPLSLSMG	78
Linker 19	GSSGGSGGSGGSGISSGLLSGRSDNHGSSGT	79
Linker 20	GSSGGSGGSGGISSGLLSGRSDNHGGGS	80
Linker 21	ASGRSDNH	81
Linker 22	LAGRSDNH	82
Linker 23	ISSGLASGRSDNH	83
Linker 24	LSGRSDAG	84
Linker 25	ISSGLLSGRSDAG	85
Linker 26	AAGLLAPPGGLSGRSDAG	86
Linker 27	SPLGLSGRSDAG	87
Linker 28	LSGRSDAGSPLGLAG	88

[0260] In some embodiments, L_1 is bound to N-terminus of A. In some embodiments, L_1 is bound to C-terminus of A. In some embodiments, L_2 is bound to N-terminus of B. In some embodiments, L_2 is bound to C-terminus of B. In some embodiments, P_1 becomes unbound from A when L_1 is cleaved by the tumor specific protease thereby exposing A to CD28. In some embodiments, P_2 becomes unbound from B when L_2 is cleaved by the tumor specific protease thereby exposing B to PD-L1.

[0261] In some embodiments, L_1 or L_2, comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof. In some embodiments, the modified amino acid or a modified non-natural amino acid comprises a post-translational modification. In some embodiments, L_1 or L_2 comprise a modification including, but not limited, to acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Modifications are made anywhere to L_1 or L_2 including the peptide backbone, or the amino acid side chains.

Peptide (P_1 and P_2)

[0262] P_1 or P_2 is designed to be optimized for a specific antigen-binding domain through an iterative process of phage display and quantitative binding assays designed to select for those peptides that are able to prevent binding to CD28 or PD-L1. A directed evolution-based process that includes phage libraries is used for identifying P_1 or P_2. Multiple cycles of selection and amplification of potential inhibitory peptides that are capable of blocking the antigen binding domain from binding to its target of CD28 or PD-L1 with the goal of optimizing masked PD-L1 x CD28 antibodies in serum and limiting cleavage, thereby reducing toxicity. Discovery of P_1 or P_2 is depicted in **Fig. 18.**

[0263] In some embodiments, P_1 impairs binding of A to CD28. In some embodiments, P_1 is bound to A through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof. In some embodiments, P_1 is bound to A at or near an antigen binding site. In some embodiments, P_1 becomes unbound from A when L_1 is cleaved by the tumor specific protease thereby exposing A to CD28. In some embodiments, P_1 has less than 70% sequence identity to CD28. In some embodiments, P_1 has less than 75% sequence identity to CD28. In some embodiments, P_1 has less than 80% sequence identity to CD28. In some embodiments, P_1 has less than 85% sequence identity to CD28. In some embodiments, P_1 has less than 90% sequence identity to CD28. In some embodiments, P_1 has less than 95% sequence identity to CD28. In some embodiments, P_1 has less than 98% sequence identity to CD28. In some embodiments, P_1 has less than 99% sequence identity to CD28. In some embodiments, P_1 comprises a de novo amino acid sequence that shares less than 10% sequence identity to CD28.

[0264] In some embodiments, P_2 impairs binding of B to PD-L1. In some embodiments, P_2 is bound to B through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof. In some embodiments, P_2 is bound to B at or near an antigen binding site. In some embodiments, P_2 becomes unbound from B when L_2 is cleaved by the tumor specific protease thereby exposing B to the PD-L1. In some embodiments, P_2 has less than 70% sequence identity to the PD-L1. In some embodiments, P_2 has less than 75% sequence identity to the PD-L1. In some embodiments, P_2 has less than 80% sequence identity to the PD-L1. In some embodiments, P_2 has less than 85% sequence identity to the PD-L1. In some embodiments, P_2 has less than 90% sequence identity to the PD-L1. In some embodiments, P_2 has less than 95% sequence identity to the PD-L1. In some embodiments, P_2 has less than 98% sequence identity to the PD-L1. In some embodiments, P_2 has less than 99% sequence identity to the PD-L1. In some embodiments, P_2 comprises a de novo amino acid sequence that shares less than 10% sequence identity to the PD-L1.

[0265] In some embodiments, P_1 or P_2 comprises a peptide sequence of at least 5 amino acids in length. In some embodiments, P_1 or P_2 comprises a peptide sequence of at least 6 amino acids in length. In some embodiments, P_1 or P_2 comprises a peptide sequence of at least 10 amino acids in length. In some embodiments, P_1 or P_2 comprises a peptide sequence of at least 10 amino acids in length and no more than 20 amino acids in length. In some embodiments, P_1 or P_2 comprises a peptide sequence of at least 16 amino acids in length. In some embodiments, P_1 or P_2 comprises a peptide sequence of no more than 40 amino acids in length. In some embodiments, P_1 or P_2 comprises at least two cysteine amino acid residues. In some embodiments, P_1 or P_2 comprises a cyclic peptide or a linear peptide. In some embodiments, P_1 or P_2 comprises a cyclic peptide. In some embodiments, P_1 or P_2 comprises a linear peptide.

[0266] In some embodiments, P_1 or P_2 comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof. In some embodiments, the modified amino acid or a modified non-natural amino acid comprises a post-translational modification. In some embodiments P_1 or P_2 comprise a modification including, but not limited to acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Modifications are made anywhere to P_1 or P_2 including the peptide backbone, the amino acid side chains, and the terminus.

[0267] In some embodiments, P_1 or P_2 does not comprise albumin or an albumin fragment. In some embodiments, P_1 or P_2 does not comprise an albumin binding domain.

Polynucleotides Encoding Multispecific Antibodies that Bind to CD28 and PD-L1

[0268] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding the multispecific antibodies disclosed herein. Described herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding multispecific antibodies that comprise a CD28 binding domain and a PD-L1 binding domain, wherein when the CD28 binding domain is a single chain variable fragment (scFv), then the PD-L1 binding domain is not a scFv.

[0269] In some embodiments, the isolated recombinant nucleic acid molecules encode multispecific antibodies according to the formula:

A-L-B (Formula I)

wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; and L comprises a linker that connects A to B. In some embodiments, the isolated recombinant nucleic acid molecules encode multispecific antibodies comprising the formula:

A-L-B (Formula I)

wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; and L comprises a linker that connects A to B. In some embodiments, the isolated recombinant nucleic acid molecules encode multispecific antibodies comprising the formula:

A-L-B (Formula I)

wherein A is the CD28 binding domain; B is the PD-L1 binding domain; and L is a linker that connects A to B. In some embodiments, the isolated recombinant nucleic acid molecules encode multispecific antibodies according to the formula:

A-L-B (Formula I)

wherein A is the CD28 binding domain; B is the PD-L1 binding domain; and L is a linker that connects A to B.

[0270] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 20.

[0271] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 21.

[0272] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 22.

[0273] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 23.

[0274] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 42.

[0275] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 48.

[0276] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 49.

[0277] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 43.

[0278] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 44.

[0279] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 50.

[0280] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 51.

[0281] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 45.

[0282] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 46.

[0283] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 52.

[0284] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 53.

[0285] Disclosed herein, in some embodiments, are isolated recombinant nucleic acid molecules encoding an isolated polypeptide comprising an amino acid according to SEQ ID NO: 47.

Pharmaceutical Compositions

[0286] Disclosed herein, in some embodiments, are pharmaceutical compositions comprising: (a) multispecific antibodies as disclosed herein; and (b) a pharmaceutically acceptable excipient.

[0287] In some embodiments, the pharmaceutical composition comprises (a) multispecific antibodies that comprise a CD28 binding domain and a PD-L1 binding domain, wherein when the CD28 binding domain is a single chain variable fragment (scFv), then the PD-L1 binding domain is not a scFv; and (b) a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises (a) multispecific antibodies according to the formula:

A-L-B (Formula I)

wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; and L comprises a linker that connects A to B; and (b) a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises (a) a multispecific antibodies comprising the formula:

A-L-B (Formula I)

wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; and L comprises a linker that connects A to B; and (b) a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises (a) a multispecific antibodies comprising the formula:

A-L-B (Formula I)

wherein A is the CD28 binding domain; B is the PD-L1 binding domain; and L is a linker that connects A to B; and (b) a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises (a) multispecific antibodies according to the formula:

A-L-B (Formula I)

wherein A is the CD28 binding domain; B is the PD-L1 binding domain; and L is a linker that connects A to B; and (b) a pharmaceutically acceptable excipient.

[0288] In some embodiments, the multispecific antibody further comprises a detectable label, a therapeutic agent, or a pharmacokinetic modifying moiety. In some embodiments, the detectable label comprises a fluorescent label, a radiolabel, an enzyme, a nucleic acid probe, or a contrast agent.

[0289] For administration to a subject, the multispecific antibody as disclosed herein, may be provided in a pharmaceutical composition together with one or more pharmaceutically acceptable carriers or excipients.

The term "pharmaceutically acceptable carrier" includes, but is not limited to, any carrier that does not interfere with the effectiveness of the biological activity of the ingredients and that is not toxic to the patient to whom it is administered. Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Such carriers can be formulated by conventional methods and can be administered to the subject at a suitable dose. Preferably, the compositions are sterile. These compositions may also contain adjuvants such as preservative, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents.

[0290] The pharmaceutical composition may be in any suitable form, (depending upon the desired method of administration). It may be provided in unit dosage form, may be provided in a sealed container and may be provided as part of a kit. Such a kit may include instructions for use. It may include a plurality of said unit dosage forms.

[0291] The pharmaceutical composition may be adapted for administration by any appropriate route, including a parenteral (e.g., subcutaneous, intramuscular, or intravenous) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by mixing the active ingredient with the carrier(s) or excipient(s) under sterile conditions.

[0292] Dosages of the substances of the present disclosure can vary between wide limits, depending upon the disease or disorder to be treated, the age and condition of the individual to be treated, etc. and a physician will ultimately determine appropriate dosages to be used.

Methods of Use

[0293] In some embodiments, are methods of treating cancer in a subject in need thereof comprising administering to the subject a multispecific antibody as disclosed herein that binds to CD28 and PD-L1.

[0294] In some embodiments, the cancer comprises cancer cells that express PD-L1.

[0295] In some embodiments, the cancer is a hematological malignancy. In some embodiments, wherein the cancer is leukemia or lymphoma. In some embodiments, the cancer is lymphoma, and wherein the lymphoma is B-cell lymphoma. In some embodiments, the cancer is a solid tumor. In some embodiments, the solid tumor is sarcoma, breast cancer, lung cancer, or carcinoma. In some embodiments, the solid tumor is lung cancer, and wherein the lung cancer is non-small cell lung cancer.

[0296] In some embodiments, the multispecific antibody induces T cell mediated cytotoxicity of tumor cells. In some embodiments, the administering to the subject of the multispecific antibody is sufficient to reduce or eliminate the cancer as compared to a baseline measurement of the cancer taken from the subject prior to the administering of the multispecific antibody. In some embodiments, the reduction is at least about 1-fold, 5-fold, 10-fold, 20-fold, 40-fold, 60-fold, 80-fold, or up to about 100 fold.

[0297] In some embodiments, the multispecific antibody is administered to the subject as a single agent therapy.

[0298] In some embodiments, the subject is refractory to checkpoint inhibitor therapy.

[0299] In some embodiments, the subject has relapsed from checkpoint inhibitor therapy.

[0300] In some embodiments, the multispecific antibody is not administered as a part of a treatment regimen with a second therapeutic agent. In some embodiments, the multispecific antibody is not administered as a part of a treatment regimen with a second therapeutic agent comprising a tumor binding domain. In some embodiments, the multispecific antibody is not administered as a part of a treatment regimen with a second therapeutic agent comprising an anti-CD19 antibody. In some embodiments, the multispecific antibody is not administered as a part of a treatment regimen with a second therapeutic agent comprising an antibody that has an anti-CD19 binding domain and an anti-CD3 binding domain.

[0301] In some embodiments, the multispecific antibody is any multispecific antibody as disclosed herein that binds to CD28 and PD-L1.

[0302] Disclosed herein are methods of treating cancer in a subject in need thereof comprising administering to the subject a multispecific antibody that comprises a CD28 binding domain and a PD-L1 binding domain wherein the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain is not administered as part of a treatment regimen with another multispecific antibody that targets a cancer antigen different from PD-L1 or CD28. In some embodiments, the multispecific antibody comprises a CD28 binding domain and a PD-L1 binding domain, wherein when the CD28 binding domain is a single chain variable fragment (scFv), then the PD-L1 binding domain is not a scFv. In some embodiments, the multispecific antibody is according to the following formula: **A-L-B (Formula I)** wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; and L comprises a linker that connects A to B. In some embodiments, the CD28 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′. In some embodiments, the CD28 binding domain comprises the single chain variable fragment. In some embodiments, the CD28 binding domain comprises the single domain antibody. In some embodiments, the CD28 binding domain comprises the Fab or the Fab′. In some embodiments, the PD-L1 binding domain comprises a single domain antibody, a Fab, or a Fab′. In some embodiments, the PD-L1 binding domain comprises the Fab or the Fab′. In some embodiments, the PD-L1 binding domain comprises the Fab or the Fab′ and the CD28 binding domain comprises the single chain variable fragment. In some embodiments, the PD-L1 binding domain that comprises the Fab or the Fab′ comprises a Fab heavy chain polypeptide comprising a Fab heavy chain variable domain and a Fab light chain polypeptide comprising a Fab light chain variable domain. In some embodiments, the CD28 binding domain that comprises the single chain variable fragment comprises a scFv heavy chain variable domain and a scFv light chain variable domain.

[0303] In some embodiments, the subject is refractory to checkpoint inhibitor therapy.

[0304] In some embodiments, the subject has relapsed from checkpoint inhibitor therapy.

[0305] In some embodiments, the linker connects the C-terminus of A to an N-terminus of B. In some embodiments, the linker connects the N-terminus of A to a C-terminus of B. In some embodiments, the linker connects the C-terminus of A to the N-terminus of the Fab heavy chain polypeptide. In some embodiments, the linker connects the N-terminus of A to the C-terminus of the Fab heavy chain polypeptide.

In some embodiments, the linker connects the C-terminus of A to the N-terminus of the Fab light chain polypeptide. In some embodiments, the linker connects the N-terminus of A to the C-terminus of the Fab light chain polypeptide. In some embodiments, the linker connects the Fab light chain polypeptide to the scFv light chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the scFv heavy chain variable domain.In some embodiments, the linker connects the Fab heavy chain polypeptide to the scFv light chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the scFv heavy chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the N-terminus of the scFv light chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the N-terminus of the scFv heavy chain variable domain. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv heavy chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv light chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv heavy chain variable domain. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

[0306] In some embodiments, the linker is at least 5 amino acids in length. In some embodiments, the linker is no more than 30 amino acids in length. In some embodiments, the linker is at least 5 amino acids and no more than 30 amino acids in length. In some embodiments, the linker is 5 amino acids in length. In some embodiments, the linker is 15 amino acids in length. In some embodiments, the linker is selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1. In some embodiments, L_1 or L_2 has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3. In some embodiments, the linker comprises an amino acid sequence of SEQ ID NO: 18 (GGGGSGGGGSGGGGS) or SEQ ID NO: 19 (GGGGS).

[0307] In some embodiments, the scFv heavy chain variable domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the scFv heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.In some embodiments, the scFv light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the scFv light chain variable domain comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the Fab heavy chain variable domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-

CDR1, the HC-CDR2, and the HC-CDR3 of the Fab heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the Fab light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the Fab light chain variable domain comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0308] In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7 . In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7 and has at least 80% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7. In some embodiments, the scFv heavy chain variable domain comprises an amino acid sequence according to SEQ ID NO: 7. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8 and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8. In some embodiments, the scFv light chain variable domain comprises an amino acid sequence according to SEQ ID NO: 8. In some embodiments, the scFv comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9 and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9. In some embodiments, the scFv comprises an amino acid sequence according to SEQ ID NO: 9. In some embodimens, the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17.In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17 and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17. In some embodiments, the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 17. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16. In some embodiments, the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 16. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21. In some embodiments, the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22. In some embodiments, the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 22.

[0309] Disclosed herein are methods of treating cancer in a subject in need thereof comprising administering to the subject a multispecific antibody that comprises a CD28 binding domain and a PD-L1 binding domain wherein the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain is not administered as part of a treatment regimen with another multispecific antibody that targets a cancer antigen different from PD-L1 or CD28. In some embodiments, the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain is administered to the subject as a single agent therapy. In some embodiments, the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain comprises an IgG framework, an IgA framework, an IgE framework, or an IgM framework. In some embodiments, the CD28 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′. In some embodiments, the PD-L1 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′. In some embodiments, the PD-L1 binding domain comprises a single chain variable fragment and the CD28 binding domain comprises a single chain variable fragment. In some embodiments, the CD28 binding domain comprises an anti-CD28 light chain polypeptide. In some embodiments, the anti-CD28 light chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 light chain. In some embodiments, the CD28 binding domain comprises an anti-CD28 heavy chain polypeptide. In some embodiments, the anti-CD28 heavy chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 heavy chain. In some embodiments, the PD-L1 binding domain comprises an anti-PD-L1 light chain polypeptide. In some embodiments, the anti-PD-L1 light chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 light chain. In some embodiments, the PD-L1 binding domain comprises an anti-PD-L1 heavy chain polypeptide. In some embodiments, the anti- PD-L1 heavy chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 heavy chain. In some embodiments, the multispecific antibody further comprises a fragment crystallizable (Fc) region. In some embodiments, the Fc region comprises an IgG CH2 domain and an IgG CH3 domain. In some embodiments, the Fc region comprises a heterodimeric Fc region. In some embodiments, the Fc region comprises at least one amino acid modification that increases the half-life of the multispecific antibody. In some embodiments, the Fc region comprises at least one amino acid modification that modulates its interaction with an Fc receptor.In some embodiments, the Fc region comprises at least one amino acid modification that increases binding of the Fc region to an Fc receptor. In some embodiments, the Fc region comprises at least one amino acid modification that decreases glycosylation of the Fc region. In some embodiments, the modification is an amino acid substitution, deletion, or addition. In some embodiments, the modification is an amino acid substitution. In some embodiments, the at least one amino acid modification that decreases glycosylation of the Fc region comprises an amino acid substitution at a position corresponding to position N297 of human IgG1, wherein the numbering is according to the EU index of Kabat. In some embodiments, the Fc region is afucosylated.

[0310] In some embodiments, the anti-CD28 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 the anti-CD28 light chain polypeptide: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-CD28 heavy chain polypeptide comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-CD28 heavy chain polypeptide comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0311] In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-PD-L1 heavy chain polypeptide the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0312] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26.

[0313] In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35.

[0314] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0315] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35.

[0316] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29.

[0317] In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38.

[0318] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0319] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38.

[0320] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3. In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32.

[0321] In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3. In some embodiments, the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41.

[0322] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0323] In some embodiments, the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32; and the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise: LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41.

Combination Therapy

[0324] In some embodiments, are methods of treating cancer in a subject in need thereof comprising administering to the subject the multispecific antibodies comprising a CD28 binding domain and a PD-L1 binding domain as described herein in combination with an anti-cancer therapy.

[0325] In some embodiments, the subject is refractory to checkpoint inhibitor therapy.

[0326] In some embodiments, the subject has relapsed from checkpoint inhibitor therapy.

[0327] In some embodiments, the anti-cancer therapy comprises a small molecule, a cell-based therapy, or an antibody-based therapy.

[0328] In some embodiments, the antibody-based therapy is a T cell engager.

[0329] In some embodiments, the T cell engager comprises a formula according to: D-L$_0$-E **(Formula II)**, wherein D comprises an effector cell binding domain that binds to an effector cell antigen, E comprises a tumor antigen binding domain that binds to a tumor antigen, and L$_0$ comprises a linker that connects D to E. In some embodiments, D comprises a single chain variable fragment, a single domain antibody, or a Fab fragment. In some embodiments, D comprises the single chain variable fragment. In some embodiments, E comprises a single chain variable fragment, a single domain antibody, or a Fab fragment. In some embodiments, E comprises the Fab fragment. In some embodiments, the effector cell antigen comprises CD3. In some embodiments, the effector cell binding domain comprises complementary determining regions (CDRs) selected from the group consisting of muromonab-CD3 (OKT3), otelixizumab (TRX4), teplizumab (MGA031), visilizumab (Nuvion), SP34, X35, VIT3, BMA030 (BW264/56), CLB-T3/3, CRIS7, YTH12.5, F111-409, CLB-T3.4.2, TR-66, WT32, SPv-T3b, 11D8, XIII-141, XIII-46, XIII-87, 12F6, T3/RW2-8C8, T3/RW2-4B6, OKT3D, M-T301, SMC2, F101.01, UCHT-1, WT-31, 15865, 15865v12, 15865v16, and 15865v19. In some embodiments, the effector cell binding domain comprises an amino acid sequence as disclosed in **Table 11.**

Table 11. Effector cell binding domain comprises an amino acid sequences (CDRs as determined by IMGT numbering system).

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
SP34.185 CD3: HC: CDR1	GFTFNKYA	89
SP34.185 CD3: HC: CDR2	IRSKYNNYAT	90
SP34.185 CD3: HC: CDR3	VRHGNFGNSYISYWAY	91
SP34.185 CD3: LC: CDR1	TGAVTSGNY	92
SP34.185 CD3: LC: CDR2	GTK	93
SP34.185 CD3: LC: CDR3	VLWYSNRWV	94
SP34.194 CD3: HC: CDR1	GFTFNTYA	95
SP34.194 CD3: HC: CDR2	IRSKYNNYAT	90
SP34.194 CD3: HC: CDR3	VRHGNFGNSYVSWFAY	96
SP34.194 CD3: LC: CDR1	TGAVTTSNY	97
SP34.194 CD3: LC: CDR2	GT	98
SP34.194 CD3: LC: CDR3	ALWYSNLWV	99
SP34.185 scFv (VH – linker 1 – VL)	EVQLVESGGGLVQPGGSLKLSCAAS**GFTFNKYA**MNWVRQAPGKGLEWVAR**IRSKYNNYAT**YYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYC**VRHGNFGNSYISYWAY**WGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTLTCGSS**TGAVTSGNY**PNWVQQKPGQAPRGLIG**GTK**FLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYC**VLWYSNRWV**FGGGTKLTVL	100

SP34.194 scFv (VL – linker 1 – VH)	QTVVTQEPSLTVSPGGTVTLTCRSS**TGAVTTSNY**ANWVQQKPGQAPRGLIG**GT**NKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYC**ALWYSNLWV**FGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLKLSCAAS**GFTFNTYA**MNWVRQAPGKGLEWVAR**IRSKYNNYAT**YYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYC**VRHGNFGNSYVSWFAY**WGQGTLVTVSS	101

[0330] In some embodiments, the tumor antigen comprises epidermal growth factor receptor (EGFR), prostate-specific membrane antigen (PSMA), or tumor-associated calcium signal transducer 2 (referred to herein after as TROP2).

[0331] In some embodiments, the tumor antigen comprises EGFR. In some embodiments, the cancer has cells that express EGFR. In some embodiments, the cancer comprises colorectal cancer (CRC), squamous cell carcinoma of the head and Neck (SCCHN), non-small cell lung cancer (NSCLC), prostate cancer, breast cancer, colon/rectum cancer, head and neck cancer, esophagogastric cancer, liver cancer, glioblastoma, cervical cancer, ovarian cancer, bladder cancer, kidney cancer, or pancreatic cancer. In some embodiments, the tumor antigen binding domain comprises an amino acid sequence as disclosed in **Table 12.**

Table 12. Tumor antigen binding domain amino acid sequences – anti-EGFR (CDRS defined by IMGT)

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
EGFR: LC: CDR1	QSIGTN	102
EGFR: LC: CDR2	YAS	103
EGFR: LC: CDR3	QQNNNWPTT	104
EGFR: HC: CDR1	GFSLTNYG	105
EGFR: HC: CDR2	IWSGGNT	106
EGFR: HC: CDR3	ARALTYYDYEFAY	107
EGFR Fab LC v1	QILLTQSPVILSVSPGERVSFSCRAS**QSIGTN**IHWYQQRTNGSPRLLIK**YAS**ESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYC**QQNNNWPTT**FGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	108
EGFR Fab LC v2	DILLTQSPVILSVSPGERVSFSCRAS**QSIGTN**IHWYQQRTNGSPRLLIK**YAS**ESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYC**QQNNNWPTT**FGAGTKL	109

	ELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
EGFR Fab HC	QVQLKQSGPGLVQPSQSLSITCTVS**GFSLTNYG**VHWVRQSPGKGLEWLGV**IWSGGNT**DYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYC**ARALTYYDYEFAY**WGQGTLVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	110
EGFR Fab HC (N88Q)	QVQLKQSGPGLVQPSQSLSITCTVS**GFSLTNYG**VHWVRQSPGKGLEWLGV**IWSGGNT**DYNTPFTSRLSINKDNSKSQVFFKMNSLQSQDTAIYYC**ARALTYYDYEFAY**WGQGTLVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	111

[0332] In some embodiments, the tumor antigen comprises TROP2. In some embodiments, the cancer has cells that express TROP2. In some instances, the cancer is a solid tumor cancer. In some embodiments, the cancer is lung, breast (e.g. HER2+; ER/PR+; TNBC), cervical, ovarian, colorectal, pancreatic gastric, urothelial, endometrial, head and neck, or glioma. In some embodiments, the tumor antigen binding domain comprises an amino acid sequence as disclosed in **Table 13**

Table 13. Tumor antigen binding domain amino acid sequences – anti-TROP2 (CDRS defined by IMGT)

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
TROP2: HC: CDR1	GYTFTNYG	112
TROP2: HC: CDR2	INTYTGEP	113
TROP2: HC: CDR3	ARGGFGSSYWYFDV	114
TROP2: LC: CDR1	QDVSIA	115
TROP2: LC: CDR2	SAS	116
TROP2: LC: CDR3	QQHYITPLT	117
TROP2 Fab LC	DIQLTQSPSSLSASVGDRVSITCKAS**QDVSIA**VAWYQQKPGKAPKLLIY**SAS**YRYTGVPDRFSGSGSGTDFTLTISSLQPEDFAVYYC**QQHYITPLT**FGAGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	118

TROP2 Fab HC	QVQLQQSGSELKKPGASVKVSCKAS**GYTFTNYG**MNWVKQAPGQGLKWMGW**INTYTGEP**TYTDDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFC**ARGGFGSSYWYFDV**WGQGSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	119

[0333] In some embodiments, the tumor antigen comprises PSMA. In some embodiments, the cancer comprises prostate cancer. In some embodiments, the cancer comprises metastatic castrate-resistant prostate cancer (mCRPC). In some embodiments, the tumor antigen binding domain comprises an amino acid sequence as disclosed in **Table 14.**

Table 14. Tumor antigen binding domain amino acid sequences – anti-PSMA (CDRS defined by IMGT)

Construct Description	**Amino Acid Sequence (N to C)**	**SEQ ID NO:**
PSMA: HC: CDR1	GFAFSRYG	120
PSMA: HC: CDR2	IWYDGSNK	121
PSMA: HC: CDR3	ARGGDFLYYYYYGMDV	122
PSMA: LC: CDR1	QGISNY	123
PSMA: LC: CDR2	EA	124
PSMA: LC: CDR3	QNYNSAPFT	125
006 PSMA Fab LC	DIQMTQSPSSLSASVGDRVTITCRAS**QGISNY**LAWYQQKTGKVPKFLIY**EA**STLQSGVPSRFSGGGSGTDFTLTISSLQPEDVATYYC**QNYNSAPFT**FGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	126
006 PSMA Fab HC	QVQLVESGGGVVQPGRSLRLSCAAS**GFAFSRYG**MHWVRQAPGKGLEWVAV**IWYDGSNK**YYADSVKGRFTISRDNSKNTQYLQMNSLRAEDTAVYYC**ARGGDFLYYYYYGMDV**WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	127

[0334] In some embodiments, the T cell engager molecule is selectively activated in tumor microenvironments.

[0335] In some embodiments, the multispecific antibodies described herein are selectively activated in tumor microenvironments.

[0336] In some embodiments, the T cell engager is according to the following subformula: **P_3-L_3-D-L_0-E (Formula IIa)** wherein D comprises the CD3 binding domain; E comprises the tumor antigen binding domain; L_0 comprises the linker that connects D to E; P_3 comprises a peptide that binds to D and L_3 comprises a linking moiety that connects D to P_3 and is a substrate for a tumor specific protease.

[0337] In some embodiments, the T cell engager is according to the following subformula: **D-L_0-E-L_4-P_4 (Formula IIb)** wherein D comprises the CD3 binding domain; E comprises the tumor antigen binding domain; L_0 comprises the linker that connects D to E; P_4 comprises a peptide that binds to E and L_4 comprises a linking moiety that connects E to P_4 and is a substrate for a tumor specific protease.

[0338] In some embodiments, the T cell engager is according to the following subformula: **P_3-L_3-D-L_0-E-L_4-P_4 (Formula IIc)** wherein D comprises the CD3 binding domain; E comprises the tumor antigen binding domain; L_0 comprises the linker that connects D to E; P_3 comprises a peptide that binds to D and L_3 comprises a linking moiety that connects D to P_3 and is a substrate for a tumor specific protease; P_4 comprises a peptide that binds to E and L_4 comprises a linking moiety that connects E to P_4 and is a substrate for a tumor specific protease.

[0339] In some embodiments, the T cell engager comprises the half-life extending molecule (H_1).

Linking Moiety (L_3 or L_4)

[0340] In some embodiments, L_3 or L_4 is a peptide sequence having at least 5 to no more than 50 amino acids. In some embodiments L_3 or L_4 is a peptide sequence having at least 10 to no more than 30 amino acids. In some embodiments, L_3 or L_4 is a peptide sequence having at least 10 amino acids. In some embodiments, L_3 or L_4 is a peptide sequence having at least 18 amino acids. In some embodiments, L_3 or L_4 is a peptide sequence having at least 26 amino acids. In some embodiments, L_3 or L_4 has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3. In some embodiments, L_3 or L_4 has a formula comprising $(G_2S)_n$, wherein n is an integer of at least 1. In some embodiments, L_3 or L_4 has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1. In some embodiments, the tumor specific protease is selected from the group consisting of metalloprotease, serine protease, cysteine protease, threonine protease, and aspartic protease. In some embodiments L_3 or L_4 comprises a urokinase cleavable amino acid sequence, a matriptase cleavable amino acid sequence, a legumain cleavable amino acid sequence, or a matrix metalloprotease cleavable amino acid sequence. In some embodiments, L_3 or L_4 comprises a sequence as disclosed in **Table 10** or a sequence substantially identical thereto (e.g., a sequence that has 0, 1, or 2 amino acid modifications).

[0341] In some embodiments, L_3 is bound to N-terminus of D. In some embodiments, L_3 is bound to C-terminus of D. In some embodiments, L_4 is bound to N-terminus of E. In some embodiments, L_4 is bound to

C-terminus of E. In some embodiments, P_3 becomes unbound from D when L_3 is cleaved by the tumor specific protease thereby exposing D to CD3. In some embodiments, P_4 becomes unbound from E when L_4 is cleaved by the tumor specific protease thereby exposing E to the tumor antigen.

[0342] In some embodiments, L_3 or L_4, comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof. In some embodiments, the modified amino acid or a modified non-natural amino acid comprises a post-translational modification. In some embodiments, L_3 or L_4 comprise a modification including, but not limited, to acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Modifications are made anywhere to L_3 or L_4 including the peptide backbone, or the amino acid side chains.

Peptide (P_3 and P_4)

[0343] P_3 or P_4 is designed to be optimized for a specific antigen-binding domain through an iterative process of phage display and quantitative binding assays designed to select for those peptides that are able to prevent binding to CD3 or the tumor antigen. A directed evolution-based process that includes phage libraries is used for identifying P_3 or P_4. Multiple cycles of selection and amplification of potential inhibitory peptides that are capable of blocking the antigen binding domain from binding to its target of CD3 or the tumor antigen with the goal of optimizing masked T cell engager antibodies in serum and limiting cleavage, thereby reducing toxicity. Discovery of P_3 or P_4 is depicted in **Fig. 18.**

[0344] In some embodiments, P_3 impairs binding of D to CD3. In some embodiments, P_3 is bound to D through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof. In some embodiments, P_3 is bound to D at or near an antigen binding site. In some embodiments, P_3 becomes unbound from D when L_3 is cleaved by the tumor specific protease thereby exposing D to CD3. In some embodiments, P_3 has less than 70% sequence identity to CD3. In some embodiments, P_3 has less than 75% sequence identity to CD3. In some embodiments, P_3 has less than 80% sequence identity to CD3. In some embodiments, P_3 has less than 85% sequence identity to CD3. In some embodiments, P_3 has less than 90% sequence identity to CD3. In some embodiments, P_3 has less than 95% sequence identity to CD3. In some embodiments, P_3 has less than 98% sequence identity to CD3. In some embodiments, P_3 has less than 99% sequence identity to CD3. In some embodiments, P_3 comprises a de novo amino acid sequence that shares less than 10% sequence identity to CD3.

[0345] In some embodiments, P_4 impairs binding of E to the tumor antigen antigen. In some embodiments, P_4 is bound to E through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof. In some embodiments, P_4 is bound to E at or near an antigen binding site. In some embodiments, P_4 becomes unbound from E when L_4 is cleaved by the tumor specific protease thereby exposing E to the tumor antigen. In some embodiments, P_4 has less than 70% sequence identity to the the tumor antigen. In some embodiments, P_4 has less than 75% sequence identity to the tumor antigen. In some embodiments, P_4 has less than 80% sequence identity to the tumor antigen. In some embodiments, P_4 has less than 85% sequence identity to the tumor antigen. In some embodiments, P_4 has less than 90% sequence identity to the tumor antigen. In some embodiments, P_4 has less than 95% sequence identity to the tumor antigen. In some embodiments, P_4 has less than 98% sequence identity to the tumor antigen. In some embodiments, P_4 has less than 99% sequence identity to the tumor antigen. In some embodiments, P_4 comprises a de novo amino acid sequence that shares less than 10% sequence identity to the tumor antigen.

[0346] In some embodiments, P_3 or P_4 comprises a peptide sequence of at least 5 amino acids in length. In some embodiments, P_3 or P_4 comprises a peptide sequence of at least 6 amino acids in length. In some embodiments, P_3 or P_4 comprises a peptide sequence of at least 10 amino acids in length. In some embodiments, P_3 or P_4 comprises a peptide sequence of at least 10 amino acids in length and no more than 20 amino acids in length. In some embodiments, P_3 or P_4 comprises a peptide sequence of at least 16 amino acids in length. In some embodiments, P_3 or P_4 comprises a peptide sequence of no more than 40 amino acids in length. In some embodiments, P_3 or P_4 comprises at least two cysteine amino acid residues. In some embodiments, P_3 or P_4 comprises a cyclic peptide or a linear peptide. In some embodiments, P_3 or P_4 comprises a cyclic peptide. In some embodiments, P_3 or P_4 comprises a linear peptide.

[0347] In some embodiments, P_3 or P_4 comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof. In some embodiments, the modified amino acid or a modified non-natural amino acid comprises a post-translational modification. In some embodiments P_3 or P_4 comprise a modification including, but not limited to acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Modifications are made anywhere to P_3 or P_4 including the peptide backbone, the amino acid side chains, and the terminus.

[0348] In some embodiments, P_3 or P_4 does not comprise albumin or an albumin fragment. In some embodiments, P_3 or P_4 does not comprise an albumin binding domain.

Production of Antibodies

[0349] In some embodiments, polypeptides described herein (e.g., antibodies and its binding fragments) are produced using any method known in the art to be useful for the synthesis of polypeptides (e.g., antibodies), in particular, by chemical synthesis or by recombinant expression, and are preferably produced by recombinant expression techniques.

[0350] In some instances, an antibody or its binding fragment thereof is expressed recombinantly, and the nucleic acid encoding the antibody or its binding fragment is assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., 1994, BioTechniques 17:242), which involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligation of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0351] Alternatively, a nucleic acid molecule encoding an antibody is optionally generated from a suitable source (e.g., an antibody cDNA library, or cDNA library generated from any tissue or cells expressing the immunoglobulin) by PCR amplification using synthetic primers hybridizable to the 3′ and 5′ ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence.

[0352] In some instances, an antibody or its binding is optionally generated by immunizing an animal, such as a mouse, to generate polyclonal antibodies or, more preferably, by generating monoclonal antibodies, e.g., as described by Kohler and Milstein (1975, Nature 256:495-497) or, as described by Kozbor et al. (1983, Immunology Today 4:72) or Cole et al. (1985 in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). Alternatively, a clone encoding at least the Fab portion of the antibody is optionally obtained by screening Fab expression libraries (e.g., as described in Huse et al., 1989, Science 246:1275-1281) for clones of Fab fragments that bind the specific antigen or by screening antibody libraries (See, e.g., Clackson et al., 1991, Nature 352:624; Hane et al., 1997 Proc. Natl. Acad. Sci. USA 94:4937).

[0353] In some embodiments, techniques developed for the production of “chimeric antibodies” (Morrison et al., 1984, Proc. Natl. Acad. Sci. 81:851-855; Neuberger et al., 1984, Nature 312:604-608; Takeda et al., 1985, Nature 314:452-454) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity are used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region.

[0354] In some embodiments, techniques described for the production of single chain antibodies (U.S. Pat. No. 4,694,778; Bird, 1988, Science 242:423-42; Huston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; and Ward et al., 1989, Nature 334:544-54) are adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli are also optionally used (Skerra et al., 1988, Science 242:1038-1041).

[0355] In some embodiments, an expression vector comprising the nucleotide sequence of an antibody or the nucleotide sequence of an antibody is transferred to a host cell by conventional techniques (e.g., electroporation, liposomal transfection, and calcium phosphate precipitation), and the transfected cells are then cultured by conventional techniques to produce the antibody. In specific embodiments, the expression of the antibody is regulated by a constitutive, an inducible or a tissue, specific promoter.

[0356] In some embodiments, a variety of host-expression vector systems is utilized to express an antibody, or its binding fragment described herein. Such host-expression systems represent vehicles by which the coding sequences of the antibody is produced and subsequently purified, but also represent cells that are, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody or its binding fragment in situ. These include, but are not limited to, microorganisms such as bacteria (e.g., E. coli and B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing an antibody or its binding fragment coding sequences; yeast (e.g., Saccharomyces Pichia) transformed with recombinant yeast expression vectors containing an antibody or its binding fragment coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing an antibody or its binding fragment coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus (CaMV) and tobacco mosaic virus (TMV)) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing an antibody or its binding fragment coding sequences; or mammalian cell systems (e.g., COS, CHO, BH, 293, 293T, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g. the adenovirus late promoter; the vaccinia virus 7.5K promoter).

[0357] For long-term, high-yield production of recombinant proteins, stable expression is preferred. In some instances, cell lines that stably express an antibody are optionally engineered. Rather than using expression vectors that contain viral origins of replication, host cells are transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells are then allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci that in turn are cloned and expanded into cell lines. This method can advantageously be used to engineer cell lines which express the antibody or its binding fragments.

[0358] In some instances, a number of selection systems are used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., 1977, Cell 11:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 192, Proc. Natl. Acad. Sci. USA 48:202), and adenine phosphoribosyltransferase (Lowy et al., 1980, Cell 22:817) genes are employed in tk−, hgprt− or aprt− cells, respectively. Also, antimetabolite resistance are used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., 1980, Proc. Natl. Acad. Sci. USA 77:357; O'Hare et al., 1981, Proc. Natl. Acad. Sci. USA 78:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Clinical Pharmacy 12:488-505; Wu and Wu, 1991, Biotherapy 3:87-95; Tolstoshev, 1993, Ann. Rev. Pharmacol. Toxicol. 32:573-596; Mulligan, 1993, Science 260:926-932; and Morgan and Anderson, 1993, Ann. Rev. Biochem. 62:191-217; May 1993, TIB TECH 11(5):155-215) and hygro, which confers resistance to hygromycin (Santerre et al., 1984, Gene 30:147). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds., 1993, Current Protocols in Molecular Biology, John Wiley & Sons, NY; Kriegler, 1990, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY; and in Chapters 12 and 13, Dracopoli et al. (eds), 1994, Current Protocols in Human Genetics, John Wiley & Sons, NY.; Colberre-Garapin et al., 1981, J. Mol. Biol. 150:1).

[0359] In some instances, the expression levels of an antibody are increased by vector amplification (for a review, see Bebbington and Hentschel, the use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol. 3. (Academic Press, New York, 1987)). When a marker in the vector system expressing an antibody is amplifiable, an increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the nucleotide sequence of the antibody, production of the antibody will also increase (Crouse et al., 1983, Mol. Cell Biol. 3:257).

[0360] In some instances, any method known in the art for purification of an antibody is used, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins.

Expression Vectors

[0361] In some embodiments, vectors include any suitable vectors derived from either a eukaryotic or prokaryotic sources. In some cases, vectors are obtained from bacteria (e.g. E. coli), insects, yeast (e.g. Pichia pastoris), algae, or mammalian sources. Exemplary bacterial vectors include pACYC177, pASK75, pBAD vector series, pBADM vector series, pET vector series, pETM vector series, pGEX vector series, pHAT, pHAT2, pMal-c2, pMal-p2, pQE vector series, pRSET A, pRSET B, pRSET C, pTrcHis2 series, pZA31-Luc, pZE21-MCS-1, pFLAG ATS, pFLAG CTS, pFLAG MAC, pFLAG Shift-12c, pTAC-MAT-1, pFLAG CTC, or pTAC-MAT-2.

[0362] Exemplary insect vectors include pFastBac1, pFastBac DUAL, pFastBac ET, pFastBac HTa, pFastBac HTb, pFastBac HTc, pFastBac M30a, pFastBact M30b, pFastBac, M30c, pVL1392, pVL1393, pVL1393 M10, pVL1393 M11, pVL1393 M12, FLAG vectors such as pPolh-FLAG1 or pPolh-MAT 2, or MAT vectors such as pPolh-MAT1, or pPolh-MAT2.

[0363] In some cases, yeast vectors include Gateway® pDEST™ 14 vector, Gateway® pDEST™ 15 vector, Gateway® pDEST™ 17 vector, Gateway® pDEST™ 24 vector, Gateway® pYES-DEST52 vector, pBAD-DEST49 Gateway® destination vector, pAO815 Pichia vector, pFLD1 Pichi pastoris vector, pGAPZA,B, & C Pichia pastoris vector, pPIC3.5K Pichia vector, pPIC6 A, B, & C Pichia vector, pPIC9K Pichia vector, pTEF1/Zeo, pYES2 yeast vector, pYES2/CT yeast vector, pYES2/NT A, B, & C yeast vector, or pYES3/CT yeast vector.

[0364] Exemplary algae vectors include pChlamy-4 vector or MCS vector.

[0365] Examples of mammalian vectors include transient expression vectors or stable expression vectors. Mammalian transient expression vectors may include pRK5, p3xFLAG-CMV 8, pFLAG-Myc-CMV 19, pFLAG-Myc-CMV 23, pFLAG-CMV 2, pFLAG-CMV 6a,b,c, pFLAG-CMV 5.1, pFLAG-CMV 5a,b,c, p3xFLAG-CMV 7.1, pFLAG-CMV 20, p3xFLAG-Myc-CMV 24, pCMV-FLAG-MAT1, pCMV-FLAG-MAT2, pBICEP-CMV 3, or pBICEP-CMV 4. Mammalian stable expression vector may include pFLAG-CMV 3, p3xFLAG-CMV 9, p3xFLAG-CMV 13, pFLAG-Myc-CMV 21, p3xFLAG-Myc-CMV 25, pFLAG-CMV 4, p3xFLAG-CMV 10, p3xFLAG-CMV 14, pFLAG-Myc-CMV 22, p3xFLAG-Myc-CMV 26, pBICEP-CMV 1, or pBICEP-CMV 2.

[0366] In some instances, a cell-free system is a mixture of cytoplasmic and/or nuclear components from a cell and is used for in vitro nucleic acid synthesis. In some cases, a cell-free system utilizes either prokaryotic cell components or eukaryotic cell components. Sometimes, a nucleic acid synthesis is obtained in a cell-free system based on for example Drosophila cell, Xenopus egg, or HeLa cells. Exemplary cell-free systems include, but are not limited to, E. coli S30 Extract system, E. coli T7 S30 system, or PURExpress®.

Host Cells

[0367] In some embodiments, a host cell includes any suitable cell such as a naturally derived cell or a genetically modified cell. In some instances, a host cell is a production host cell. In some instances, a host cell is a eukaryotic cell. In other instances, a host cell is a prokaryotic cell. In some cases, a eukaryotic cell includes fungi (e.g., yeast cells), animal cell or plant cell. In some cases, a prokaryotic cell is a bacterial cell. Examples of bacterial cell include gram-positive bacteria or gram-negative bacteria. Sometimes the gram-negative bacteria is anaerobic, rod-shaped, or both.

[0368] In some instances, gram-positive bacteria include Actinobacteria, Firmicutes or Tenericutes. In some cases, gram-negative bacteria include Aquificae, Deinococcus-Thermus, Fibrobacteres–Chlorobi/Bacteroidetes (FCB group), Fusobacteria, Gemmatimonadetes, Nitrospirae, Planctomycetes–Verrucomicrobia/ Chlamydiae (PVC group), Proteobacteria, Spirochaetes or Synergistetes. Other bacteria can be Acidobacteria, Chloroflexi, Chrysiogenetes, Cyanobacteria, Deferribacteres, Dictyoglomi, Thermodesulfobacteria or Thermotogae. A bacterial cell can be Escherichia coli, Clostridium botulinum, or Coli bacilli.

[0369] Exemplary prokaryotic host cells include, but are not limited to, BL21, Mach1™, DH10B™, TOP10, DH5α, DH10Bac™, OmniMax™, MegaX™, DH12S™, INV110, TOP10F', INVαF, TOP10/P3, ccdB Survival, PIR1, PIR2, Stbl2™, Stbl3™, or Stbl4™.

[0370] In some instances, animal cells include a cell from a vertebrate or from an invertebrate. In some cases, an animal cell includes a cell from a marine invertebrate, fish, insects, amphibian, reptile, or mammal. In some cases, a fungus cell includes a yeast cell, such as brewer's yeast, baker's yeast, or wine yeast.

[0371] Fungi include ascomycetes such as yeast, mold, filamentous fungi, basidiomycetes, or zygomycetes. In some instances, yeast includes Ascomycota or Basidiomycota. In some cases, Ascomycota includes Saccharomycotina (true yeasts, e.g. Saccharomyces cerevisiae (baker's yeast)) or Taphrinomycotina (e.g.

Schizosaccharomycetes (fission yeasts)). In some cases, Basidiomycota includes Agaricomycotina (e.g. Tremellomycetes) or Pucciniomycotina (e.g. Microbotryomycetes).

[0372] Exemplary yeast or filamentous fungi include, for example, the genus: Saccharomyces, Schizosaccharomyces, Candida, Pichia, Hansenula, Kluyveromyces, Zygosaccharomyces, Yarrowia, Trichosporon, Rhodosporidi, Aspergillus, Fusarium, or Trichoderma. Exemplary yeast or filamentous fungi include, for example, the species: Saccharomyces cerevisiae, Schizosaccharomyces pombe, Candida utilis, Candida boidini, Candida albicans, Candida tropicalis, Candida stellatoidea, Candida glabrata, Candida krusei, Candida parapsilosis, Candida guilliermondii, Candida viswanathii, Candida lusitaniae, Rhodotorula mucilaginosa, Pichia metanolica, Pichia angusta, Pichia pastoris, Pichia anomala, Hansenula polymorpha, Kluyveromyces lactis, Zygosaccharomyces rouxii, Yarrowia lipolytica, Trichosporon pullulans, Rhodosporidium toru-Aspergillus niger, Aspergillus nidulans, Aspergillus awamori, Aspergillus oryzae, Trichoderma reesei, Yarrowia lipolytica, Brettanomyces bruxellensis, Candida stellata, Schizosaccharomyces pombe, Torulaspora delbrueckii, Zygosaccharomyces bailii, Cryptococcus neoformans, Cryptococcus gattii, or Saccharomyces boulardii.

[0373] Exemplary yeast host cells include, but are not limited to, Pichia pastoris yeast strains such as GS115, KM71H, SMD1168, SMD1168H, and X-33; and Saccharomyces cerevisiae yeast strain such as INVSc1.

[0374] In some instances, additional animal cells include cells obtained from a mollusk, arthropod, annelid or sponge. In some cases, an additional animal cell is a mammalian cell, e.g., from a primate, ape, equine, bovine, porcine, canine, feline or rodent. In some cases, a rodent includes mouse, rat, hamster, gerbil, hamster, chinchilla, fancy rat, or guinea pig.

[0375] Exemplary mammalian host cells include, but are not limited to, 293A cell line, 293FT cell line, 293F cells , 293 H cells, CHO DG44 cells, CHO-S cells, CHO-K1 cells, FUT8 KO CHOK1, Expi293F™ cells, Flp-In™ T-REx™ 293 cell line, Flp-In™-293 cell line, Flp-In™-3T3 cell line, Flp-In™-BHK cell line, Flp-In™-CHO cell line, Flp-In™-CV-1 cell line, Flp-In™-Jurkat cell line, FreeStyle™ 293-F cells, FreeStyle™ CHO-S cells, GripTite™ 293 MSR cell line, GS-CHO cell line, HepaRG™ cells, T-REx™ Jurkat cell line, Per.C6 cells, T-REx™-293 cell line, T-REx™-CHO cell line, and T-REx™-HeLa cell line.

[0376] In some instances, a mammalian host cell is a stable cell line, or a cell line that has incorporated a genetic material of interest into its own genome and has the capability to express the product of the genetic material after many generations of cell division. In some cases, a mammalian host cell is a transient cell line, or a cell line that has not incorporated a genetic material of interest into its own genome and does not have the capability to express the product of the genetic material after many generations of cell division.

[0377] Exemplary insect host cells include, but are not limited to, Drosophila S2 cells, Sf9 cells, Sf21 cells, High Five™ cells, and expresSF+® cells.

[0378] In some instances, plant cells include a cell from algae. Exemplary insect cell lines include, but are not limited to, strains from Chlamydomonas reinhardtii 137c, or Synechococcus elongatus PPC 7942.

Articles of Manufacture

[0379] In another aspect of the disclosure, an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic.

[0380] The label or package insert indicates that the composition is used for treating the condition of choice. The article of manufacture in this embodiment of the disclosure may further comprise a package insert indicating that the compositions can be used to treat a particular condition.

[0381] Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

EMBODIMENTS

[0382] Embodiment 1 comprises a multispecific antibody comprising a CD28 binding domain and a PD-L1 binding domain.

[0383] Embodiment 2 comprises a multispecific antibody of embodiment 1, wherein when the CD28 binding domain is a single chain variable fragment (scFv), then the PD-L1 binding domain is not a scFv.

[0384] Embodiment 3 comprises a multispecific antibody of any one of embodiments 1-2, wherein the multispecific antibody is according to the following formula: A-L-B (Formula I) wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; and L comprises a linker that connects A to B.

[0385] Embodiment 4 comprises a multispecific antibody of any one of embodiments 1-3, wherein the CD28 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′.

[0386] Embodiment 5 comprises a multispecific antibody of embodiment 4, wherein the CD28 binding domain comprises the single chain variable fragment.

[0387] Embodiment 6 comprises a multispecific antibody of embodiment 4, wherein the CD28 binding domain comprises the single domain antibody.

[0388] Embodiment 7 comprises a multispecific antibody of embodiment 4, wherein the CD28 binding domain comprises the Fab or the Fab′.

[0389] Embodiment 8 comprises a multispecific antibody of any one of embodiments 1-7, wherein the PD-L1 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′.

[0390] Embodiment 9 comprises a multispecific antibody of embodiment 8, wherein the PD-L1 binding domain comprises the Fab or the Fab′.

[0391] Embodiment 10 comprises a multispecific antibody of embodiment 8, wherein the PD-L1 binding domain comprises the Fab or the Fab′ and the CD28 binding domain comprises the single chain variable fragment.

[0392] Embodiment 11 comprises a multispecific antibody of embodiment 9, wherein the PD-L1 binding domain that comprises the Fab or the Fab′ comprises a Fab heavy chain polypeptide comprising a Fab heavy chain variable domain and a Fab light chain polypeptide comprising a Fab light chain variable domain.

[0393] Embodiment 12 comprises a multispecific antibody of embodiment 10, wherein the CD28 binding domain that comprises the single chain variable fragment comprises a scFv heavy chain variable domain and a scFv light chain variable domain.

[0394] Embodiment 13 comprises a multispecific antibody of any one of embodiments 1-12, wherein the linker connects the C-terminus of A to an N-terminus of B.

[0395] Embodiment 14 comprises a multispecific antibody of any one of embodiments 1-12, wherein the linker connects the N-terminus of A to a C-terminus of B.

[0396] Embodiment 15 comprises a multispecific antibody of any one of embodiments 11 or 12, wherein the linker connects the C-terminus of A to the N-terminus of the Fab heavy chain polypeptide.

[0397] Embodiment 16 comprises a multispecific antibody of any one of embodiments 11 or 12, wherein the linker connects the N-terminus of A to the C-terminus of the Fab heavy chain polypeptide.

[0398] Embodiment 17 comprises a multispecific antibody of any one of embodiments 11 or 12, wherein the linker connects the C-terminus of A to the N-terminus of the Fab light chain polypeptide.

[0399] Embodiment 18 comprises a multispecific antibody of any one of embodiments 11 or 12, wherein the linker connects the N-terminus of A to the C-terminus of the Fab light chain polypeptide.

[0400] Embodiment 19 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab light chain polypeptide to the scFv light chain variable domain.

[0401] Embodiment 20 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab light chain polypeptide to the scFv heavy chain variable domain.

[0402] Embodiment 21 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab heavy chain polypeptide to the scFv light chain variable domain.

[0403] Embodiment 22 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab heavy chain polypeptide to the scFv heavy chain variable domain.

[0404] Embodiment 23 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab light chain polypeptide to the N-terminus of the scFv light chain variable domain.

[0405] Embodiment 24 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain.

[0406] Embodiment 25 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab light chain polypeptide to the N-terminus of the scFv heavy chain variable domain.

[0407] Embodiment 26 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

[0408] Embodiment 27 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv light chain variable domain.

[0409] Embodiment 28 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain.

[0410] Embodiment 29 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv heavy chain variable domain.

[0411] Embodiment 30 comprises a multispecific antibody of embodiment 12, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

[0412] Embodiment 31 comprises a multispecific antibody of any one of embodiments 3-30, wherein the linker is at least 5 amino acids in length.

[0413] Embodiment 32 comprises a multispecific antibody of any one of embodiments 3-31, wherein the linker is no more than 30 amino acids in length.

[0414] Embodiment 33 comprises a multispecific antibody of any one of embodiments 3-32, wherein the linker is at least 5 amino acids and no more than 30 amino acids in length.

[0415] Embodiment 34 comprises a multispecific antibody of any one of embodiments 3-33, wherein the linker is 5 amino acids in length.

[0416] Embodiment 35 comprises a multispecific antibody of any one of embodiments 3-33, wherein the linker is 15 amino acids in length.

[0417] Embodiment 36 comprises a multispecific antibody of any one of embodiments 3-30, wherein the linker is selected from the group consisting of $(G_2S)_n$, (GS)n, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

[0418] Embodiment 37 comprises a multispecific antibody of any one of embodiments 3-30, wherein L has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3.

[0419] Embodiment 38 comprises a multispecific antibody of any one of embodiments 3-30, wherein the L comprises an amino acid sequence of SEQ ID NO: 18 (GGGGSGGGGSGGGGS) or SEQ ID NO: 19 (GGGGS).

[0420] Embodiment 39 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv heavy chain variable domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the scFv heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0421] Embodiment 40 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the scFv light chain variable domain comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID

NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0422] Embodiment 41 comprises a multispecific antibody of any one of embodiments 12-38, wherein the Fab heavy chain variable domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the Fab heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; or HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; or HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32; and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0423] Embodiment 42 comprises a multispecific antibody of any one of embodiments 12-38, wherein the Fab light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the Fab light chain variable domain comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15; LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35; LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38; or LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41; and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0424] Embodiment 43 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv heavy chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 7.

[0425] Embodiment 44 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7

[0426] Embodiment 45 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7.

[0427] Embodiment 46 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7 and has at least 80% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7.

[0428] Embodiment 47 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv heavy chain variable domain comprises an amino acid sequence according to SEQ ID NO: 7.

[0429] Embodiment 48 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 8.

[0430] Embodiment 49 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8.

[0431] Embodiment 50 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8.

[0432] Embodiment 51 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8 and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8.

[0433] Embodiment 52 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv light chain variable domain comprises an amino acid sequence according to SEQ ID NO: 8.

[0434] Embodiment 53 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 9.

[0435] Embodiment 54 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9.

[0436] Embodiment 55 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9.

[0437] Embodiment 56 comprises a multispecific antibody of any one of embodiments 12-38, wherein the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9 and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9.

[0438] Embodiment 57 comprises a multispecific antibody of any one of embodiments 11-38, wherein the scFv comprises an amino acid sequence according to SEQ ID NO: 9.

[0439] Embodiment 58 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47.

[0440] Embodiment 59 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

[0441] Embodiment 60 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

[0442] Embodiment 61 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17 and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

[0443] Embodiment 62 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47.

[0444] Embodiment 63 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46.

[0445] Embodiment 64 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

[0446] Embodiment 65 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

[0447] Embodiment 66 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

[0448] Embodiment 67 comprises a multispecific antibody of any one of embodiments 11-57, wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46.

[0449] Embodiment 68 comprises a multispecific antibody of any one of embodiments 12-38, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 21.

[0450] Embodiment 69 comprises a multispecific antibody of any one of embodiments 12-38, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0451] Embodiment 70 comprises a multispecific antibody of any one of embodiments 12-38, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0452] Embodiment 71 comprises a multispecific antibody of any one of embodiments 12-38, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21.

[0453] Embodiment 72 comprises a multispecific antibody of any one of embodiments 12-38, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 22.

[0454] Embodiment 73 comprises a multispecific antibody of any one of embodiments 12-38, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0455] Embodiment 74 comprises a multispecific antibody of any one of embodiments 12-38, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0456] Embodiment 75 comprises a multispecific antibody of any one of embodiments 12-38, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 22.

[0457] Embodiment 76 comprises a multispecific antibody comprising a CD28 binding domain and a PD-L1 binding domain wherein the multispecific antibody is selectively activated in a tumor microenvironment.

[0458] Embodiment 77 comprises a multispecific antibody of embodiment 76, wherein the CD28 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′.

[0459] Embodiment 78 comprises a multispecific antibody of embodiment 77, wherein the CD28 binding domain comprises the single chain variable fragment.

[0460] Embodiment 79 comprises a multispecific antibody of embodiment 77, wherein the CD28 binding domain comprises the single domain antibody.

[0461] Embodiment 80 comprises a multispecific antibody of embodiment 77, wherein the CD28 binding domain comprises the Fab or the Fab′.

[0462] Embodiment 81 comprises a multispecific antibody of any one of embodiments 76-81, wherein the PD-L1 binding domain comprises a single chain variable fragment, single domain antibody, a Fab, or a Fab′.

[0463] Embodiment 82 comprises a multispecific antibody of embodiment 81, wherein the PD-L1 binding domain comprises the Fab or the Fab′.

[0464] Embodiment 83 comprises a multispecific antibody of embodiment 81, wherein the PD-L1 binding domain comprises the Fab or the Fab′ and the CD28 binding domain comprises the single chain variable fragment.

[0465] Embodiment 84 comprises a multispecific antibody of any one of embodiments 81-83, wherein the PD-L1 binding domain that comprises the Fab or the Fab′ comprises a Fab heavy chain polypeptide comprising a Fab heavy chain variable domain and a Fab light chain polypeptide comprising a Fab light chain variable domain.

[0466] Embodiment 85 comprises a multispecific antibody of any one of embodiments 77-78, or 80-84, wherein the CD28 binding domain that comprises the single chain variable fragment comprises a scFv heavy chain variable domain and a scFv light chain variable domain.

[0467] Embodiment 86 comprises a multispecific antibody of any one of embodiments 76-85, wherein the multispecific antibody is according to the following formula: P_1-L_1-A-L-B (Formula Ia) wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; L comprises a linker that connects A to B; P_1 comprises a peptide that binds to A and L_1 comprises a linking moiety that connects A to P_1 and is a substrate for a tumor specific protease.

[0468] Embodiment 87 comprises a multispecific antibody of any one of embodiments 76-85, wherein the multispecific antibody is according to the following formula: A-L-B-L_2-P_2 (Formula Ib) wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; L comprises a linker that connects A to B; P_2 comprises a peptide that binds to B and L_2 comprises a linking moiety that connects B to P_2 and is a substrate for a tumor specific protease.

[0469] Embodiment 88 comprises a multispecific antibody of any one of embodiments 76-85, wherein the multispecific antibody is according to the following formula: P_1-L_1-A-L-B-L_2-P_2 (Formula Ic) wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; L comprises a linker that connects A to B; P1 comprises a peptide that binds to A and L_1 comprises a linking moiety that connects A to P_1 and is a substrate for a tumor specific protease; P_2 comprises a peptide that binds to B and L_2 comprises a linking moiety that connects B to P_2 and is a substrate for a tumor specific protease.

[0470] Embodiment 89 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the C-terminus of A to an N-terminus of B.

[0471] Embodiment 90 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the N-terminus of A to a C-terminus of B.

[0472] Embodiment 91 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the C-terminus of A to the N-terminus of the Fab heavy chain polypeptide.

[0473] Embodiment 92 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the N-terminus of A to the C-terminus of the Fab heavy chain polypeptide.

[0474] Embodiment 93 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the C-terminus of A to the N-terminus of the Fab light chain polypeptide.

[0475] Embodiment 94 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the N-terminus of A to the C-terminus of the Fab light chain polypeptide.

[0476] Embodiment 95 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab light chain polypeptide to the scFv light chain variable domain.

[0477] Embodiment 96 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab light chain polypeptide to the scFv heavy chain variable domain.

[0478] Embodiment 97 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab heavy chain polypeptide to the scFv light chain variable domain.

[0479] Embodiment 98 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab heavy chain polypeptide to the scFv heavy chain variable domain.

[0480] Embodiment 99 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab light chain polypeptide to the N-terminus of the scFv light chain variable domain.

[0481] Embodiment 100 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain.

[0482] Embodiment 101 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab light chain polypeptide to the N-terminus of the scFv heavy chain variable domain.

[0483] Embodiment 102 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

[0484] Embodiment 103 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv light chain variable domain.

[0485] Embodiment 104 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain.

[0486] Embodiment 105 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv heavy chain variable domain.

[0487] Embodiment 106 comprises a multispecific antibody of any one of embodiments 86-88, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

[0488] Embodiment 107 comprises a multispecific antibody of any one of embodiments 86-106, wherein the linker is at least 5 amino acids in length.

[0489] Embodiment 108 comprises a multispecific antibody of any one of embodiments 86-107, wherein the linker is no more than 30 amino acids in length.

[0490] Embodiment 109 comprises a multispecific antibody of any one of embodiments 86-108, wherein the linker is at least 5 amino acids and no more than 30 amino acids in length.

[0491] Embodiment 110 comprises a multispecific antibody of any one of embodiments 86-109, wherein the linker is 5 amino acids in length.

[0492] Embodiment 111 comprises a multispecific antibody of any one of embodiments 86-109, wherein the linker is 15 amino acids in length.

[0493] Embodiment 112 comprises a multispecific antibody of any one of embodiments 86-109, wherein the linker is selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

[0494] Embodiment 113 comprises a multispecific antibody of any one of embodiments 86-109, wherein L has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3.

[0495] Embodiment 114 comprises a multispecific antibody of any one of embodiments 86-109, wherein the L comprises an amino acid sequence of SEQ ID NO: 18 (GGGGSGGGGSGGGGS) or SEQ ID NO: 19 (GGGGS).

[0496] Embodiment 115 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv heavy chain variable domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the scFv heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0497] Embodiment 116 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the scFv light chain variable domain comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0498] Embodiment 117 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab heavy chain variable domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the Fab heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; or HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; or HC-CDR1: SEQ ID

NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32; and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0499] Embodiment 118 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the Fab light chain variable domain comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15; LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35; LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38; or LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41; and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0500] Embodiment 119 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv heavy chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 7.

[0501] Embodiment 120 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7

[0502] Embodiment 121 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7.

[0503] Embodiment 122 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7 and has at least 80% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7.

[0504] Embodiment 123 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv heavy chain variable domain comprises an amino acid sequence according to SEQ ID NO: 7.

[0505] Embodiment 124 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 8.

[0506] Embodiment 125 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8.

[0507] Embodiment 126 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8.

[0508] Embodiment 127 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8 and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8.

[0509] Embodiment 128 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv light chain variable domain comprises an amino acid sequence according to SEQ ID NO: 8.

[0510] Embodiment 129 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 9.

[0511] Embodiment 130 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9.

[0512] Embodiment 131 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9.

[0513] Embodiment 132 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9 and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9.

[0514] Embodiment 133 comprises a multispecific antibody of any one of embodiments 86-114, wherein the scFv comprises an amino acid sequence according to SEQ ID NO: 9.

[0515] Embodiment 134 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47.

[0516] Embodiment 135 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

[0517] Embodiment 136 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

[0518] Embodiment 137 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17 and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

[0519] Embodiment 138 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47.

[0520] Embodiment 139 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46.

[0521] Embodiment 140 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

[0522] Embodiment 141 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

[0523] Embodiment 142 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

[0524] Embodiment 143 comprises a multispecific antibody of any one of embodiments 86-114, wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46.

[0525] Embodiment 144 comprises a multispecific antibody of any one of embodiments 86-114, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 21.

[0526] Embodiment 145 comprises a multispecific antibody of any one of embodiments 86-114, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0527] Embodiment 146 comprises a multispecific antibody of any one of embodiments 86-114, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0528] Embodiment 147 comprises a multispecific antibody of any one of embodiments 86-114, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21.

[0529] Embodiment 148 comprises a multispecific antibody of any one of embodiments 86-114, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 22.

[0530] Embodiment 149 comprises a multispecific antibody of any one of embodiments 86-114, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0531] Embodiment 150 comprises a multispecific antibody of any one of embodiments 86-114, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0532] Embodiment 151 comprises a multispecific antibody of any one of embodiments 86-114, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 22.

[0533] Embodiment 152 comprises a multispecific antibody of any one of embodiments 86-151, wherein the multispecific antibodies of Formula Ia, Formula Ib, Formula Ic further comprise a half-life extending molecule (H_1).

[0534] Embodiment 153 comprises a multispecific antibody of embodiment 152, wherein H_1 is connected to P_1.

[0535] Embodiment 154 comprises a multispecific antibody of embodiment 152, wherein H_1 is connected to P_2.

[0536] Embodiment 155 comprises a multispecific antibody of any one of embodiments 152-154, wherein H_1 does not block A binding to CD28.

[0537] Embodiment 156 comprises a multispecific antibody of any one of embodiments 152-155, wherein H_1 does not block B binding to PD-L1.

[0538] Embodiment 157 comprises a multispecific antibody of any one of embodiments 152-156, H_1 comprises a linking moiety (L_5) that connects H_1 to P_1 or H_1 to P_2.

[0539] Embodiment 158 comprises a multispecific antibody of any one of embodiments 152-157, wherein the half-life extending molecule ($H_{1)}$ does not have binding affinity to PD-L1.

[0540] Embodiment 159 comprises a multispecific antibody of any one of embodiments 152-158, wherein the half-life extending molecule (H_1) does not have binding affinity to CD28.

[0541] Embodiment 160 comprises a multispecific antibody of any one of embodiments 152-159, wherein the half-life extending molecule ($H_{1)}$ does not shield the multispecific antibody from CD28.

[0542] Embodiment 161 comprises a multispecific antibody of any one of embodiments 152-160, wherein H_1 comprises a sequence according to SEQ ID NOs: 54-57.

[0543] Embodiment 162 comprises a multispecific antibody of any one of embodiments 152-161, wherein H_1 comprises an amino acid sequence that has repetitive sequence motifs.

[0544] Embodiment 163 comprises a multispecific antibody of any one of embodiments 152-162, wherein H_1 comprises an amino acid sequence that has highly ordered secondary structure.

[0545] Embodiment 164 comprises a multispecific antibody of any one of embodiments 152-163, wherein H_1 comprises a polymer.

[0546] Embodiment 165 comprises a multispecific antibody of embodiment 164, wherein the polymer is polyethylene glycol (PEG).

[0547] Embodiment 166 comprises a multispecific antibody of any one of embodiments of embodiments 152-163, wherein H_1 comprises albumin.

[0548] Embodiment 167 comprises a multispecific antibody of any one of embodiments of embodiments 152-163, wherein H_1 comprises an Fc domain.

[0549] Embodiment 168 comprises a multispecific antibody of any one of embodiments of embodiment 166, wherein the albumin is serum albumin.

[0550] Embodiment 169 comprises a multispecific antibody of embodiment 168, wherein the albumin is human serum albumin.

[0551] Embodiment 170 comprises a multispecific antibody of any one of embodiments of embodiments 152-163, wherein H_1 comprises a polypeptide, a ligand, or a small molecule.

[0552] Embodiment 171 comprises a multispecific antibody of embodiment 170, wherein the polypeptide, the ligand or the small molecule binds serum protein or a fragment thereof, a circulating immunoglobulin or a fragment thereof, or CD35/CR1.

[0553] Embodiment 172 comprises a multispecific antibody of embodiment 170, wherein the serum protein comprises a thyroxine-binding protein, a transthyretin, a 1-acid glycoprotein, a transferrin, transferrin receptor or a transferrin-binding portion thereof, a fibrinogen, or an albumin.

[0554] Embodiment 173 comprises a multispecific antibody of embodiment 171, wherein the circulating immunoglobulin molecule comprises IgGl, IgG2, IgG3, IgG4, slgA, IgM or IgD.

[0555] Embodiment 174 comprises a multispecific antibody of embodiment 171, wherein the serum protein is albumin.

[0556] Embodiment 175 comprises a multispecific antibody of embodiment 170, wherein the polypeptide is an antibody.

[0557] Embodiment 176 comprises a multispecific antibody of embodiment 175, wherein the antibody comprises a single domain antibody, a single chain variable fragment or a Fab.

[0558] Embodiment 177 comprises a multispecific antibody of embodiment 176, wherein the single domain antibody comprises a single domain antibody that binds to albumin.

[0559] Embodiment 178 comprises a multispecific antibody of embodiment 177, wherein the single domain antibody is a human or humanized antibody.

[0560] Embodiment 179 comprises a multispecific antibody of any one of embodiments 176-178, wherein the single domain antibody is selected from the group consisting of 645gH1gL1, 645dsgH5gL4, 23-13-A01 -sc02, A10m3 or a fragment thereof, DOM7r-31, DOM7h-11-15, Alb-1, Alb-8, Alb-23, 10G, 10E and SA21.

[0561] Embodiment 180 comprises a multispecific antibody of embodiment 176, wherein the single domain antibody comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the single domain antibody comprise: HC-CDR1: SEQ ID NO: 54, HC-CDR2: SEQ ID NO: 55, and HC-CDR3: SEQ ID NO: 56; and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of the HC-CDR1, HC-CDR2, or HC-CDR3.

[0562] Embodiment 181 comprises a multispecific antibody of embodiment 176, wherein H_1 comprises an amino acid sequence according to SEQ ID NO: 57.

[0563] Embodiment 182 comprises a multispecific antibody of embodiment 176, wherein H_1 comprises an amino acid sequence that has at least 80% sequence identity to SEQ ID NO: 57.

[0564] Embodiment 183 comprises a multispecific antibody of embodiment 176, wherein H_1 comprises an amino acid sequence that has at least 85% sequence identity to SEQ ID NO: 57.

[0565] Embodiment 184 comprises a multispecific antibody of embodiment 176, wherein H_1 comprises an amino acid sequence that has at least 90% sequence identity to SEQ ID NO: 57.

[0566] Embodiment 185 comprises a multispecific antibody of embodiment 176, wherein H_1 comprises an amino acid sequence that has at least 95% sequence identity to SEQ ID NO: 57.

[0567] Embodiment 186 comprises a multispecific antibody of embodiment 176, wherein H_1 comprises an amino acid sequence that has at least 99% sequence identity to SEQ ID NO: 57.

[0568] Embodiment 187 comprises a multispecific antibody of any one of embodiments 152-186, wherein H_1 comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof.

[0569] Embodiment 188 comprises a multispecific antibody of embodiment 187, wherein the modified amino acid or a modified non-natural amino acid comprises a post-translational modification.

[0570] Embodiment 189 comprises a multispecific antibody of any one of embodiments 152-188, wherein H_1 comprises a linking moiety (L_5) that connects H_1 to P_1 or P_2.

[0571] Embodiment 190 comprises a multispecific antibody of embodiment 189, wherein L_5 is a peptide sequence having at least 5 to no more than 50 amino acids.

[0572] Embodiment 191 comprises a multispecific antibody of embodiment 190, wherein $L_5$is a peptide sequence having at least 10 to no more than 30 amino acids.

[0573] Embodiment 192 comprises a multispecific antibody of embodiment 191, wherein L_5 is a peptide sequence having at least 10 amino acids.

[0574] Embodiment 193 comprises a multispecific antibody of embodiment 192, wherein L_5 is a peptide sequence having at least 18 amino acids.

[0575] Embodiment 194 comprises a multispecific antibody of embodiment 193, wherein L_5 is a peptide sequence having at least 26 amino acids.

[0576] Embodiment 195 comprises a multispecific antibody of embodiment 189, wherein L_5 has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

[0577] Embodiment 196 comprises a multispecific antibody of any one of embodiments 86-195, wherein L_1 or L_2 is a peptide sequence having at least 5 to no more than 50 amino acids.

[0578] Embodiment 197 comprises a multispecific antibody of any one of embodiments 86-195, wherein L_1 or L_2 is a peptide sequence having at least 10 to no more than 30 amino acids.

[0579] Embodiment 198 comprises a multispecific antibody of any one of embodiments 86-195, wherein L_1or L_2 is a peptide sequence having at least 10 amino acids.

[0580] Embodiment 199 comprises a multispecific antibody of any one of embodiments 86-195, wherein L_1 or L_2 is a peptide sequence having at least 18 amino acids.

[0581] Embodiment 200 comprises a multispecific antibody of any one of embodiments 86-195, wherein L_1 or L_2 is a peptide sequence having at least 26 amino acids.

[0582] Embodiment 201 comprises a multispecific antibody of any one of embodiments 86-195, wherein L_1 or L_2 has a formula comprising (G2S)n (SEQ ID NO: 233), wherein n is an integer from 1 to 3.

[0583] Embodiment 202 comprises a multispecific antibody of any one of embodiments 86-195, wherein L_1 or L_2 has a formula comprising (G2S)n, wherein n is an integer of at least 1.

[0584] Embodiment 203 comprises a multispecific antibody of any one of embodiments 86-195, wherein L_1 or L_2 has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58),

$(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

[0585] Embodiment 204 comprises a multispecific antibody of any one of embodiments 86-203, wherein the tumor specific protease is selected from the group consisting of metalloprotease, serine protease, cysteine protease, threonine protease, and aspartic protease.

[0586] Embodiment 205 comprises a multispecific antibody of any one of embodiments 86-203, wherein L_1 or L_2 comprises a urokinase cleavable amino acid sequence, a matriptase cleavable amino acid sequence, a legumain cleavable amino acid sequence, or a matrix metalloprotease cleavable amino acid sequence.

[0587] Embodiment 206 comprises a multispecific antibody of any one of embodiments 86-205, wherein L_1 or L_2 comprises a sequence according to SEQ ID NOs: 18-19, 62-88.

[0588] Embodiment 207 comprises a multispecific antibody of any one of embodiments 86-206, wherein L_1 is bound to N-terminus of A.

[0589] Embodiment 208 comprises a multispecific antibody of any one of embodiments 86-206, wherein L_1 is bound to C-terminus of A.

[0590] Embodiment 209 comprises a multispecific antibody of any one of embodiments 86-206, wherein L_2 is bound to N-terminus of B.

[0591] Embodiment 210 comprises a multispecific antibody of any one of embodiments 86-206, wherein L_2 is bound to C-terminus of B.

[0592] Embodiment 211 comprises a multispecific antibody of any one of embodiments 86-206, wherein P_1 becomes unbound from A when L_1 is cleaved by the tumor specific protease thereby exposing A to CD28.

[0593] Embodiment 212 comprises a multispecific antibody of any one of embodiments 86-206, wherein P_2 becomes unbound from B when L_2 is cleaved by the tumor specific protease thereby exposing B to PD-L1.

[0594] Embodiment 213 comprises a multispecific antibody of any one of embodiments 86-213, wherein L_1 or L_2, comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof.

[0595] Embodiment 214 comprises a multispecific antibody of embodiment 213, wherein the modified amino acid or a modified non-natural amino acid comprises a post-translational modification.

[0596] Embodiment 215 comprises a multispecific antibody of any one of embodiments 86-214, wherein P_1 impairs binding of A to CD28.

[0597] Embodiment 216 comprises a multispecific antibody of any one of embodiments 86-215, wherein P_1 is bound to A through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof.

[0598] Embodiment 217 comprises a multispecific antibody of any one of embodiments 86-216, wherein P_1 is bound to A at or near an antigen binding site.

[0599] Embodiment 218 comprises a multispecific antibody of any one of embodiments 86-217, wherein P_1 becomes unbound from A when L1 is cleaved by the tumor specific protease thereby exposing A to CD28.

[0600] Embodiment 219 comprises a multispecific antibody of any one of embodiments 86-218, wherein P_1 has less than 75% sequence identity to CD28.

[0601] Embodiment 220 comprises a multispecific antibody of any one of embodiments 86-218, wherein P_1 has less than 80% sequence identity to CD28.

[0602] Embodiment 221 comprises a multispecific antibody of any one of embodiments 86-218, wherein P_1 has less than 85% sequence identity to CD28.

[0603] Embodiment 222 comprises a multispecific antibody of any one of embodiments 86-218, wherein P_1 has less than 90% sequence identity to CD28.

[0604] Embodiment 223 comprises a multispecific antibody of any one of embodiments 86-218, wherein P_1 has less than 95% sequence identity to CD28.

[0605] Embodiment 224 comprises a multispecific antibody of any one of embodiments 86-218, wherein P_1 comprises a de novo amino acid sequence that shares less than 10% sequence identity to CD28.

[0606] Embodiment 225 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 impairs binding of B to PD-L1.

[0607] Embodiment 226 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 is bound to B through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof.

[0608] Embodiment 227 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 is bound to B at or near an antigen binding site.

[0609] Embodiment 228 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 becomes unbound from B when L_2 is cleaved by the tumor specific protease thereby exposing B to the PD-L1.

[0610] Embodiment 229 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 has less than 70% sequence identity to the PD-L1.

[0611] Embodiment 230 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 has less than 75% sequence identity to the PD-L1.

[0612] Embodiment 231 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 has less than 80% sequence identity to the PD-L1.

[0613] Embodiment 232 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 has less than 85% sequence identity to the PD-L1.

[0614] Embodiment 233 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 has less than 90% sequence identity to the PD-L1.

[0615] Embodiment 234 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 has less than 95% sequence identity to the PD-L1.

[0616] Embodiment 235 comprises a multispecific antibody of any one of embodiments 87-224, wherein P_2 comprises a de novo amino acid sequence that shares less than 10% sequence identity to the PD-L1.

[0617] Embodiment 236 comprises a multispecific antibody of any one of embodiments 86-235, wherein P_1 or P_2 comprises a peptide sequence of at least 5 amino acids in length.

[0618] Embodiment 237 comprises a multispecific antibody of any one of embodiments 86-235, wherein P_1 or P_2 comprises a peptide sequence of at least 6 amino acids in length.

[0619] Embodiment 238 comprises a multispecific antibody of any one of embodiments 86-235, wherein P_1 or P_2 comprises a peptide sequence of at least 10 amino acids in length.

[0620] Embodiment 239 comprises a multispecific antibody of any one of embodiments 86-235, wherein P_1 or P_2 comprises a peptide sequence of at least 10 amino acids in length and no more than 20 amino acids in length.

[0621] Embodiment 240 comprises a multispecific antibody of any one of embodiments 86-235, wherein P_1 or P_2 comprises a peptide sequence of at least 16 amino acids in length.

[0622] Embodiment 241 comprises a multispecific antibody of any one of embodiments 86-235, wherein P_1 or P_2 comprises a peptide sequence of no more than 40 amino acids in length.

[0623] Embodiment 242 comprises a multispecific antibody of any one of embodiments 86-241, wherein P_1 or P_2 comprises at least two cysteine amino acid residues.

[0624] Embodiment 243 comprises a multispecific antibody of any one of embodiments 86-242, wherein P_1 or P_2 comprises a cyclic peptide or a linear peptide.

[0625] Embodiment 244 comprises a multispecific antibody of any one of embodiments 86-242, wherein P_1 or P_2 comprises a cyclic peptide.

[0626] Embodiment 245 comprises a multispecific antibody of any one of embodiments 86-242, wherein P_1 or P_2 comprises a linear peptide.

[0627] Embodiment 246 comprises a multispecific antibody of any one of embodiments 86-245, wherein P_1 or P_2 comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof.

[0628] Embodiment 247 comprises a multispecific antibody of any one of embodiments 86-246, wherein P1 or P_2 does not comprise albumin or an albumin fragment.

[0629] Embodiment 248 comprises a multispecific antibody of any one of embodiments 86-247, wherein P1 or P_2 does not comprise an albumin binding domain.

[0630] Embodiment 249 comprises an isolated recombinant nucleic acid molecule encoding a polypeptide of the multispecific antibody of any one of embodiments 1-248.

[0631] Embodiment 250 comprises a pharmaceutical composition comprising: (a) the multispecific antibody of any one of embodiments 1-248; and (b) a pharmaceutically acceptable excipient.

[0632] Embodiment 251 comprises a pharmaceutical composition comprising: (a) the multispecific antibody of any one of embodiments 1-248, (b) an anti-cancer therapy, and (c) a pharmaceutically acceptable excipient.

[0633] Embodiment 252 comprises a pharmaceutical composition of embodiment 251, wherein the anti-cancer therapy comprises a small molecule, a cell-based therapy, or an antibody-based therapy.

[0634] Embodiment 253 comprises a pharmaceutical composition of embodiment 252, wherein the antibody-based therapy is a T cell engager.

[0635] Embodiment 254 comprises a pharmaceutical composition of embodiment 253, wherein the T cell engager comprises a formula according to: D-L_0-E (Formula II), wherein D comprises an effector cell binding domain that binds to an effector cell antigen, E comprises a tumor antigen binding domain that binds to a tumor antigen, and L_0 comprises a linker that connects D to E.

[0636] Embodiment 255 comprises a pharmaceutical composition of embodiment 254, wherein D comprises a single chain variable fragment, a single domain antibody, or a Fab fragment.

[0637] Embodiment 256 comprises a pharmaceutical composition of embodiment 255, wherein D comprises the single chain variable fragment.

[0638] Embodiment 257 comprises a pharmaceutical composition of any one of embodiments 254-256, wherein E comprises a single chain variable fragment, a single domain antibody, or a Fab fragment.

[0639] Embodiment 258 comprises a pharmaceutical composition of embodiment 257, wherein E comprises the Fab fragment.

[0640] Embodiment 259 comprises a pharmaceutical composition of any one of embodiments 254-258, wherein the effector cell antigen comprises CD3.

[0641] Embodiment 260 comprises a pharmaceutical composition of embodiment 259, wherein the effector cell binding domain comprises complementary determining regions (CDRs) selected from the group consisting of muromonab-CD3 (OKT3), otelixizumab (TRX4), teplizumab (MGA031), visilizumab (Nuvion), SP34, X35, VIT3, BMA030 (BW264/56), CLB-T3/3, CRIS7, YTH12.5, F111-409, CLB-T3.4.2, TR-66, WT32, SPv-T3b, 11D8, XIII-141, XIII-46, XIII-87, 12F6, T3/RW2-8C8, T3/RW2-4B6, OKT3D, M-T301, SMC2, F101.01, UCHT-1, WT-31, 15865, 15865v12, 15865v16, and 15865v19.

[0642] Embodiment 261 comprises a pharmaceutical composition of embodiment 259, wherein the effector cell binding domain comprises an amino acid sequence according to SEQ ID NOs: 89-101.

[0643] Embodiment 262 comprises a pharmaceutical composition of any one of embodiments 254-261, wherein the tumor antigen comprises epidermal growth factor receptor (EGFR), prostate-specific membrane antigen (PSMA), or tumor-associated calcium signal transducer 2 (referred to herein after as TROP2).

[0644] Embodiment 263 comprises a pharmaceutical composition of embodiment 262, wherein the tumor antigen comprises EGFR.

[0645] Embodiment 264 comprises a pharmaceutical composition of embodiment 263, wherein the tumor antigen binding domain comprises an amino acid sequence according to SEQ ID NOs: 102-111.

[0646] Embodiment 265 comprises a pharmaceutical composition of embodiment 263, wherein the tumor antigen comprises EGFR, and the tumor binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, and LC-CDR1, LC-CDR2, and LC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 comprise HC-CDR1: SEQ ID NO: 105; HC-CDR2: SEQ ID NO: 106; HC-CDR3: SEQ ID NO: 107; and wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 comprise:LC-CDR1: SEQ ID NO: 102; LC-CDR2: SEQ ID NO: 103; and LC-CDR3: SEQ ID NO: 104.

[0647] Embodiment 266 comprises a pharmaceutical composition of embodiment 263, wherein the tumor antigen comprises EGFR, and the T cell engager comprises amino acid sequences with at least 95% sequence identity according to SEQ ID NOs: 139-142.

[0648] Embodiment 267 comprises a pharmaceutical composition of embodiment 263, wherein the tumor antigen comprises EGFR, and the T cell engager comprises amino acid sequences according to SEQ ID NOs: 139-142.

[0649] Embodiment 268 comprises a pharmaceutical composition of embodiment 262, wherein the tumor antigen comprises TROP2.

[0650] Embodiment 269 comprises a pharmaceutical composition of embodiment 268, wherein the tumor antigen comprises TROP2, and the tumor binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, and LC-CDR1, LC-CDR2, and LC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 comprise HC-CDR1: SEQ ID NO: 112; HC-CDR2: SEQ ID NO: 113; HC-CDR3: SEQ ID NO: 114; and wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 comprise:LC-CDR1: SEQ ID NO: 115; LC-CDR2: SEQ ID NO: 116; and LC-CDR3: SEQ ID NO: 117.

[0651] Embodiment 270 comprises a pharmaceutical composition of embodiment 268, wherein the tumor antigen comprises TROP2, and the T cell engager comprises amino acid sequences with at least 95% sequence identity according to SEQ ID NOs: 143-150.

[0652] Embodiment 271 comprises a pharmaceutical composition of embodiment 268, Wherein the tumor antigen comprises TROP2, and the T cell engager comprises amino acid sequences according to SEQ ID NOs: 143-150.

[0653] Embodiment 272 comprises a pharmaceutical composition of embodiment 268, wherein the tumor antigen binding domain comprises an amino acid sequence according to SEQ ID NOs: 112-119.

[0654] Embodiment 273 comprises a pharmaceutical composition of embodiment 262, wherein the tumor antigen comprises PSMA.

[0655] Embodiment 274 comprises a pharmaceutical composition of embodiment 273, wherein the tumor antigen binding domain comprises an amino acid sequence according to SEQ ID NOs: 120-127.

[0656] Embodiment 275 comprises a pharmaceutical composition of embodiment 273, wherein the tumor antigen comprises PSMA, and the tumor binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, and LC-CDR1, LC-CDR2, and LC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 comprise HC-CDR1: SEQ ID NO: 120; HC-CDR2: SEQ ID NO: 121; HC-CDR3: SEQ ID NO: 122; and wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 comprise:LC-CDR1: SEQ ID NO: 123; LC-CDR2: SEQ ID NO: 124; and LC-CDR3: SEQ ID NO: 125.

[0657] Embodiment 276 comprises a pharmaceutical composition of embodiment 273, wherein the tumor antigen comprises PSMA, and the T cell engager comprises amino acid sequences with at least 95% sequence identity according to SEQ ID NOs: 151-160.

[0658] Embodiment 277 comprises a pharmaceutical composition of embodiment 273, wherein the tumor antigen comprises PSMA, and the T cell engager comprises amino acid sequences according to SEQ ID NOs: 151-160.

[0659] Embodiment 278 comprises a pharmaceutical composition of any one of embodiments 253-277, wherein the T cell engager molecule is selectively activated in tumor microenvironments.

[0660] Embodiment 279 comprises a pharmaceutical composition of any one of embodiments 253-278, wherein the T cell engager is according to the following subformula: P_3-L_3-D-L_0-E (Formula IIa) wherein D comprises the CD3 binding domain; E comprises the tumor antigen binding domain; L0 comprises the linker that connects D to E; P_3 comprises a peptide that binds to D and L_3 comprises a linking moiety that connects D to P_3 and is a substrate for a tumor specific protease.

[0661] Embodiment 280 comprises a pharmaceutical composition of any one of embodiments 253-278, wherein the T cell engager is according to the following subformula: D-L_0-E-L_4-P_4 (Formula IIb) wherein D comprises the CD3 binding domain; E comprises the tumor antigen binding domain; L0 comprises the linker that connects D to E; P4 comprises a peptide that binds to E and L4 comprises a linking moiety that connects E to P4 and is a substrate for a tumor specific protease.

[0662] Embodiment 281 comprises a pharmaceutical composition of any one of embodiments 253-278, wherein the T cell engager is according to the following subformula: P_3-L_3-D-L_0-E-L_4-P_4 (Formula IIc) wherein D comprises the CD3 binding domain; E comprises the tumor antigen binding domain; L0 comprises the linker that connects D to E; P_3 comprises a peptide that binds to D and L_3 comprises a linking moiety that connects D to P_3 and is a substrate for a tumor specific protease; P_4 comprises a peptide that binds to E and L_4 comprises a linking moiety that connects E to P_4 and is a substrate for a tumor specific protease.

[0663] Embodiment 282 comprises a pharmaceutical composition of any one of embodiments 253-281, wherein the T cell engager comprises H_1.

[0664] Embodiment 283 comprises a pharmaceutical composition of embodiment 282, wherein H_1 comprises a sequence according to SEQ ID NO: 54-57.

[0665] Embodiment 284 comprises a pharmaceutical composition of any one of embodiments 282-283, wherein H_1 comprises a single domain antibody.

[0666] Embodiment 285 comprises a pharmaceutical composition of any one of embodiments 282-284, wherein the single domain antibody comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the single domain antibody comprise: HC-CDR1: SEQ ID NO: 54, HC-CDR2: SEQ ID NO: 55, and HC-CDR3: SEQ ID NO: 56.

[0667] Embodiment 286 comprises a pharmaceutical composition of any one of embodiments 279-285, wherein L_3 or L_4 is a peptide sequence having at least 5 to no more than 50 amino acids.

[0668] Embodiment 287 comprises a pharmaceutical composition of any one of embodiments 279-285, wherein L_3 or L_4 is a peptide sequence having at least 10 to no more than 30 amino acids.

[0669] Embodiment 288 comprises a pharmaceutical composition of any one of embodiments 279-285, wherein L_3 or L_4 is a peptide sequence having at least 10 amino acids.

[0670] Embodiment 289 comprises a pharmaceutical composition of any one of embodiments 279-285, wherein L_3 or L_4 is a peptide sequence having at least 18 amino acids.

[0671] Embodiment 290 comprises a pharmaceutical composition of any one of embodiments 279-285, wherein L_3 or L_4 is a peptide sequence having at least 26 amino acids.

[0672] Embodiment 291 comprises a pharmaceutical composition of any one of embodiments 279-285, wherein L_3 or L_4 has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3.

[0673] Embodiment 292 comprises a pharmaceutical composition of any one of embodiments 279-285, wherein L_3 or L_4 has a formula comprising $(G_2S)_n$, wherein n is an integer of at least 1.

[0674] Embodiment 293 comprises a pharmaceutical composition of any one of embodiments 279-285, wherein L_3 or L4 has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

[0675] Embodiment 294 comprises a pharmaceutical composition of any one of embodiments 279-293, wherein the tumor specific protease is selected from the group consisting of metalloprotease, serine protease, cysteine protease, threonine protease, and aspartic protease.

[0676] Embodiment 295 comprises a pharmaceutical composition of any one of embodiments 279-293, wherein L_3 or L_4 comprises a urokinase cleavable amino acid sequence, a matriptase cleavable amino acid sequence, a legumain cleavable amino acid sequence, or a matrix metalloprotease cleavable amino acid sequence.

[0677] Embodiment 296 comprises a pharmaceutical composition of any one of embodiments 279-295, wherein L_3 or $_{L4}$ comprises a sequence according to SEQ ID NOs: 18-19, 62-88.

[0678] Embodiment 297 comprises a pharmaceutical composition of any one of embodiments 279-296, wherein L_3 is bound to N-terminus of D.

[0679] Embodiment 298 comprises a pharmaceutical composition of any one of embodiments 279-296, wherein L_3 is bound to C-terminus of D.

[0680] Embodiment 299 comprises a pharmaceutical composition of any one of embodiments 279-296, wherein L_4 is bound to N-terminus of E.

[0681] Embodiment 300 comprises a pharmaceutical composition of any one of embodiments 279-296, wherein L_4 is bound to C-terminus of E.

[0682] Embodiment 301 comprises a pharmaceutical composition of any one of embodiments 279-300, wherein P_3 becomes unbound from D when L_3 is cleaved by the tumor specific protease thereby exposing D to CD3.

[0683] Embodiment 302 comprises a pharmaceutical composition of any one of embodiments 279-301, wherein P_4 becomes unbound from E when L_4 is cleaved by the tumor specific protease thereby exposing E to the tumor antigen.

[0684] Embodiment 303 comprises a pharmaceutical composition of any one of embodiments 279-302, wherein P_3 impairs binding of D to CD3.

[0685] Embodiment 304 comprises a pharmaceutical composition of any one of embodiments 279-303, wherein P_3 is bound to D through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof.

[0686] Embodiment 305 comprises a pharmaceutical composition of any one of embodiments 279-304, wherein P_3 is bound to D at or near an antigen binding site.

[0687] Embodiment 306 comprises a pharmaceutical composition of any one of embodiments 279-305, wherein P_3 becomes unbound from D when L_3 is cleaved by the tumor specific protease thereby exposing D to CD3.

[0688] Embodiment 307 comprises a pharmaceutical composition of any one of embodiments 279-306, wherein P_3 has less than 70% sequence identity to CD3.

[0689] Embodiment 308 comprises a pharmaceutical composition of any one of embodiments 279-306, wherein P_3 has less than 85% sequence identity to CD3.

[0690] Embodiment 309 comprises a pharmaceutical composition of any one of embodiments 279-306, wherein P_3 has less than 90% sequence identity to CD3.

[0691] Embodiment 310 comprises a pharmaceutical composition of any one of embodiments 279-306, wherein P_3 has less than 95% sequence identity to CD3.

[0692] Embodiment 311 comprises a pharmaceutical composition of any one of embodiments 279-306, wherein P_3 has less than 98% sequence identity to CD3.

[0693] Embodiment 312 comprises a pharmaceutical composition of any one of embodiments 279-306, wherein P_3 has less than 99% sequence identity to CD3.

[0694] Embodiment 313 comprises a pharmaceutical composition of any one of embodiments 279-306, wherein P_3 comprises the amino acid sequence according to SEQ ID NO: 161 (GSQCLGPEWEVCPY) or SEQ ID NO: 162 (VYCGPEFDESVGCM).

[0695] Embodiment 314 comprises a pharmaceutical composition of any one of embodiments 279-306, wherein P_3 comprises a de novo amino acid sequence that shares less than 10% sequence identity to CD3.

[0696] Embodiment 315 comprises a pharmaceutical composition of any one of embodiments 280-314, wherein P_4 impairs binding of E to the tumor antigen.

[0697] Embodiment 316 comprises a pharmaceutical composition of any one of embodiments 280-315, wherein P_4 is bound to E through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof.

[0698] Embodiment 317 comprises a pharmaceutical composition of any one of embodiments 280-316, wherein P_4 is bound to E at or near an antigen binding site.

[0699] Embodiment 318 comprises a pharmaceutical composition of any one of embodiments 280-317, wherein P_4 becomes unbound from E when L4 is cleaved by the tumor specific protease thereby exposing E to the tumor antigen.

[0700] Embodiment 319 comprises a pharmaceutical composition of any one of embodiments 280-318, wherein P_4 has less than 70% sequence identity to the tumor antigen.

[0701] Embodiment 320 comprises a pharmaceutical composition of any one of embodiments 280-318, wherein P_4 has less than 80% sequence identity to the tumor antigen.

[0702] Embodiment 321 comprises a pharmaceutical composition of any one of embodiments 280-318, wherein P_4 has less than 85% sequence identity to the tumor antigen.

[0703] Embodiment 322 comprises a pharmaceutical composition of any one of embodiments 280-318, wherein P_4 has less than 90% sequence identity to the tumor antigen.

[0704] Embodiment 323 comprises a pharmaceutical composition of any one of embodiments 280-318, wherein P_4 has less than 95% sequence identity to the tumor antigen.

[0705] Embodiment 324 comprises a pharmaceutical composition of any one of embodiments 280-318, wherein P_4 comprises a de novo amino acid sequence that shares less than 10% sequence identity to the tumor antigen.

[0706] Embodiment 325 comprises a pharmaceutical composition of any one of embodiments 279-324, wherein P_3 or P_4 comprises a peptide sequence of at least 5 amino acids in length.

[0707] Embodiment 326 comprises a pharmaceutical composition of any one of embodiments 279-324, wherein P_3 or P_4 comprises a peptide sequence of at least 6 amino acids in length.

[0708] Embodiment 327 comprises a pharmaceutical composition of any one of embodiments 279-324, wherein P_3 or P_4 comprises a peptide sequence of at least 10 amino acids in length.

[0709] Embodiment 328 comprises a pharmaceutical composition of any one of embodiments 279-324, wherein P_3 or P_4 comprises a peptide sequence of at least 10 amino acids in length and no more than 20 amino acids in length.

[0710] Embodiment 329 comprises a pharmaceutical composition of any one of embodiments 279-328, wherein P_3 or P_4 comprises a peptide sequence of at least 16 amino acids in length.

[0711] Embodiment 330 comprises a pharmaceutical composition of any one of embodiments 279-329, wherein P_3 or P_4 comprises a peptide sequence of no more than 40 amino acids in length.

[0712] Embodiment 331 comprises a pharmaceutical composition of any one of embodiments 279-330, wherein P_3 or P_4 comprises at least two cysteine amino acid residues.

[0713] Embodiment 332 comprises a pharmaceutical composition of any one of embodiments 279-331, wherein P_3 or P_4 comprises a cyclic peptide or a linear peptide.

[0714] Embodiment 333 comprises a pharmaceutical composition of any one of embodiments 279-332, wherein P_3 or P_4 comprises a cyclic peptide.

[0715] Embodiment 334 comprises a pharmaceutical composition of any one of embodiments 279-332, wherein P_3 or P_4 comprises a linear peptide.

[0716] Embodiment 335 comprises a pharmaceutical composition of any one of embodiments 280-334, wherein P4 comprises the amino acid sequence according to SEQ ID NO: 163 (PCRSHIDVAKPICV).

[0717] Embodiment 336 comprises a pharmaceutical composition of any one of embodiments 279-335, wherein the tumor antigen comprises EGFR, and the T cell engager comprises the amino acid sequence SEQ ID NOs: 164-178.

[0718] Embodiment 337 comprises a pharmaceutical composition of any one of embodiments 280-335, wherein P4 comprises the amino acid sequence according to SEQ ID NO: 179 (SVLFCVKNLYCWVT), SEQ ID NO: 180 (VDFCKIYSWPVCHQ), SEQ ID NO: 181 (IDFCMLYNWPICAG).

[0719] Embodiment 338 comprises a pharmaceutical composition of any one of embodiments 279-335, wherein the tumor antigen comprises TROP2, and the T cell engager comprises the amino acid sequence SEQ ID NOs: 182-219.

[0720] Embodiment 339 comprises a pharmaceutical composition of any one of embodiments 279-335, wherein the tumor antigen comprises PSMA, and the T cell engager comprises the amino acid sequence SEQ ID NOs: 220-231.

[0721] Embodiment 340 comprises a method of treating cancer in a subject in need thereof comprising administering to the subject the multispecific antibody of any one of embodiments 1-248 or the pharmaceutical composition of embodiment 249.

[0722] Embodiment 341 comprises a method of embodiment 340, wherein the multispecific antibody induces T cell mediated cytotoxicity of tumor cells.

[0723] Embodiment 342 comprises a method of any one of embodiments 340-341, wherein the cancer is a hematological malignancy.

[0724] Embodiment 343 comprises a method of any one of embodiments 340-342, wherein the cancer is leukemia or lymphoma.

[0725] Embodiment 344 comprises a method of any one of embodiments 340-343, wherein the cancer is lymphoma, and wherein the lymphoma is B-cell lymphoma.

[0726] Embodiment 345 comprises a method of any one of embodiments 340-341, wherein the cancer is a solid tumor.

[0727] Embodiment 346 comprises a method of embodiment 345, wherein the solid tumor expresses PD-L1.

[0728] Embodiment 347 comprises a method of any one of embodiments 345-346, wherein the solid tumor is sarcoma, breast cancer, lung cancer, or carcinoma.

[0729] Embodiment 348 comprises a method of any one of embodiments 345-347, wherein the solid tumor is lung cancer, and wherein the lung cancer is non-small cell lung cancer.

[0730] Embodiment 349 comprises a method of any one of embodiments 340-348, wherein the multispecific antibody is administered in combination with an anti-cancer therapy.

[0731] Embodiment 350 comprises a method of embodiment 349, wherein the multispecific antibody and the anti-cancer therapy are administered in the same pharmaceutical composition.

[0732] Embodiment 351 comprises a method of embodiment 349, wherein the multispecific antibody and the anti-cancer therapy are administered as separate pharmaceutical compositions.

[0733] Embodiment 352 comprises a method of any one of embodiments 340-351, wherein the subject is refractory to checkpoint inhibitor therapy.

[0734] Embodiment 353 comprises a method of any one of embodiments 340-352, wherein the subject has relapsed from checkpoint inhibitor therapy.

[0735] Embodiment 354 comprises a method of any one of embodiments 349-353, wherein the anti-cancer therapy comprises a small molecule, a cell-based therapy, or an antibody-based therapy.

[0736] Embodiment 355 comprises a method of embodiment 354, wherein the antibody-based therapy is a T cell engager.

[0737] Embodiment 356 comprises a method of embodiment 355, wherein the T cell engager comprises a formula according to: D-L_0-E (Formula II), wherein D comprises an effector cell binding domain that binds to an effector cell antigen, E comprises a tumor antigen binding domain that binds to a tumor antigen, and L0 comprises a linker that connects D to E.

[0738] Embodiment 357 comprises a method of embodiment 356, wherein D comprises a single chain variable fragment, a single domain antibody, or a Fab fragment.

[0739] Embodiment 358 comprises a method of embodiment 357, wherein D comprises the single chain variable fragment.

[0740] Embodiment 359 comprises a method of any one of embodiments 356-358, wherein E comprises a single chain variable fragment, a single domain antibody, or a Fab fragment.

[0741] Embodiment 360 comprises a method of embodiment 359, wherein E comprises the Fab fragment.

[0742] Embodiment 361 comprises a method of any one of embodiments 356-360, wherein the effector cell antigen comprises CD3.

[0743] Embodiment 362 comprises a method of any one of embodiments 356-361, wherein the effector cell binding domain comprises complementary determining regions (CDRs) selected from the group consisting of muromonab-CD3 (OKT3), otelixizumab (TRX4), teplizumab (MGA031), visilizumab (Nuvion), SP34, X35, VIT3, BMA030 (BW264/56), CLB-T3/3, CRIS7, YTH12.5, F111-409, CLB-T3.4.2, TR-66, WT32, SPv-T3b, 11D8, XIII-141, XIII-46, XIII-87, 12F6, T3/RW2-8C8, T3/RW2-4B6, OKT3D, M-T301, SMC2, F101.01, UCHT-1, WT-31, 15865, 15865v12, 15865v16, and 15865v19.

[0744] Embodiment 363 comprises a method of any one of embodiments 356-362, wherein the effector cell binding domain comprises an amino acid sequence according to SEQ ID NOs: 89-101.

[0745] Embodiment 364 comprises a method of any one of embodiments 356-363, wherein the tumor antigen comprises epidermal growth factor receptor (EGFR), prostate-specific membrane antigen (PSMA), or tumor-associated calcium signal transducer 2 (referred to herein after as TROP2).

[0746] Embodiment 365 comprises a method of embodiment 364, wherein the tumor antigen comprises EGFR.

[0747] Embodiment 366 comprises a method of any one of embodiments 364-365, wherein the cancer has cells that express EGFR.

[0748] Embodiment 367 comprises a method of any one of embodiments 364-367, wherein the cancer comprises colorectal cancer (CRC), squamous cell carcinoma of the head and Neck (SCCHN), non-small cell lung cancer (NSCLC), prostate cancer, breast cancer, colon/rectum cancer, head and neck cancer, esophagogastric cancer, liver cancer, glioblastoma, cervical cancer, ovarian cancer, bladder cancer, kidney cancer, or pancreatic cancer.

[0749] Embodiment 368 comprises a method of any one of embodiments 364-367, wherein the tumor antigen binding domain comprises an amino acid sequence according to SEQ ID NOs: 102-111.

[0750] Embodiment 369 comprises a method of any one of embodiments 364-368, wherein the tumor antigen comprises EGFR, and the tumor binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, and LC-CDR1, LC-CDR2, and LC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 comprise HC-CDR1: SEQ ID NO: 105; HC-CDR2: SEQ ID NO: 106; HC-CDR3: SEQ ID NO: 107; and wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 comprise:LC-CDR1: SEQ ID NO: 102; LC-CDR2: SEQ ID NO: 103; and LC-CDR3: SEQ ID NO: 104.

[0751] Embodiment 370 comprises a method of any one of embodiments 364-369, wherein the tumor antigen comprises EGFR, and the T cell engager comprises amino acid sequences with at least 95% sequence identity according to SEQ ID NOs: 139-142.

[0752] Embodiment 371 comprises a method of any one of embodiments 364-369, wherein the tumor antigen comprises EGFR, and the T cell engager comprises amino acid sequences according to SEQ ID NOs: 139-142.

[0753] Embodiment 372 comprises a method of embodiment 364, wherein the tumor antigen comprises TROP2.

[0754] Embodiment 373 comprises a method of embodiment 372, wherein the cancer has cells that express TROP2.

[0755] Embodiment 374 comprises a method of any one of embodiments 372-373, wherein the cancer is a solid tumor cancer.

[0756] Embodiment 375 comprises a method of any one of embodiments 372-374, wherein the cancer is lung, breast (e.g. HER2+; ER/PR+; TNBC), cervical, ovarian, colorectal, pancreatic gastric, urothelial, endometrial, head and neck, or glioma.

[0757] Embodiment 376 comprises a method of any one of embodiments 372-375, wherein the tumor antigen binding domain comprises an amino acid sequence according to SEQ ID NOs: 112-119.

[0758] Embodiment 377 comprises a method of any one of embodiments 340-376, wherein the tumor antigen comprises TROP2, and the tumor binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, and LC-CDR1, LC-CDR2, and LC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 comprise HC-CDR1: SEQ ID NO: 112; HC-CDR2: SEQ ID NO: 113; HC-CDR3: SEQ ID NO: 114; and wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 comprise:LC-CDR1: SEQ ID NO: 115; LC-CDR2: SEQ ID NO: 116; and LC-CDR3: SEQ ID NO: 117.

[0759] Embodiment 378 comprises a method of any one of embodiments 372-377, wherein the tumor antigen comprises TROP2, and the T cell engager comprises amino acid sequences with at least 95% sequence identity according to SEQ ID NOs: 143-150.

[0760] Embodiment 379 comprises a method of any one of embodiments 372-378, wherein the tumor antigen comprises TROP2, and the T cell engager comprises amino acid sequences according to SEQ ID NOs: 143-150.

[0761] Embodiment 380 comprises a method of embodiment 364, wherein the tumor antigen comprises PSMA.

[0762] Embodiment 381 comprises a method of embodiment 380, wherein the cancer comprises prostate cancer.

[0763] Embodiment 382 comprises a method of any one of embodiments 380-381, wherein the cancer comprises metastatic castrate-resistant prostate cancer (mCRPC).

[0764] Embodiment 383 comprises a method of any one of embodiments 380-382, wherein the tumor antigen binding domain comprises an amino acid sequence according to SEQ ID NOs: 120-127.

[0765] Embodiment 384 comprises a method of any one of embodiments 380-383, wherein the tumor antigen comprises PSMA, and the tumor binding domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, and LC-CDR1, LC-CDR2, and LC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 comprise HC-CDR1: SEQ ID NO: 120; HC-CDR2: SEQ ID NO: 121; HC-CDR3: SEQ ID NO: 122; and wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 comprise:LC-CDR1: SEQ ID NO: 123; LC-CDR2: SEQ ID NO: 124; and LC-CDR3: SEQ ID NO: 125.

[0766] Embodiment 385 comprises a method of any one of embodiments 380-384, wherein the tumor antigen comprises PSMA, and the T cell engager comprises amino acid sequences with at least 95% sequence identity according to SEQ ID NOs: 151-160.

[0767] Embodiment 386 comprises a method of any one of embodiments 380-385, wherein the tumor antigen comprises PSMA, and the T cell engager comprises amino acid sequences according to SEQ ID NOs: 151-160.

[0768] Embodiment 387 comprises a method of any one of embodiments 356-386, wherein the T cell engager molecule is selectively activated in tumor microenvironments.

[0769] Embodiment 388 comprises a method of any one of embodiments 356-387, wherein the T cell engager is according to the following subformula: P_3-L_3-D-L_0-E (Formula IIa) wherein D comprises the CD3 binding domain; E comprises the tumor antigen binding domain; L_0 comprises the linker that connects D to E; P_3 comprises a peptide that binds to D and L_3 comprises a linking moiety that connects D to P_3 and is a substrate for a tumor specific protease.

[0770] Embodiment 389 comprises a method of any one of embodiments 356-387, wherein the T cell engager is according to the following subformula: D-L_0-E-L_4-P_4 (Formula IIb) wherein D comprises the CD3 binding domain; E comprises the tumor antigen binding domain; L_0 comprises the linker that connects

D to E; P_4 comprises a peptide that binds to E and L_4 comprises a linking moiety that connects E to P_4 and is a substrate for a tumor specific protease.

[0771] Embodiment 390 comprises a method of any one of embodiments 356-387, wherein the T cell engager is according to the following subformula: P_3-L_3-D-L_0-E-L_4-P_4 (Formula IIc) wherein D comprises the CD3 binding domain; E comprises the tumor antigen binding domain; L_0 comprises the linker that connects D to E; P_3 comprises a peptide that binds to D and L_3 comprises a linking moiety that connects D to P_3 and is a substrate for a tumor specific protease; P4 comprises a peptide that binds to E and L_4 comprises a linking moiety that connects E to P_4 and is a substrate for a tumor specific protease.

[0772] Embodiment 391 comprises a method of any one of embodiments 356-390, wherein the T cell engager comprises H_1.

[0773] Embodiment 392 comprises a method of embodiment 391, wherein H_1 comprises a sequence according to SEQ ID NO: 54-57.

[0774] Embodiment 393 comprises a method of embodiment 391, wherein H_1 comprises a single domain antibody.

[0775] Embodiment 394 comprises a method of embodiment 393, wherein the single domain antibody comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the single domain antibody comprise: HC-CDR1: SEQ ID NO: 54, HC-CDR2: SEQ ID NO: 55, and HC-CDR3: SEQ ID NO: 56.

[0776] Embodiment 395 comprises a method of any one of embodiments 388-394, wherein L_3 or L_4 is a peptide sequence having at least 5 to no more than 50 amino acids.

[0777] Embodiment 396 comprises a method of any one of embodiments 388-394, wherein L_3 or L_4 is a peptide sequence having at least 10 to no more than 30 amino acids.

[0778] Embodiment 397 comprises a method of any one of embodiments 388-394, wherein L_3 or L_4 is a peptide sequence having at least 10 amino acids.

[0779] Embodiment 398 comprises a method of any one of embodiments 388-394, wherein L_3 or L_4 is a peptide sequence having at least 18 amino acids.

[0780] Embodiment 399 comprises a method of any one of embodiments 388-394, wherein L_3 or L_4 is a peptide sequence having at least 26 amino acids.

[0781] Embodiment 400 comprises a method of any one of embodiments 388-394, wherein L_3 or L_4 has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3.

[0782] Embodiment 401 comprises a method of any one of embodiments 388-394, wherein L_3 or L_4 has a formula comprising $(G_2S)_n$, wherein n is an integer of at least 1.

[0783] Embodiment 402 comprises a method of any one of embodiments 388-394, wherein L3 or L4 has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

[0784] Embodiment 403 comprises a method of any one of embodiments 388-402, wherein the tumor specific protease is selected from the group consisting of metalloprotease, serine protease, cysteine protease, threonine protease, and aspartic protease.

[0785] Embodiment 404 comprises a method of any one of embodiments 388-402, wherein L_3 or L_4 comprises a urokinase cleavable amino acid sequence, a matriptase cleavable amino acid sequence, a legumain cleavable amino acid sequence, or a matrix metalloprotease cleavable amino acid sequence.

[0786] Embodiment 405 comprises a method of any one of embodiments 388-394, wherein L_3 or L_4 comprises a sequence according to SEQ ID NOs: 18-19, 62-88.

[0787] Embodiment 406 comprises a method of any one of embodiments 388-394, wherein L_3 is bound to N-terminus of D.

[0788] Embodiment 407 comprises a method of any one of embodiments 388-394, wherein L_3 is bound to C-terminus of D.

[0789] Embodiment 408 comprises a method of any one of embodiments 388-394, wherein L_4 is bound to N-terminus of E.

[0790] Embodiment 409 comprises a method of any one of embodiments 388-394, wherein L_4 is bound to C-terminus of E.

[0791] Embodiment 410 comprises a method of any one of embodiments 388-409, wherein P_3 becomes unbound from D when L_3 is cleaved by the tumor specific protease thereby exposing D to CD3.

[0792] Embodiment 411 comprises a method of any one of embodiments 388-410, wherein P_4 becomes unbound from E when L_4 is cleaved by the tumor specific protease thereby exposing E to the tumor antigen.

[0793] Embodiment 412 comprises a method of any one of embodiments 388-411, wherein P_3 impairs binding of D to CD3.

[0794] Embodiment 413 comprises a method of any one of embodiments 388-412, wherein P_3 is bound to D through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof.

[0795] Embodiment 414 comprises a method of any one of embodiments 388-413, wherein P_3 is bound to D at or near an antigen binding site.

[0796] Embodiment 415 comprises a method of any one of embodiments 388-414, wherein P_3 becomes unbound from D when L3 is cleaved by the tumor specific protease thereby exposing D to CD3.

[0797] Embodiment 416 comprises a method of any one of embodiments 388-415, wherein P_3 has less than 70% sequence identity to CD3.

[0798] Embodiment 417 comprises a method of any one of embodiments 388-415, wherein P_3 has less than 85% sequence identity to CD3.

[0799] Embodiment 418 comprises a method of any one of embodiments 388-415, wherein P_3 has less than 90% sequence identity to CD3.

[0800] Embodiment 419 comprises a method of any one of embodiments 388-415, wherein P_3 has less than 95% sequence identity to CD3.

[0801] Embodiment 420 comprises a method of any one of embodiments 388-415, wherein P_3 has less than 98% sequence identity to CD3.

[0802] Embodiment 421 comprises a method of any one of embodiments 388-415, wherein P_3 has less than 99% sequence identity to CD3.

[0803] Embodiment 422 comprises a method of any one of embodiments 388-421, wherein P_3 comprises the amino acid sequence according to SEQ ID NO: 161 (GSQCLGPEWEVCPY) or SEQ ID NO: 162 (VYCGPEFDESVGCM).

[0804] Embodiment 423 comprises a method of any one of embodiments 388-422, wherein P_3 comprises a de novo amino acid sequence that shares less than 10% sequence identity to CD3.

[0805] Embodiment 424 comprises a method of any one of embodiments 388-423, wherein P_4 impairs binding of E to the tumor antigen.

[0806] Embodiment 425 comprises a method of any one of embodiments 388-424, wherein P_4 is bound to E through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof.

[0807] Embodiment 426 comprises a method of any one of embodiments 388-425, wherein P_4 is bound to E at or near an antigen binding site.

[0808] Embodiment 427 comprises a method of any one of embodiments 388-426, wherein P_4 becomes unbound from E when L4 is cleaved by the tumor specific protease thereby exposing E to the tumor antigen.

[0809] Embodiment 428 comprises a method of any one of embodiments 388-427, wherein P_4 has less than 70% sequence identity to the tumor antigen.

[0810] Embodiment 429 comprises a method of any one of embodiments 388-428, wherein P_4 has less than 80% sequence identity to the tumor antigen.

[0811] Embodiment 430 comprises a method of any one of embodiments 388-429, wherein P_4 has less than 85% sequence identity to the tumor antigen.

[0812] Embodiment 431 comprises a method of any one of embodiments 388-430, wherein P_4 has less than 90% sequence identity to the tumor antigen.

[0813] Embodiment 432 comprises a method of any one of embodiments 388-431, wherein P_4 has less than 95% sequence identity to the tumor antigen.

[0814] Embodiment 433 comprises a method of any one of embodiments 388-432, wherein P_4 comprises a de novo amino acid sequence that shares less than 10% sequence identity to the tumor antigen.

[0815] Embodiment 434 comprises a method of any one of embodiments 388-433, wherein P_3 or P_4 comprises a peptide sequence of at least 5 amino acids in length.

[0816] Embodiment 435 comprises a method of any one of embodiments 388-434, wherein P_3 or P_4 comprises a peptide sequence of at least 6 amino acids in length.

[0817] Embodiment 436 comprises a method of any one of embodiments 388-435, wherein P_3 or P_4 comprises a peptide sequence of at least 10 amino acids in length.

[0818] Embodiment 437 comprises a method of any one of embodiments 388-436, wherein P_3 or P_4 comprises a peptide sequence of at least 10 amino acids in length and no more than 20 amino acids in length.

[0819] Embodiment 438 comprises a method of any one of embodiments 388-437, wherein P_3 or P_4 comprises a peptide sequence of at least 16 amino acids in length.

[0820] Embodiment 439 comprises a method of any one of embodiments 388-438, wherein P_3 or P_4 comprises a peptide sequence of no more than 40 amino acids in length.

[0821] Embodiment 440 comprises a method of any one of embodiments 388-439, wherein P_3 or P_4 comprises at least two cysteine amino acid residues.

[0822] Embodiment 441 comprises a method of any one of embodiments 388-440, wherein P_3 or P_4 comprises a cyclic peptide or a linear peptide.

[0823] Embodiment 442 comprises a method of any one of embodiments 388-440, wherein P_3 or P_4 comprises a cyclic peptide.

[0824] Embodiment 443 comprises a method of any one of embodiments 388-440, wherein P_3 or P_4 comprises a linear peptide.

[0825] Embodiment 444 comprises a method of any one of embodiments 388-440, wherein P_4 comprises the amino acid sequence according to SEQ ID NO: 163 (PCRSHIDVAKPICV).

[0826] Embodiment 445 comprises a method of any one of embodiments 364-390 wherein the tumor antigen comprises EGFR, and the T cell engager comprises the amino acid sequence SEQ ID NOs: 164-178.

[0827] Embodiment 446 comprises a method of any one of embodiments 364-390, wherein P4 comprises the amino acid sequence according to SEQ ID NO: 179 (SVLFCVKNLYCWVT), SEQ ID NO: 180 (VDFCKIYSWPVCHQ), SEQ ID NO: 181 (IDFCMLYNWPICAG).

[0828] Embodiment 447 comprises a method of any one of embodiments 364-390, wherein the tumor antigen comprises TROP2, and the T cell engager comprises the amino acid sequence SEQ ID NOs: 182-219.

[0829] Embodiment 448 comprises a method of any one of embodiments 364-390, wherein the tumor antigen comprises PSMA, and the T cell engager comprises the amino acid sequence SEQ ID NOs: 220-231.

[0830] Embodiment 449 comprises a method of treating cancer in a subject in need thereof comprising administering to the subject a multispecific antibody that comprises a CD28 binding domain and a PD-L1 binding domain wherein the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain is not administered as part of a treatment regimen with another multispecific antibody that targets a cancer antigen different from PD-L1 or CD28.

[0831] Embodiment 450 comprises a method of embodiment 449, wherein the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain is administered to the subject as a single agent therapy.

[0832] Embodiment 451 comprises a method of any one of embodiments 449-450, wherein the multispecific antibody that comprises the CD28 binding domain and the PD-L1 binding domain comprises an IgG framework, an IgA framework, an IgE framework, or an IgM framework.

[0833] Embodiment 452 comprises a method of any one of embodiments 449-451, wherein the CD28 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′.

[0834] Embodiment 453 comprises a method of any one of embodiments 449-452, wherein the PD-L1 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′.

[0835] Embodiment 454 comprises a method of any one of embodiments 449-453, wherein the PD-L1 binding domain comprises a single chain variable fragment and the CD28 binding domain comprises a single chain variable fragment.

[0836] Embodiment 455 comprises a method of any one of embodiments 449-454, wherein the CD28 binding domain comprises an anti-CD28 light chain polypeptide.

[0837] Embodiment 456 comprises a method of any one of embodiments 449-455, wherein the anti-CD28 light chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 light chain.

[0838] Embodiment 457 comprises a method of any one of embodiments 449-456, wherein the CD28 binding domain comprises an anti-CD28 heavy chain polypeptide.

[0839] Embodiment 458 comprises a method of any one of embodiments 449-457, wherein the anti-CD28 heavy chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 heavy chain.

[0840] Embodiment 459 comprises a method of any one of embodiments 449-458, wherein the PD-L1 binding domain comprises an anti-PD-L1 light chain polypeptide.

[0841] Embodiment 460 comprises a method of any one of embodiments 449-459, the anti-PD-L1 light chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 light chain.

[0842] Embodiment 461 comprises a method of any one of embodiments 449-460, wherein the PD-L1 binding domain comprises an anti-PD-L1 heavy chain polypeptide.

[0843] Embodiment 462 comprises a method of any one of embodiments 449-461, the anti- PD-L1 heavy chain polypeptide comprises a variable domain of an IgG1, IgG2, IgG3, or IgG4 heavy chain.

[0844] Embodiment 463 comprises a method of any one of embodiments 449-462, wherein the multispecific antibody further comprises a fragment crystallizable (Fc) region.

[0845] Embodiment 464 comprises a method of embodiment 463, wherein the Fc region comprises an IgG CH2 domain and an IgG CH3 domain.

[0846] Embodiment 465 comprises a method of any one of embodiments 464-465, wherein the Fc region comprises a heterodimeric Fc region.

[0847] Embodiment 466 comprises a method of any one of embodiments 463-465, wherein the Fc region comprises at least one amino acid modification that increases the half-life of the multispecific antibody.

[0848] Embodiment 467 comprises a method of any one of embodiments 463-466, wherein the Fc region comprises at least one amino acid modification that modulates its interaction with an Fc receptor.

[0849] Embodiment 468 comprises a method of any one of embodiments 463-467, wherein the Fc region comprises at least one amino acid modification that increases binding of the Fc region to an Fc receptor.

[0850] Embodiment 469 comprises a method of any one of embodiments 463-468, wherein the Fc region comprises at least one amino acid modification that decreases glycosylation of the Fc region.

[0851] Embodiment 470 comprises a method of embodiment 469, wherein the modification is an amino acid substitution, deletion, or addition.

[0852] Embodiment 471 comprises a method of embodiment 470, wherein the modification is an amino acid substitution.

[0853] Embodiment 472 comprises a method of any one of embodiments 469-471, wherein the at least one amino acid modification that decreases glycosylation of the Fc region comprises an amino acid substitution at a position corresponding to position N297 of human IgG1, wherein the numbering is according to the EU index of Kabat.

[0854] Embodiment 473 comprises a method of any one of embodiments 463-472, wherein the Fc region is afucosylated.

[0855] Embodiment 474 comprises a method of any one of embodiments 455-473, wherein the anti-CD28 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 the anti-CD28 light chain polypeptide: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0856] Embodiment 475 comprises a method of any one of embodiments 457-474, wherein the anti-CD28 heavy chain polypeptide comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-CD28 heavy chain polypeptide comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0857] Embodiment 476 comprises a method of any one of embodiments 459-475, wherein the anti-PD-L1 light chain polypeptide comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the anti-PD-L1 light chain polypeptide comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; LC-CDR3: SEQ ID NO: 35; LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38; or LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41; and LC-CDR3: SEQ ID NO: 15, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0858] Embodiment 477 comprises a method of any one of embodiments 457-476, wherein the anti-PD-L1 heavy chain polypeptide the anti-PD-L1 heavy chain polypeptide comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the anti-PD-L1 heavy chain polypeptide comprises: HC-CDR1: SEQ ID NO: 10; HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; or HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0859] Embodiment 478 comprises a method of any one of embodiments 449-477, wherein the multispecific antibody induces T cell mediated cytotoxicity of tumor cells.

[0860] Embodiment 479 comprises a method of any one of embodiments 449-478, wherein the administering to the subject of the multispecific antibody is sufficient to reduce or eliminate the cancer as compared to a baseline measurement of the cancer taken from the subject prior to the administering of the multispecific antibody.

[0861] Embodiment 480 comprises a method of embodiment 479, wherein the reduction is at least about 1-fold, 5-fold, 10-fold, 20-fold, 40-fold, 60-fold, 80-fold, or up to about 100-fold.

[0862] Embodiment 481 comprises a method of any one of embodiments 449-480, wherein the cancer is a hematological malignancy.

[0863] Embodiment 482 comprises a method of any one of embodiments 449-480, wherein the cancer is leukemia or lymphoma.

[0864] Embodiment 483 comprises a method of any one of embodiments 449-480, wherein the cancer is lymphoma, and wherein the lymphoma is B-cell lymphoma.

[0865] Embodiment 484 comprises a method of any one of embodiments 449-480, wherein the cancer is a solid tumor.

[0866] Embodiment 485 comprises a method of embodiment 484, wherein the solid tumor expresses PD-L1.

[0867] Embodiment 486 comprises a method of any one of embodiments 484-485, wherein the solid tumor is sarcoma, breast cancer, lung cancer, or carcinoma.

[0868] Embodiment 487 comprises a method of embodiment 486, wherein the solid tumor is lung cancer, and wherein the lung cancer is non-small cell lung cancer.

[0869] Embodiment 488 comprises a method of any one of embodiments 449-487, wherein the multispecific antibody is selectively activated in tumor microenvironments.

[0870] Embodiment 489 comprises a method of any one of embodiments 449-488, wherein the multispecific antibody is according to the following formula: P_1-L_1-A-L-B (Formula Ia) wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; L comprises a linker that connects A to B; P_1 comprises a peptide that binds to A and L_1 comprises a linking moiety that connects A to P_1 and is a substrate for a tumor specific protease.

[0871] Embodiment 490 comprises a method of any one of embodiments 449-488, wherein the multispecific antibody is according to the following formula: A-L-B-L_2-P_2 (Formula Ib) wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; L comprises a linker that connects A to B; P_2 comprises a peptide that binds to B and L_2 comprises a linking moiety that connects B to P_2 and is a substrate for a tumor specific protease.

[0872] Embodiment 491 comprises a method of any one of embodiments 449-488, wherein the multispecific antibody is according to the following formula: P_1-L_1-A-L-B-L_2-P_2 (Formula Ic) wherein A comprises the CD28 binding domain; B comprises the PD-L1 binding domain; L comprises a linker that connects A to B; P_1 comprises a peptide that binds to A and L_1 comprises a linking moiety that connects A to P_1 and is a substrate for a tumor specific protease; P_2 comprises a peptide that binds to B and L_2 comprises a linking moiety that connects B to P_2 and is a substrate for a tumor specific protease.

[0873] Embodiment 492 comprises a method of any one of embodiments 489-491, wherein the linker connects the C-terminus of A to an N-terminus of B.

[0874] Embodiment 493 comprises a method of any one of embodiments 489-491, wherein the linker connects the N-terminus of A to a C-terminus of B.

[0875] Embodiment 494 comprises a method of any one of embodiments 489-491, wherein the linker connects the C-terminus of A to the N-terminus of the Fab heavy chain polypeptide.

[0876] Embodiment 495 comprises a method of any one of embodiments 489-491, wherein the linker connects the N-terminus of A to the C-terminus of the Fab heavy chain polypeptide.

[0877] Embodiment 496 comprises a method of any one of embodiments 489-491, wherein the linker connects the C-terminus of A to the N-terminus of the Fab light chain polypeptide.

[0878] Embodiment 497 comprises a method of any one of embodiments 489-491, wherein the linker connects the N-terminus of A to the C-terminus of the Fab light chain polypeptide.

[0879] Embodiment 498 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab light chain polypeptide to the scFv light chain variable domain.

[0880] Embodiment 499 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab light chain polypeptide to the scFv heavy chain variable domain.

[0881] Embodiment 500 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab heavy chain polypeptide to the scFv light chain variable domain.

[0882] Embodiment 501 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab heavy chain polypeptide to the scFv heavy chain variable domain.

[0883] Embodiment 502 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab light chain polypeptide to the N-terminus of the scFv light chain variable domain.

[0884] Embodiment 503 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain.

[0885] Embodiment 504 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab light chain polypeptide to the N-terminus of the scFv heavy chain variable domain.

[0886] Embodiment 505 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

[0887] Embodiment 506 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv light chain variable domain.

[0888] Embodiment 507 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain.

[0889] Embodiment 508 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv heavy chain variable domain.

[0890] Embodiment 509 comprises a method of any one of embodiments 489-491, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

[0891] Embodiment 510 comprises a method of any one of embodiments 489-509, wherein the linker is at least 5 amino acids in length.

[0892] Embodiment 511 comprises a method of any one of embodiments 489-509, wherein the linker is no more than 30 amino acids in length.

[0893] Embodiment 512 comprises a method of any one of embodiments 489-509, wherein the linker is at least 5 amino acids and no more than 30 amino acids in length.

[0894] Embodiment 513 comprises a method of any one of embodiments 489-509, wherein the linker is 5 amino acids in length.

[0895] Embodiment 514 comprises a method of any one of embodiments 489-509, wherein the linker is 15 amino acids in length.

[0896] Embodiment 515 comprises a method of any one of embodiments 489-509, wherein the linker is selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

[0897] Embodiment 516 comprises a method of any one of embodiments 489-509, wherein L has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3.

[0898] Embodiment 517 comprises a method of any one of embodiments 489-509, wherein the L comprises an amino acid sequence of SEQ ID NO: 18 (GGGGSGGGGSGGGGS) or SEQ ID NO: 19 (GGGGS).

[0899] Embodiment 518 comprises a method of any one of embodiments 489-517, wherein the scFv heavy chain variable domain comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the scFv heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0900] Embodiment 519 comprises a method of any one of embodiments 489-517, wherein the scFv light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the scFv light chain variable domain comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0901] Embodiment 520 comprises a method of any one of embodiments 489-517, wherein the Fab heavy chain variable domain comprises complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and

HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the Fab heavy chain variable domain comprise: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; or HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; or HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32; and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

[0902] Embodiment 521 comprises a method of any one of embodiments 489-518, wherein the Fab light chain variable domain comprises complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 of the Fab light chain variable domain comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15; LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35; LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38; or LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41; and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

[0903] Embodiment 522 comprises a method of any one of embodiments 489-517, wherein the scFv heavy chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 7.

[0904] Embodiment 523 comprises a method of any one of embodiments 489-517, wherein the scFv heavy chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7

[0905] Embodiment 524 comprises a method of any one of embodiments 489-517, wherein the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7.

[0906] Embodiment 525 comprises a method of any one of embodiments 489-517, wherein the scFv heavy chain variable domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7 and has at least 80% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7.

[0907] Embodiment 526 comprises a method of any one of embodiments 489-517, wherein the scFv heavy chain variable domain comprises an amino acid sequence according to SEQ ID NO: 7.

[0908] Embodiment 527 comprises a method of any one of embodiments 489-518, wherein the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 8.

[0909] Embodiment 528 comprises a method of any one of embodiments 489-517, wherein the scFv light chain variable domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8.

[0910] Embodiment 529 comprises a method of any one of embodiments 489-517, wherein the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8.

[0911] Embodiment 530 comprises a method of any one of embodiments 489-517, wherein the scFv light chain variable domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8 and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8.

[0912] Embodiment 531 comprises a method of any one of embodiments 489-517, wherein the scFv light chain variable domain comprises an amino acid sequence according to SEQ ID NO: 8.

[0913] Embodiment 532 comprises a method of any one of embodiments 489-517, wherein the scFv comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 9.

[0914] Embodiment 533 comprises a method of any one of embodiments 489-517, wherein the scFv comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9.

[0915] Embodiment 534 comprises a method of any one of embodiments 489-517, wherein the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9.

[0916] Embodiment 535 comprises a method of any one of embodiments 489-517, wherein the scFv comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9 and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9.

[0917] Embodiment 536 comprises a method of any one of embodiments 489-517, wherein the scFv comprises an amino acid sequence according to SEQ ID NO: 9.

[0918] Embodiment 537 comprises a method of any one of embodiments 489-517, wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47.

[0919] Embodiment 538 comprises a method of any one of embodiments 489-517, wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

[0920] Embodiment 539 comprises a method of any one of embodiments 489-517, wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

[0921] Embodiment 540 comprises a method of any one of embodiments 489-517, wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17 and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

[0922] Embodiment 541 comprises a method of any one of embodiments 489-517, wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47.

[0923] Embodiment 542 comprises a method of any one of embodiments 489-517, wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46.

[0924] Embodiment 543 comprises a method of any one of embodiments 489-517, wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

[0925] Embodiment 544 comprises a method of any one of embodiments 489-517, wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

[0926] Embodiment 545 comprises a method of any one of embodiments 489-517, wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

[0927] Embodiment 546 comprises a method of any one of embodiments 489-517, wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46.

[0928] Embodiment 547 comprises a method of any one of embodiments 489-517, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 21.

[0929] Embodiment 548 comprises a method of any one of embodiments 489-517, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0930] Embodiment 549 comprises a method of any one of embodiments 489-517, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21.

[0931] Embodiment 550 comprises a method of any one of embodiments 489-517, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21.

[0932] Embodiment 551 comprises a method of any one of embodiments 489-517, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 22.

[0933] Embodiment 552 comprises a method of any one of embodiments 489-517, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0934] Embodiment 553 comprises a method of any one of embodiments 489-517, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

[0935] Embodiment 554 comprises a method of any one of embodiments 489-517, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 22.

[0936] Embodiment 555 comprises a method of any one of embodiments 489-554, wherein the multispecific antibodies of Formula Ia, Formula Ib, Formula Ic further comprise a half-life extending molecule (H_1).

[0937] Embodiment 556 comprises a method of embodiment 555, wherein H_1 is connected to P_1.

[0938] Embodiment 557 comprises a method of embodiment 555, wherein H_1 is connected to P_2.

[0939] Embodiment 558 comprises a method of any one of embodiments 555-557, wherein H_1 does not block A binding to CD28.

[0940] Embodiment 559 comprises a method of any one of embodiments 555-558, wherein H_1 does not block B binding to PD-L1.

[0941] Embodiment 560 comprises a method of any one of embodiments 555-559, H_1 comprises a linking moiety (L_5) that connects H_1 to P_1 or H_1 to P_2.

[0942] Embodiment 561 comprises a method of any one of embodiments 555-560, wherein the half-life extending molecule (H_1) does not have binding affinity to PD-L1.

[0943] Embodiment 562 comprises a method of any one of embodiments 555-5561, wherein the half-life extending molecule (H_1) does not have binding affinity to CD28.

[0944] Embodiment 563 comprises a method of any one of embodiments 555-562, wherein the half-life extending molecule (H_1) does not shield the multispecific antibody from CD28.

[0945] Embodiment 564 comprises a method of any one of embodiments 555-563, wherein H_1 comprises a sequence according to SEQ ID NOs: 54-57.

[0946] Embodiment 565 comprises a method of any one of embodiments 555-564, wherein H_1 comprises an amino acid sequence that has repetitive sequence motifs.

[0947] Embodiment 566 comprises a method of any one of embodiments 555-565, wherein H_1 comprises an amino acid sequence that has highly ordered secondary structure.

[0948] Embodiment 567 comprises a method of any one of embodiments 555-566, wherein H_1 comprises a polymer.

[0949] Embodiment 568 comprises a method of embodiment 567, wherein the polymer is polyethylene glycol (PEG).

[0950] Embodiment 569 comprises a method of any one of embodiments 555-566, wherein H_1 comprises albumin.

[0951] Embodiment 570 comprises a method of any one of embodiments 555-566, wherein H_1 comprises an Fc domain.

[0952] Embodiment 571 comprises a method of embodiment 569, wherein the albumin is serum albumin.

[0953] Embodiment 572 comprises a method of embodiment 571, wherein the albumin is human serum albumin.

[0954] Embodiment 573 comprises a method of any one of embodiments 555-566, wherein H_1 comprises a polypeptide, a ligand, or a small molecule.

[0955] Embodiment 574 comprises a method of embodiment 573, wherein the polypeptide, the ligand or the small molecule binds serum protein or a fragment thereof, a circulating immunoglobulin or a fragment thereof, or CD35/CR1.

[0956] Embodiment 575 comprises a method of embodiment 574, wherein the serum protein comprises a thyroxine-binding protein, a transthyretin, a 1-acid glycoprotein, a transferrin, transferrin receptor or a transferrin-binding portion thereof, a fibrinogen, or an albumin.

[0957] Embodiment 576 comprises a method of embodiment 574, wherein the circulating immunoglobulin molecule comprises IgGl, IgG2, IgG3, IgG4, slgA, IgM or IgD.

[0958] Embodiment 577 comprises a method of embodiment 574, wherein the serum protein is albumin.

[0959] Embodiment 578 comprises a method of embodiment 573, wherein the polypeptide is an antibody.

[0960] Embodiment 579 comprises a method of embodiment 578, wherein the antibody comprises a single domain antibody, a single chain variable fragment or a Fab.

[0961] Embodiment 580 comprises a method of embodiment 579, wherein the single domain antibody comprises a single domain antibody that binds to albumin.

[0962] Embodiment 581 comprises a method of embodiment 579, wherein the single domain antibody is a human or humanized antibody.

[0963] Embodiment 582 comprises a method of embodiment 579, wherein the single domain antibody is selected from the group consisting of 645gH1gL1, 645dsgH5gL4, 23-13-A01 -sc02, A10m3 or a fragment thereof, DOM7r-31, DOM7h-11-15, Alb-1, Alb-8, Alb-23, 10G, 10E and SA21.

[0964] Embodiment 583 comprises a method of embodiment 579, wherein the single domain antibody comprises complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 of the single domain antibody comprise: HC-CDR1: SEQ ID NO: 54, HC-CDR2: SEQ ID NO: 55, and HC-CDR3: SEQ ID NO: 56; and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of the HC-CDR1, HC-CDR2, or HC-CDR3.

[0965] Embodiment 584 comprises a method of any one of embodiments 555-566, wherein H_1 comprises an amino acid sequence according to SEQ ID NO: 57.

[0966] Embodiment 585 comprises a method of any one of embodiments 555-566, wherein H_1 comprises an amino acid sequence that has at least 80% sequence identity to SEQ ID NO: 57.

[0967] Embodiment 586 comprises a method of any one of embodiments 555-566, wherein H_1 comprises an amino acid sequence that has at least 85% sequence identity to SEQ ID NO: 57.

[0968] Embodiment 587 comprises a method of any one of embodiments 555-566, wherein H_1 comprises an amino acid sequence that has at least 90% sequence identity to SEQ ID NO: 57.

[0969] Embodiment 588 comprises a method of any one of embodiments 555-566, wherein H_1 comprises an amino acid sequence that has at least 95% sequence identity to SEQ ID NO: 57.

[0970] Embodiment 589 comprises a method of any one of embodiments 555-566, wherein H_1 comprises an amino acid sequence that has at least 99% sequence identity to SEQ ID NO: 57.

[0971] Embodiment 590 comprises a method of any one of embodiments 555-566, wherein H_1 comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof.

[0972] Embodiment 591 comprises a method of embodiment 590, wherein the modified amino acid or a modified non-natural amino acid comprises a post-translational modification.

[0973] Embodiment 592 comprises a method of any one of embodiments 555-591, wherein H_1 comprises a linking moiety (L5) that connects H_1 to P_1 or P_2.

[0974] Embodiment 593 comprises a method of embodiment 592, wherein L_5 is a peptide sequence having at least 5 to no more than 50 amino acids.

[0975] Embodiment 594 comprises a method of embodiment 592, wherein L_5 is a peptide sequence having at least 10 to no more than 30 amino acids.

[0976] Embodiment 595 comprises a method of embodiment 592, wherein L_5 is a peptide sequence having at least 10 amino acids.

[0977] Embodiment 596 comprises a method of embodiment 592, wherein L_5 is a peptide sequence having at least 18 amino acids.

[0978] Embodiment 597 comprises a method of embodiment 592, wherein L_5 is a peptide sequence having at least 26 amino acids.

[0979] Embodiment 598 comprises a method of embodiment 592, wherein L_5 has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

[0980] Embodiment 599 comprises a method of any one of embodiments 489-598, wherein L_1 or L_2 is a peptide sequence having at least 5 to no more than 50 amino acids.

[0981] Embodiment 600 comprises a method of any one of embodiments 489-598, wherein L_1 or L_2 is a peptide sequence having at least 10 to no more than 30 amino acids.

[0982] Embodiment 601 comprises a method of any one of embodiments 489-598, wherein L_1 or L_2 is a peptide sequence having at least 10 amino acids.

[0983] Embodiment 602 comprises a method of any one of embodiments 489-598, wherein L_1 or L_2 is a peptide sequence having at least 18 amino acids.

[0984] Embodiment 603 comprises a method of any one of embodiments 489-598, wherein L_1 or L_2 is a peptide sequence having at least 26 amino acids.

[0985] Embodiment 604 comprises a method of any one of embodiments 489-598, wherein L_1 or L_2 has a formula comprising $(G_2S)n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3.

[0986] Embodiment 605 comprises a method of any one of embodiments 489-598, wherein L_1 or L_2 has a formula comprising $(G_2S)n$, wherein n is an integer of at least 1.

[0987] Embodiment 606 comprises a method of any one of embodiments 489-598, wherein L_1 or L_2 has a formula selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

[0988] Embodiment 607 comprises a method of any one of embodiments 489-606, wherein the tumor specific protease is selected from the group consisting of metalloprotease, serine protease, cysteine protease, threonine protease, and aspartic protease.

[0989] Embodiment 608 comprises a method of any one of embodiments 489-606, wherein L_1 or L_2 comprises a urokinase cleavable amino acid sequence, a matriptase cleavable amino acid sequence, a legumain cleavable amino acid sequence, or a matrix metalloprotease cleavable amino acid sequence.

[0990] Embodiment 609 comprises a method of any one of embodiments 489-606, wherein L_1 or L_2 comprises a sequence according to SEQ ID NOs: 18-19, 62-88.

[0991] Embodiment 610 comprises a method of any one of embodiments 489-609, wherein L_1 is bound to N-terminus of A.

[0992] Embodiment 611 comprises a method of any one of embodiments 489-609, wherein L_1 is bound to C-terminus of A.

[0993] Embodiment 612 comprises a method of any one of embodiments 489-609, wherein L_2 is bound to N-terminus of B.

[0994] Embodiment 613 comprises a method of any one of embodiments 489-609, wherein L_2 is bound to C-terminus of B.

[0995] Embodiment 614 comprises a method of any one of embodiments 489-613, wherein P_1 becomes unbound from A when L1 is cleaved by the tumor specific protease thereby exposing A to CD28.

[0996] Embodiment 615 comprises a method of any one of embodiments 489-614, wherein P2 becomes unbound from B when L2 is cleaved by the tumor specific protease thereby exposing B to PD-L1.

[0997] Embodiment 616 comprises a method of any one of embodiments 489-615, wherein L_1 or L_2, comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof.

[0998] Embodiment 617 comprises a method of embodiment 616, wherein the modified amino acid or a modified non-natural amino acid comprises a post-translational modification.

[0999] Embodiment 618 comprises a method of any one of embodiments 489-617, wherein P_1 impairs binding of A to CD28.

[1000] Embodiment 619 comprises a method of any one of embodiments 489-618, wherein P_1 is bound to A through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof.

[1001] Embodiment 620 comprises a method of any one of embodiments 489-619, wherein P_1 is bound to A at or near an antigen binding site.

[1002] Embodiment 621 comprises a method of any one of embodiments 489-620, wherein P_1 becomes unbound from A when L1 is cleaved by the tumor specific protease thereby exposing A to CD28.

[1003] Embodiment 622 comprises a method of any one of embodiments 489-621, wherein P_1 has less than 75% sequence identity to CD28.

[1004] Embodiment 623 comprises a method of any one of embodiments 489-622, wherein P_1 has less than 80% sequence identity to CD28.

[1005] Embodiment 624 comprises a method of any one of embodiments 489-623, wherein P_1 has less than 85% sequence identity to CD28.

[1006] Embodiment 625 comprises a method of any one of embodiments 489-624, wherein P_1 has less than 90% sequence identity to CD28.

[1007] Embodiment 626 comprises a method of any one of embodiments 489-625, wherein P_1 has less than 95% sequence identity to CD28.

[1008] Embodiment 627 comprises a method of any one of embodiments 489-626, wherein P_1 comprises a de novo amino acid sequence that shares less than 10% sequence identity to CD28.

[1009] Embodiment 628 comprises a method of any one of embodiments 489-627, wherein P_2 impairs binding of B to PD-L1.

[1010] Embodiment 629 comprises a method of any one of embodiments 489-628, wherein P_2 is bound to B through ionic interactions, electrostatic interactions, hydrophobic interactions, Pi-stacking interactions, and H-bonding interactions, or a combination thereof.

[1011] Embodiment 630 comprises a method of any one of embodiments 489-629, wherein P_2 is bound to B at or near an antigen binding site.

[1012] Embodiment 631 comprises a method of any one of embodiments 489-630, wherein P_2 becomes unbound from B when L2 is cleaved by the tumor specific protease thereby exposing B to the PD-L1.

[1013] Embodiment 632 comprises a method of any one of embodiments 489-631, wherein P_2 has less than 70% sequence identity to the PD-L1.

[1014] Embodiment 633 comprises a method of any one of embodiments 489-632, wherein P_2 has less than 75% sequence identity to the PD-L1.

[1015] Embodiment 634 comprises a method of any one of embodiments 489-633, wherein P_2 has less than 80% sequence identity to the PD-L1.

[1016] Embodiment 635 comprises a method of any one of embodiments 489-634, wherein P_2 has less than 85% sequence identity to the PD-L1.

[1017] Embodiment 636 comprises a method of any one of embodiments 489-635, wherein P_2 has less than 90% sequence identity to the PD-L1.

[1018] Embodiment 637 comprises a method of any one of embodiments 489-636, wherein P_2 has less than 95% sequence identity to the PD-L1.

[1019] Embodiment 638 comprises a method of any one of embodiments 489-637, wherein P_2 comprises a de novo amino acid sequence that shares less than 10% sequence identity to the PD-L1.

[1020] Embodiment 639 comprises a method of any one of embodiments 489-638, wherein P_1 or P_2 comprises a peptide sequence of at least 5 amino acids in length.

[1021] Embodiment 640 comprises a method of any one of embodiments 489-639, wherein P_1 or P_2 comprises a peptide sequence of at least 6 amino acids in length.

[1022] Embodiment 641 comprises a method of any one of embodiments 489-640, wherein P_1 or P_2 comprises a peptide sequence of at least 10 amino acids in length.

[1023] Embodiment 642 comprises a method of any one of embodiments 489-641, wherein P_1 or P_2 comprises a peptide sequence of at least 10 amino acids in length and no more than 20 amino acids in length.

[1024] Embodiment 643 comprises a method of any one of embodiments 489-642, wherein P_1 or P_2 comprises a peptide sequence of at least 16 amino acids in length.

[1025] Embodiment 644 comprises a method of any one of embodiments 489-641, wherein P_1 or P_2 comprises a peptide sequence of no more than 40 amino acids in length.

[1026] Embodiment 645 comprises a method of any one of embodiments 489-644, wherein P_1 or P_2 comprises at least two cysteine amino acid residues.

[1027] Embodiment 646 comprises a method of any one of embodiments 489-644, wherein P_1 or P_2 comprises a cyclic peptide or a linear peptide.

[1028] Embodiment 647 comprises a method of any one of embodiments 489-644, wherein P_1 or P_2 comprises a cyclic peptide.

[1029] Embodiment 648 comprises a method of any one of embodiments 489-644, wherein P_1 or P_2 comprises a linear peptide.

[1030] Embodiment 649 comprises a method of any one of embodiments 489-644, wherein P_1 or P_2 comprise a modified amino acid or non-natural amino acid, or a modified non-natural amino acid, or a combination thereof.

[1031] Embodiment 650 comprises a method of any one of embodiments 489-644, wherein P_1 or P_2 does not comprise albumin or an albumin fragment.

[1032] Embodiment 651 comprises a method of any one of embodiments 489-644, wherein P_1 or P_2 does not comprise an albumin binding domain.

EXAMPLES

Example 1. Immune Cell Activation Assays

[1033] This Example assesses PDL1 x CD28 multispecific antibody Ab-1 in *in vitro* immune cell activation assays using target coated beads. An exemplary schema of the PDL1 x CD28 multispecific antibodies is seen in **Figs. 1A-1B**.

[1034] Immune cell activation was measured via cytokine release and immune cell proliferation after co-culture of target coated beads and PBMCs. Briefly, M280 magnetic streptavidin beads were treated with soluble biotinylated PDL1. M280 beads were washed and seeded in a 96 well plate at 200,000 beads per well. Compounds were then titrated as single agents and added to the wells followed by 100,000 PBMCs. Human T cell activator CD3/CD28 beads (Invitrogen) were used as a positive control in the absence of compound. Wells lacking M280 target coated beads were used as negative controls. After 48hours of co-culture, cytokines were measured in the supernatant using Cytometric Bead Array (CBA) Human Th1/Th2/Th17 Cytokine Kit from BD Biosciences. The concentration of cytokines was calculated using a standard curve per manufacturer's instructions. Co-culture of PBMCs, M280 target coated beads, and compounds continued for a total of 8 days where medium and compounds were replaced on day 4. On days 1, 4, and 8, magnetic beads were removed using a magnet, cells harvested, and stained using LIVE/DEAD, anti-CD3, anti-CD4, and anti-CD8 fluorescent markers. The total amount of live cells, live CD3+ cells, live

CD4+ cells, or live CD8+ cells were measured via flow cytometry and plotted versus logarithmic compound concentration. Proliferation was determined by the increase in live cells and associated T cell populations. An exemplary schema of the assay is seen in **Fig. 2**.

[1035] Cytokine release was measured from PBMCs cultured with single agent PDL1 x CD28 multispecific antibody Ab-1. **Fig. 3A** shows data for IFNy. **Fig. 3B** shows data for TNFα. **Fig. 3C** shows data for IL-2. The data shows Ab-1does not trigger non-specific IFNy, TNFα, and IL-2 release from PBMC's and that Ab-1 requires immune cells to recognize an antigen to trigger activation.

[1036] **Figs. 4A-4D** show data for the number of live immune cells **(Fig. 4A)**, CD3+ cells **(Fig. 4B)**, CD4+ cells **(Fig. 4C)**, and CD8+ cells **(Fig. 4D)** over time in response to PBMC co-cultured with PDL1 target coated beads and Ab-1. The data shows that Ab-1does not trigger non-specific immune cell proliferation and that Ab-1 requires immune cells to recognize an antigen to trigger proliferation.

Example 2. Kinetic Binding Assays Against Human PD-L1

[1037] This Example assesses binding of Ab-1 and anti-PD-L1 Fab 1 to human PD-L1 in an in vitro assay.

[1038] Kinetic binding of Ab-1 and anti-PD-L1 Fab 1 to biotinylated human PDL1 was evaluated by bio-layer interferometry using an Octet RED96 instrument. Briefly, biosensors were loaded with antigen and baselined in buffer. Polypeptide molecules were titrated in solution at 50nM, 25nM, 12.5nM, and 6.25nM then associated onto the antigen loaded sensors. After a short association period, sensors were transferred into buffer and the dissociation of bound polypeptide molecules was measured. The timing and steps of the experiment are shown in the accompanying table. Association and dissociation signals were recorded in real time and analyzed using a 1:1 binding model within the instrument software. Analysis using a 1:1 binding model enabled the calculation of the on and off rate constants as well as affinity, KD. Off rate constants were converted to half-life as shown in Figs. 5A and 5B.

Table 15. Timing and Steps of Assay

Step	**Time**
Baseline: Octet buffer	**60sec**
Load: • **10nM Human PDL1-biotin**	**300sec**
Biocytin quench (100uM)	**300sec**
Baseline: Octet buffer	**300sec**
Association: Octet buffer • **50nM Ab-1** • **25nM Ab-1** • **12.5nM Ab-1** • **6.25nM Ab-1** • **50nM** anti-PD-L1 Fab 1 • **25nM** anti-PD-L1 Fab 1	**300sec**

- **12.5nM** anti-PD-L1 Fab 1 - **6.25nM** anti-PD-L1 Fab 1	
Dissociation: Octet Buffer	**900sec**

Example 3. Kinetic Binding Assays Against Human CD28

[1039] This Example assesses binding of Ab-1 and Ab-2 to human PD-L1 in an in vitro assay.

[1040] Kinetic binding of Ab-1 and Ab-2 to biotinylated human CD28 was evaluated by bio-layer interferometry using an Octet RED96 instrument. Briefly, biosensors were loaded with antigen and baselined in buffer. Polypeptide molecules were titrated in solution at 50nM then associated onto the antigen loaded sensors. After a short association period, sensors were transferred into buffer and the dissociation of bound polypeptide molecules was measured. The timing and steps of the experiment are shown in the accompanying table. Association and dissociation signals were recorded in real time and analyzed using a 1:1 binding model within the instrument software. Analysis using a 1:1 binding model enabled the calculation of the on and off rate constants as well as affinity, KD. Off rate constants were converted to half-life shown in Figs. 6A and 6B.

Table 16. Timing and Steps of Assay

Step	**Time**
Baseline: Octet buffer	**60sec**
Load: - **10nM Human CD28-Biotin**	**300sec**
Biocytin quench (100uM)	**300sec**
Baseline: Octet buffer	**300sec**
Association in octet buffer - **50nM Ab-2** - **50nM Ab-1**	**300sec**
Dissociation: Octet Buffer	**900sec**

Example 4. Kinetic Binding Assays Against Human and Cynomolgus Monkey PD-L1

[1041] This Example assesses binding of Ab-1 to human PD-L1 Fc and cynomolgus monkey PD-L1 Fc in an in vitro assay.

[1042] Kinetic binding of Ab-1 to human PD-L1 Fc and cynomolgus monkey PD-L1 Fc was evaluated by bio-layer interferometry using an Octet RED96 instrument. Briefly, biosensors were loaded with antigen and baselined in buffer. Polypeptide molecules were titrated in solution at 50nM then associated onto the antigen loaded sensors. After a short association period, sensors were transferred into buffer and the dissociation of bound polypeptide molecules was measured. The timing and steps of the experiment are shown in the accompanying table. Association and dissociation signals were recorded in real time and analyzed using a 1:1 binding model within the instrument software. Analysis using a 1:1 binding model enabled the calculation of the on and off rate constants as well as affinity, KD. Off rate constants were converted to half-life shown in Figs. 7A and 7B.

Table 17. Timing and Steps of Assay

Step	Time
Baseline: Octet buffer	60sec
Load: • **15nM human PDL1-Fc** • **15nM cyno PDL1-Fc**	300sec
Baseline: Octet buffer	**300sec**
Association in octet buffer • **50nM Ab-1** • **25nM Ab-1** • **12.5nM Ab-1** • **6.25nM Ab-1**	300sec
Dissociation: Octet Buffer	**900sec**

Example 5. ELISA Binding Assays of Polypeptide Complex Molecules to human PD-L1, CD28 and EGFR

[1043] The polypeptide complex molecules were evaluated for their ability to bind human PDL1 or CD28 in a standard enzyme linked immunosorbent assay (ELISA) format. Briefly, biotinylated antigen was captured on neutravidin coated plates. Polypeptide complex molecules diluted in buffer were then added to the antigen coated plates. Bound polypeptide complex was detected using a standard horse radish peroxidase conjugate secondary antibody. The concentration of polypeptide complex required to achieve 50% maximal signal (EC50) was calculated using Graphpad Prism software. Fig. 8A illustrates binding of Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, and Ab-6 to PD-L1 and is summarized in Table 18. Fig. 8B illustrates binding of Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, and Ab-6to CD28 and is summarized in Table 19.

Table 18. Summary of binding of Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, and Ab-6 to PD-L1

PD-L1 ELISA	**Ab-1**	**Ab-2**	**Ab-3**	**Ab-4**	**Ab-5**	**Ab-6**
EC50 nM	0.30	1.02	0.22	1.03	0.11	0.28

Table 19. Summary of binding of Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, and Ab-6 to CD28

CD28 ELISA	**Ab-1**	**Ab-2**	**Ab-3**	**Ab-4**	**Ab-5**	**Ab-6**
EC50 nM	1.27	1.44	0.92	3.64	0.91	1.89

Example 6. T cell Activation Assays of Ab-1 in Combination with an anti-TROP2 x CD3 T cell engager (TCE-1)

[1044] Immune cell activation was measured via cytokine release and immune cell proliferation after co-culture of non-immunogenic target coated beads and PBMCs. Briefly, M280 magnetic streptavidin beads were treated with soluble biotinylated PDL1 and soluble biotinylated TROP2. M280 beads were washed and seeded in a 96 well plate at 200,000 beads per well. Compounds were then titrated as single agents and in combination then added to the wells followed by 100,000 PBMCs. Human T cell activator CD3/CD28 beads (Invitrogen) were used as a positive control in the absence of compound. Wells lacking M280 target coated beads were used as negative controls. After 48hours of co-culture, cytokines were measured in the supernatant using Cytometric Bead Array (CBA) Human Th1/Th2/Th17 Cytokine Kit from BD Biosciences. The concentration of cytokines was calculated using a standard curve per manufacturer’s instructions. Co-culture of PBMCs, M280 target coated beads, and compounds continued for a total of 8 days where medium and compounds were replaced on day 4. On days 1, 4, and 8, magnetic beads were removed using a magnet, cells harvested, and stained using LIVE/DEAD, anti-CD3, anti-CD4, and anti-CD8 fluorescent markers. The total amount of live cells, live CD3+ cells, live CD4+ cells, or live CD8+ cells were measured via flow cytometry and plotted versus logarithmic compound concentration. Proliferation was determined by the increase in live cells and associated T cell populations. Figs. 9B-9D illustrate that PBMC activation measured by cytokine release require both Ab-1 and TCE-1, an anti- TROP2 x CD3 T cell engager. Figs. 9E – 9H illustrate immune cell proliferation after co-culture of target coated beads and PBMCs and administration of Ab-1 and the combination of Ab-1 and TCE-1, an anti-TROP2 x CD3 T cell engager. Figs. 9B-9D illustrate that immune cell proliferation from PBMCs activation measured by flow cytometry against non-immunogenic beads coated with TAA and PDL1 requires both Ab-1 and TCE-1, an anti-TROP2 x CD3 T cell engager. The sequences of TCE-1 is provided in **Table 20.**

Table 20. Amino acid sequences of TCE-1

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
TCE-1 LC TROP2 Fab LC	DIQLTQSPSSLSASVGDRVSITCKAS**QDVSIA**VAWYQQKPGKAPKLLIY**SAS**YRYTGVPDRFSGSGSGTDFTLTISSLQPEDFAVYYC**QQHYITPLT**FGAGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	118
TCE-1 HC SP34.194 scFv (VH – linker 1 – VL) + Linker 2 + TROP2 Fab HC	QTVVTQEPSLTVSPGGTVTLTCRSS**TGAVTTSNY**ANWVQQKPGQAPRGLIG**GT**NKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYC**ALWYSNLWV**FGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLKLSCAAS**GFTFNTYA**MNWVRQAPGKGLEWVAR**IRSKYNNYAT**YYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYC**VRHGNFGNSYVSWFAY**WGQGTLVTVSSGGGGSQVQLQQSGSELKKPGASVKVSCKAS**GYTFTNYG**MNWVKQAPGQGLKWMGW**INTYTGEP**TYTDDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFC**ARGGFGSSYWYFDV**WGQGSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	128

Example 7. T cell Activation Assays of Ab-1 through Ab-8 in Combination with an anti-TROP2 x CD3 T cell engager (TCE-3)

[1045] Immune cell activation was measured via cytokine release and immune cell proliferation after co-culture of target coated beads and PBMCs. Briefly, M280 magnetic streptavidin beads were treated with soluble biotinylated PDL1 and soluble biotinylated TROP2. M280 beads were washed and seeded in a 96 well plate at 200,000 beads per well. Compounds were then titrated as single agents and in combination then added to the wells followed by 100,000 PBMCs. Human T cell activator CD3/CD28 beads (Invitrogen) were used as a positive control in the absence of compound. Wells lacking M280 target coated beads were used as negative controls. After 48hours of co-culture, cytokines were measured in the supernatant using Cytometric Bead Array (CBA) Human Th1/Th2/Th17 Cytokine Kit from BD Biosciences. The concentration of cytokines was calculated using a standard curve per manufacturer's instructions. Co-culture of PBMCs, M280 target coated beads, and compounds continued for a total of 8 days where medium and compounds were replaced on day 4. On days 1, 4, and 8, magnetic beads were removed using a magnet, cells harvested, and stained using LIVE/DEAD, anti-CD3, anti-CD4, and anti-CD8 fluorescent markers. The total amount of live cells, live CD3+ cells, live CD4+ cells, or live CD8+ cells were measured via flow cytometry and plotted versus logarithmic compound concentration. Proliferation was determined by the increase in live cells and associated T cell populations.

Figs. 9I – 9K illustrate polypeptide complexes of different orientation harboring different PD-L1 binding domains (Ab-1 through Ab-8) are able to activate PBMCs as measured by cytokine release in combination with a T cell engager (TCE-3) against non-immunogenic beads coated with TAA and PD-L1. The sequences of TCE-3 is provided in **Table 21. Fig. 9L** illustrates that polypeptide complex mediated activation of PBMCs is dependent on PD-L1 surface density and the combination with a T cell engager. **Figs. 9M-9S** illustrate polypeptide complex mediated activation of PBMCs is dependent on PD-L1 surface density and the combination with a T cell engager.

Table 21. Amino acid sequences of TCE-3

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
TCE-3 HC TROP2 Fab HC	QVQLQQSGSELKKPGASVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYTDDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFCARGGFGSSYWYFDVWGQGSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	129
TCE-3 LC SP34.185 scFv + linker + TROP2 Fab LC	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAPRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSGGGGSDIQLTQSPSSLSASVGDRVSITCKASQDVSIAVAWYQQKPGKAPKLLIYSASYRY	130

	TGVPDRFSGSGSGTDFTLTISSLQPEDFAVYYCQQHYITPLTFGAGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	

Example 8. Tumor Cell Killing Assays with of Ab-1 in Combination with an anti- TROP2 X CD3 T cell engager (TCE-2)

[1046] Polypeptide complexes were evaluated in a functional in vitro tumor cell killing and cytokine release assays using the PDL1 positive tumor cell line, LNCaP. Tumor cell killing was measured using an xCelligence real time cell analyzer from Agilent that relies on sensor impedance measurements (cell index) that increased as tumor cells adhere, spread, and expand on the surface of the sensor. Likewise, as the tumor cells were killed the impedance decreased. Tumor cells were added and allowed to adhere overnight on a 96 well E-Plate. The following day polypeptide complexes as single agents or in combination with a TCE, TRACTr, or pre-cleaved TRACTr were titrated in human serum supplemented medium along with PBMCs and added to the wells. Cell index measurements were taken every 10 minutes for an additional 120hours. The cell index times number of hours (tumor cell growth kinetics) was then plotted versus concentration of polypeptide complex where the concentration required to reduce the tumor growth 50% (IC50) was calculated using Graphpad Prism software. Cytokines were measured at study endpoint using the Th1/Th2/Th17 cytometric bead array from BD Biosciences.

[1047] **Figs. 10A-10 C** illustrate results of an in vitro tumor cell killing assay using the LNCaP PDL1 positive tumor cell line in which Ab-1 and TCE-2 are co-administered in the presence of human PBMCs. In vitro tumor cell killing is synergized when Ab-1 is combined with an anti-PSMA x CD3 T cell engager, TCE-2. The sequences of TCE-2 is provided in **Table 22.**

Table 22. Amino acid sequences of TCE-2

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
TCE-2 LC	EVQLVESGGGLVQPGGSLKLSCAAS**GFTFNKYA**MNWVRQAPGKGLEWVAR**IRSKYNNYAT**YYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYC**VRHGNFGNSYISYWAY**WGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTLTCGSS**TGAVTSGNY**PNWVQQKPGQAPRGLIG**GT**KFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYC**VLWYSNRWV**FGGGTKLTVLGGGGSDIQMTQSPSSLSASVGDRVTITCRAS**QGISNY**LAWYQQKTGKVPKFLIY**EA**STLQSGVPSRFSGGGSGTDFTLTISSLQPEDVATYYC**QNYNSAPFT**F	232

	GPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
TCE-2 HC	QVQLVESGGGVVQPGRSLRLSCAAS**GFAFSRYG**MHWVRQAPGKGLEWVAV**IWYDGSNK**YYADSVKGRFTISRDNSKNTQYLQMNSLRAEDTAVYYC**ARGGDFLYYYYYGMDV**WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	127

[1048] **Fig. 10D** illustrates a graph of killing H292 tumor cells using Ab-1 and TCE-4. **Fig. 10E** illustrates a graph of killing H292 tumor cells using Ab-1 and TRACTr-1. **Fig. 10F** illustrates a graph of killing H292 tumor cells using Ab-1, TRACTr-1, and MTSP1. Polypeptide complexes enhance TRACTr tumor cell killing in the presence of human PBMCs. **Fig. 10G** illustrates a graph of IL-2 cytokine release from PBMCs cultured with Ab-1 and TCE-4. **Fig. 10H** illustrates a graph of IL-2 cytokine release from PBMCs cultured with Ab-1 and TRACTr-1. **Fig. 10I** illustrates a graph of IL-2 cytokine release from PBMCs cultured with Ab-1, TRACTr-1, and MTSP1. Polypeptide complexes enhance TRACTr tumor cell killing in the presence of human PBMCs.

[1049] The sequences of TCE-4 and TRACTr-1 are provided in **Table 23.**

Table 23. Amino acid sequences of TCE-4 and TRACTr-1

Construct Description	Amino Acid Sequence (N to C)	SEQ ID NO:
TCE-4 LC TROP2 Fab LC	DIQLTQSPSSLSASVGDRVSITCKASQDVSIAVAWYQQKPGKAPKLLIYSASYRYTGVPDRFSGSGSGTDFTLTISSLQPEDFAVYYCQQHYITPLTFGAGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	131
TCE-4 HC SP34.185 scFv + linker + TROP2 Fab HC	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTLTCGS	132

	STGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVLGGGGSQVQLQQSGSELKKPGASVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYTDDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFCARGGFGSSYWYFDVWGQGSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC	
TRACTr-1 LC TROP2 TRACTr Mask + linker + cleavable linker + linker + TROP2 Fab LC	GGVDFCKIYSWPVCHQGGGGSGGLSGRSDAGSPLGLAGSGGSDIQLTQSPSSLSASVGDRVSITCKASQDVSIAVAWYQQKPGKAPKLLIYSASYRYTGVPDRFSGSGSGTDFTLTISSLQPEDFAVYYCQQHYITPLTFGAGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	133
TRACTr-1 HC TROP2 TRACTr Albumin binding domain + linker + mask + linker + cleavable linker + linker + SP34.185 scFv + linker + TROP2 Fab HC	EVQLVESGGGLVQPGGSLRLSCAASGSTFYTAVMGWVRQAPGKGLEWVAAIRWTALTTSYADSVKGRFTISRDGAKTTLYLQMNSLRPEDTAVYYCAARGTLGLFTTADSYDYWGQGTLVTVSSGGGGSGGGSGGVYCGPEFDESVGCMGGGGSGGGLSGRSDAGSPLGLAGSGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVLGGGGSQVQLQQSGSELKKPGASVKVSCKASGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYTDDFKGRFAFSLDTSVSTAYLQISSLKADDTAVYFCARGGF	134

	GSSYWYFDVWGQGSLVTVSS ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSC	

Example 9. Pharmacokinetics of Ab-1 in Cynomolgus Monkey

[1050] Pharmacokinetics and exploratory safety of Ab-1 were evaluated in cynomolgus monkeys. Briefly, cynomolgus monkeys of approximately 3kg bodyweight were administered polypeptides as an IV bolus and observed daily for signs of adverse events. No in-life adverse events were observed. After dosing, blood was collected in K2 EDTA tubes at specific timepoints and processed to plasma. Plasma was stored frozen until analysis. Concentration of polypeptide molecules in plasma was measured via standard ELISA techniques relative to a reference standard diluted in control cyno plasma. Plasma concentration curves were fit to a standard two phase exponential equation representing distribution and elimination phases. Fitting of pharmacokinetics enabled the calculation of Cmax, half-life, volume of distribution, clearance, and 7 day area under the curve (AUC) shown in Table 24. Fig. 11 illustrates pharmacokinetics of Ab-1 in cynomolgus monkey after a single IV bolus injection.

Table 24. Figure 11 pharmacokinetic summary of Ab-1

	Ab-1 30ug/kg	Units
CMAX	10.73	nM
t1/2	2.15	hr
Vd	0.11	L
VSS	1.17	L
CL	12.09	mL/hr/kg
BW	3.00	kg
7day AUC	843	nM · min

Example 10. Cytokine release in Cynomolgus Monkey after Single IV Bolus Injection of Ab-1

[1051] Cytokine release after Ab-1 administration by IV bolus was evaluated in cynomolgus monkeys. Briefly, cynomolgus monkeys of approximately 3kg bodyweight were administered polypeptides as an IV bolus and observed daily for signs of adverse events. No in-life adverse events were observed. After dosing, blood was collected in K2 EDTA tubes at specific timepoints and processed to plasma. Plasma was stored frozen until analysis. Plasma samples were analyzed for cytokines using a non-human primate cytometric Th1/Th2 bead array kit from BD biosciences following the manufacturers instructions. Interferon gamma, tumor necrosis factor alpha, interleukin 6, interleukin 5, interleukin 4, and interleukin 2 levels in plasma were calculated relative to reference standards provided with the bead array kit. Fig. 12A – 12F illustrates cytokine release in cynomolgus monkey after a single IV bolus injection of Ab-1.

Example 11. Analysis of Liver Enzymes in Cynomolgus Monkey after Single IV Bolus Injection of Ab-1

[1052] Systemic liver enzymes after polypeptide molecule administration by IV bolus was evaluated in cynomolgus monkeys. Briefly, cynomolgus monkeys of approximately 3kg bodyweight were administered polypeptides as an IV bolus and observed daily for signs of adverse events. No in-life adverse events were observed. After dosing, blood was collected in K2 EDTA tubes at specific timepoints and processed to plasma. Plasma was stored frozen until analysis. Plasma samples were analyzed for the presence of liver enzymes aspartate transaminase (AST) and alanine aminotransferase (ALT) as signs of potential liver toxicity. AST and ALT levels remained within the normal ranges for all timepoints tested after dosing suggesting a lack of liver toxicity. AST and ALT were quantified following the instructions provided in a commercially available kit from Millipore. AST and ALT levels were calculated according to manufacturers instructions relative to a positive control reference standard. Fig. 13A – 13B illustrates serum liver enzymes in cynomolgus monkey after a single IV bolus injection of Ab-1.

CLAIMS

WHAT IS CLAIMED IS:

1. A multispecific antibody comprising a cluster of differentiation 28 (CD28) binding domain and a programmed death-ligand 1 (PD-L1) binding domain.

2. The multispecific antibody of claim 1, wherein when the CD28 binding domain is a single chain variable fragment (scFv), then the PD-L1 binding domain is not a scFv.

3. The multispecific antibody of claim 1, wherein the multispecific antibody is according to the following formula:

A-L-B

(Formula I)

wherein

A comprises the CD28 binding domain;

B comprises the PD-L1 binding domain; and

L comprises a linker that connects A to B.

4. The multispecific antibody of claim 3, wherein the CD28 binding domain comprises a single chain variable fragment, a single domain antibody, a Fab, or a Fab′.

5. The multispecific antibody of claim 4, wherein the CD28 binding domain comprises the single chain variable fragment.

6. The multispecific antibody of claim 4, wherein the CD28 binding domain comprises the single domain antibody.

7. The multispecific antibody of claim 4, wherein the CD28 binding domain comprises the Fab or the Fab′.

8. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises a single domain antibody, a Fab, or a Fab′.

9. The multispecific antibody of claim 8, wherein the PD-L1 binding domain comprises the Fab or the Fab′.

10. The multispecific antibody of claim 9, wherein the PD-L1 binding domain comprises the Fab or the Fab′ and the CD28 binding domain comprises the single chain variable fragment.

11. The multispecific antibody of claim 10, wherein the PD-L1 binding domain that comprises the Fab or the Fab′ comprises a Fab heavy chain polypeptide comprising a Fab heavy chain variable domain and a Fab light chain polypeptide comprising a Fab light chain variable domain.

12. The multispecific antibody of claim 11, wherein the CD28 binding domain that comprises the single chain variable fragment comprises a scFv heavy chain variable domain and a scFv light chain variable domain.

13. The multispecific antibody of claim 3, wherein the linker connects the C-terminus of A to an N-terminus of B.

14. The multispecific antibody of claim 3, wherein the linker connects the N-terminus of A to a C-terminus of B.

15. The multispecific antibody of claim 12, wherein the linker connects the C-terminus of A to the N-terminus of the Fab heavy chain polypeptide.

16. The multispecific antibody of claim 12, wherein the linker connects the N-terminus of A to the C-terminus of the Fab heavy chain polypeptide.

17. The multispecific antibody of claim 12, wherein the linker connects the C-terminus of A to the N-terminus of the Fab light chain polypeptide.

18. The multispecific antibody of claim 12, wherein the linker connects the N-terminus of A to the C-terminus of the Fab light chain polypeptide.

19. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the scFv light chain variable domain.

20. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the scFv heavy chain variable domain.

21. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the scFv light chain variable domain.

22. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the scFv heavy chain variable domain.

23. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the N-terminus of the scFv light chain variable domain.

24. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain.

25. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the N-terminus of the scFv heavy chain variable domain.

26. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

27. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv light chain variable domain.

28. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain.

29. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the N-terminus of the scFv heavy chain variable domain.

30. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv heavy chain variable domain.

31. The multispecific antibody of claim 3, wherein the linker is at least 5 amino acids in length.

32. The multispecific antibody of claim 31, wherein the linker is no more than 30 amino acids in length.

33. The multispecific antibody of claim 32, wherein the linker is at least 5 amino acids and no more than 30 amino acids in length.

34. The multispecific antibody of claim 33, wherein the linker is 5 amino acids in length.

35. The multispecific antibody of claim 33, wherein the linker is 15 amino acids in length.

36. The multispecific antibody of claim 3, wherein the linker is selected from the group consisting of $(G_2S)_n$, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO: 58), $(GGGS)_n$ (SEQ ID NO: 59), $(GGGGS)_n$ (SEQ ID NO: 60), and $(GSSGGS)_n$ (SEQ ID NO: 61), wherein n is an integer of at least 1.

37. The multispecific antibody of claim 3, wherein L has a formula comprising $(G_2S)_n$ (SEQ ID NO: 233), wherein n is an integer from 1 to 3.

38. The multispecific antibody of claim 3, wherein the L comprises an amino acid sequence of SEQ ID NO: 18 (GGGGSGGGGSGGGGS) or SEQ ID NO: 19 (GGGGS).

39. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises heavy chain variable domain complementarity determining regions (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 comprise: HC-CDR1: SEQ ID NO: 1; HC-CDR2: SEQ ID NO: 2; HC-CDR3: SEQ ID NO: 3, and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

40. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises light chain variable domain complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 comprise: LC-CDR1: SEQ ID NO: 4; LC-CDR2: SEQ ID NO: 5; and LC-CDR3: SEQ ID NO: 6, and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

41. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises heavy chain variable domain complementarity determining region (CDRs): HC-CDR1, HC-CDR2, and HC-CDR3, wherein the HC-CDR1, the HC-CDR2, and the HC-CDR3 comprise: HC-CDR1: SEQ ID NO: 10; HC-CDR2: SEQ ID NO: 11; HC-CDR3: SEQ ID NO: 12, HC-CDR1: SEQ ID NO: 24; HC-CDR2: SEQ ID NO: 25; HC-CDR3: SEQ ID NO: 26; or HC-CDR1: SEQ ID NO: 27; HC-CDR2: SEQ ID NO: 28; HC-CDR3: SEQ ID NO: 29; or HC-CDR1: SEQ ID NO: 30; HC-CDR2: SEQ ID NO: 31; HC-CDR3: SEQ ID NO: 32; and wherein said CDRs comprise from 0-2 amino acid modifications in at least one of said HC-CDR1, HC-CDR2, or HC-CDR3.

42. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises light chain variable domain complementarity determining regions (CDRs): LC-CDR1, LC-CDR2, and LC-CDR3, wherein the LC-CDR1, the LC-CDR2, and the LC-CDR3 comprise:LC-CDR1: SEQ ID NO: 13; LC-CDR2: SEQ ID NO: 14; and LC-CDR3: SEQ ID NO: 15; LC-CDR1: SEQ ID NO: 33; LC-CDR2: SEQ ID NO: 34; and LC-CDR3: SEQ ID NO: 35;

LC-CDR1: SEQ ID NO: 36; LC-CDR2: SEQ ID NO: 37; and LC-CDR3: SEQ ID NO: 38; or

LC-CDR1: SEQ ID NO: 39; LC-CDR2: SEQ ID NO: 40; and LC-CDR3: SEQ ID NO: 41; and wherein the CDRs comprise from 0-2 amino acid modifications in at least one of said LC-CDR1, LC-CDR2, or LC-CDR3.

43. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 7.

44. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 7

45. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7.

46. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence of at least 110 consecutive amino acid residues of SEQ ID NO: 7 and has at least 80% sequence identity to the at least 110 consecutive amino acid residues of SEQ ID NO: 7.

47. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence according to SEQ ID NO: 7.

48. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 8.

49. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence of at least 75 consecutive amino acid residues of SEQ ID NO: 8.

50. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8.

51. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence of at least 100 consecutive amino acid residues of SEQ ID NO: 8 and has at least 80% sequence identity to the at least 100 consecutive amino acid residues of SEQ ID NO: 8.

52. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence according to SEQ ID NO: 8.

53. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 9.

54. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 9.

55. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9.

56. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence of at least 210 consecutive amino acid residues of SEQ ID NO: 9 and has at least 80% sequence identity to the at least 210 consecutive amino acid residues of SEQ ID NO: 9.

57. The multispecific antibody of claim 1, wherein the CD28 binding domain comprises an amino acid sequence according to SEQ ID NO: 9.

58. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47.

59. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

60. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

61. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises an amino acid sequence of at least 215 consecutive amino acid residues of SEQ ID NO: 17 and has at least 80% sequence identity to the at least 215 consecutive amino acid residues of SEQ ID NO: 17, 43, 45, or 47.

62. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 17, 43, 45, or 47.

63. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46.

64. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises an amino acid sequence of at least 175 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

65. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

66. The multispecific antibody of claim 1, wherein the PD-L1 binding domain comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 16 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 16, 42, 44, or 46.

67. The multispecific antibody of claim 1, wherein PD-L1 binding domain comprises an amino acid sequence according to SEQ ID NO: 16, 42, 44, or 46.

68. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 21.

69. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus

of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21.

70. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 20 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 20 and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 21 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 21.

71. The multispecific antibody of claim 12, wherein the linker connects the Fab heavy chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab light chain polypeptide comprises an amino acid sequence according to SEQ ID NO: 20, and an amino acid sequence of the Fab heavy chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 21.

72. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence that has at least 80% sequence identity to the amino acid sequence according to SEQ ID NO: 22.

73. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22.

74. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain polypeptide comprises an amino acid sequence of at least 200 consecutive amino acid residues of SEQ ID NO: 23 and has at least 80% sequence identity to the at least 200 consecutive amino acid residues of SEQ ID NO: 23 and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence of at least 450 consecutive amino acid residues of SEQ ID NO: 22 and has at least 80% sequence identity to the at least 450 consecutive amino acid residues of SEQ ID NO: 22.

75. The multispecific antibody of claim 12, wherein the linker connects the Fab light chain polypeptide to the C-terminus of the scFv light chain variable domain and wherein the Fab heavy chain

polypeptide comprises an amino acid sequence according to SEQ ID NO: 23, and an amino acid sequence of the Fab light chain polypeptide that is connected to the C-terminus of the scFv light chain variable domain comprises an amino acid sequence to SEQ ID NO: 22.

76. A pharmaceutical composition comprising:

(i) the multispecific antibody of any one of claims 1-75; and
(ii) a pharmaceutically acceptable excipient.

77. An isolated recombinant nucleic acid molecule encoding a polypeptide of the multispecific antibody of any one of claims 1-75.

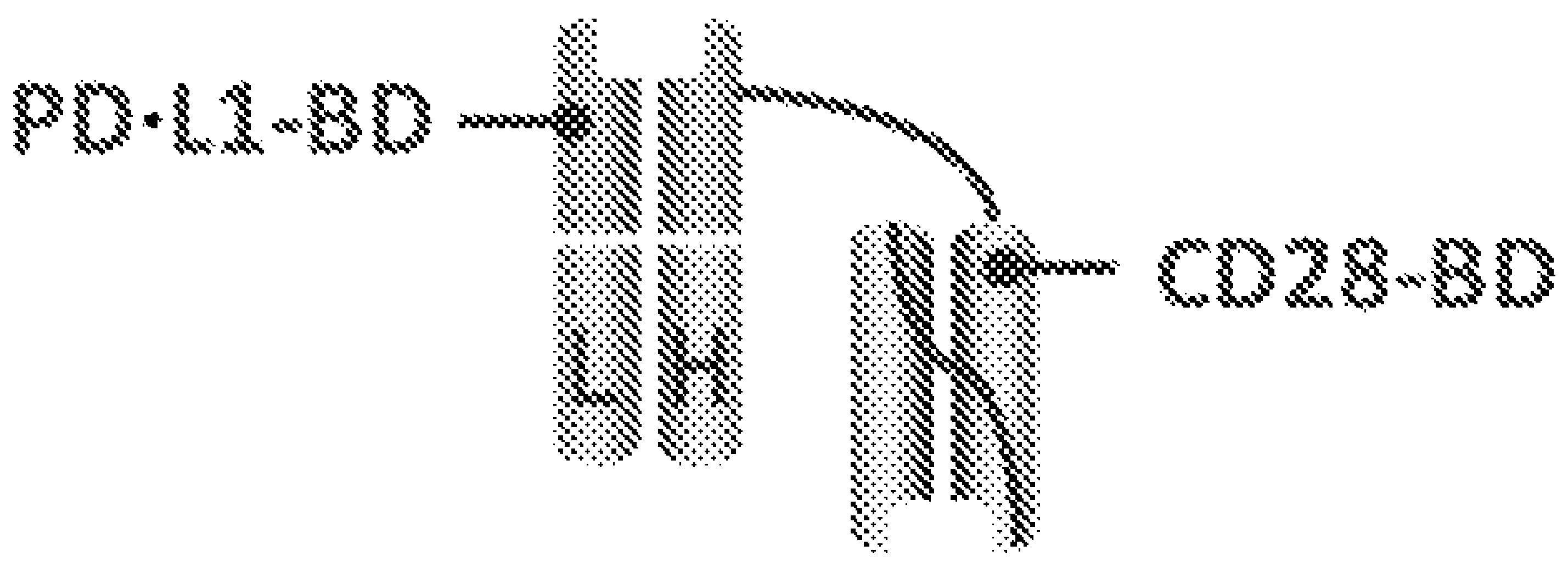


Fig. 1A

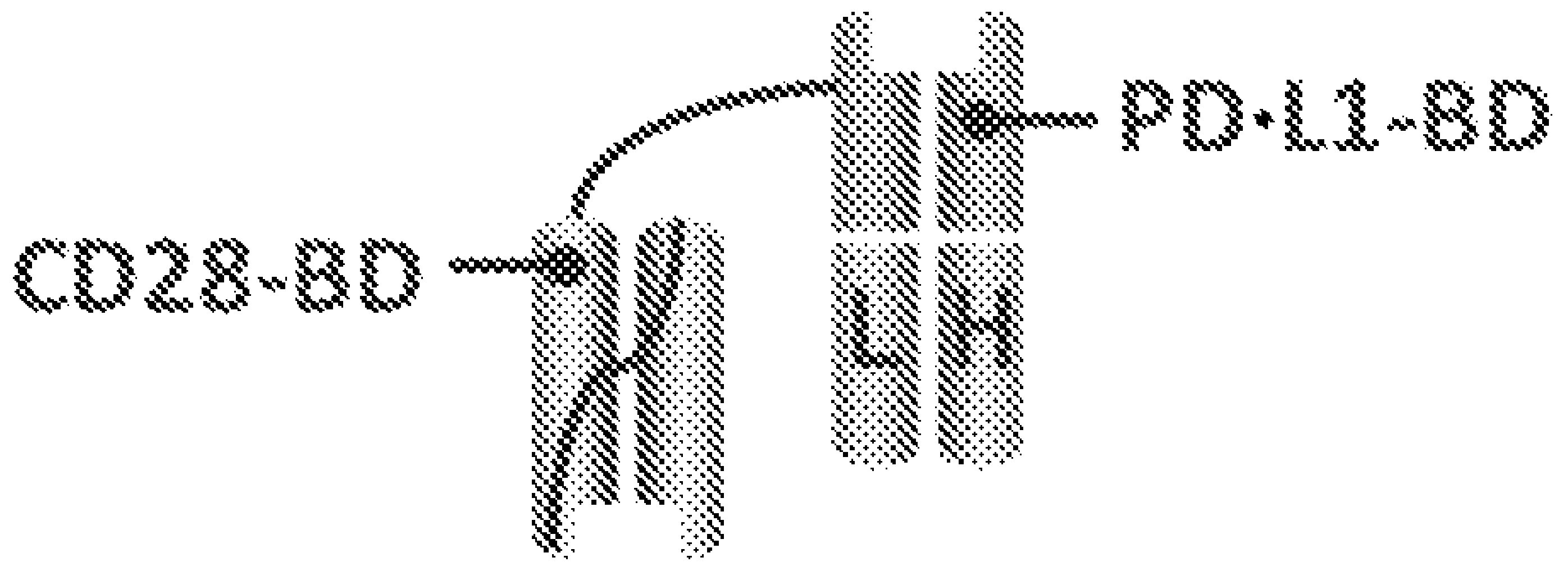
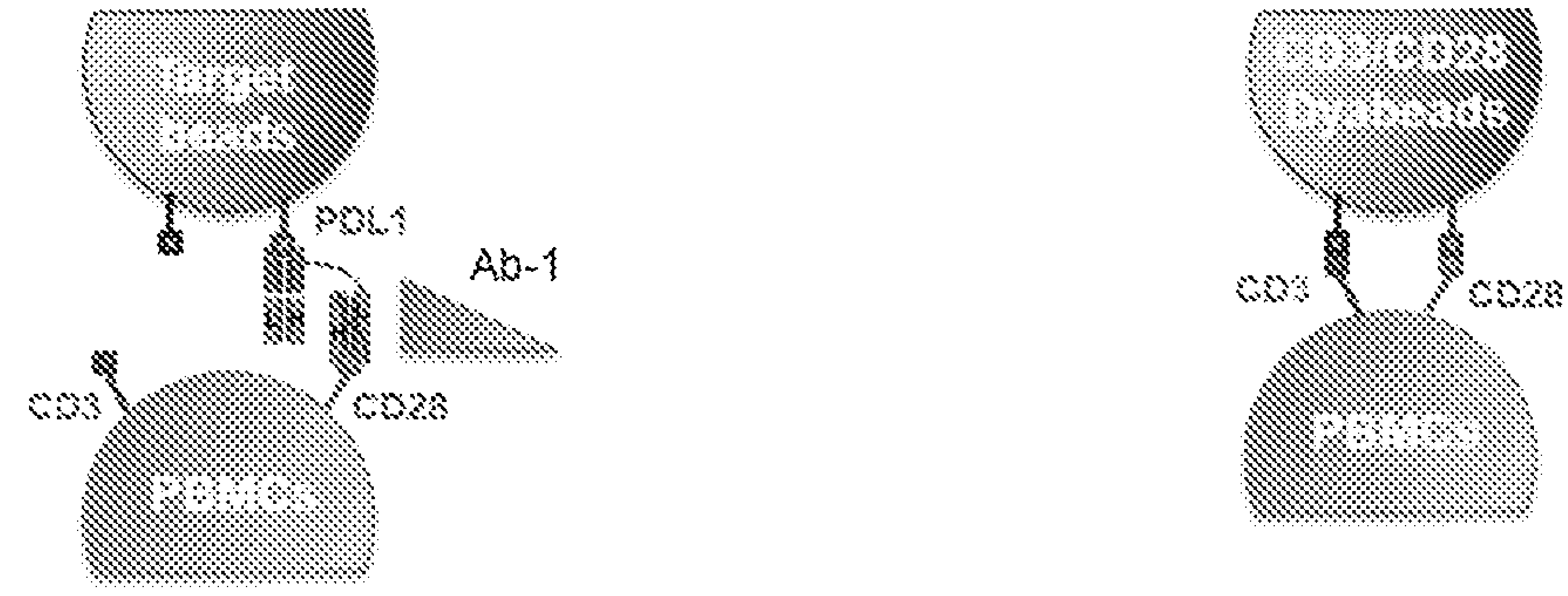


Fig. 1B



PDL1xCD28 bispecific single agent

CD3/CD28 Dynabeads alone
Positive control

Fig. 2

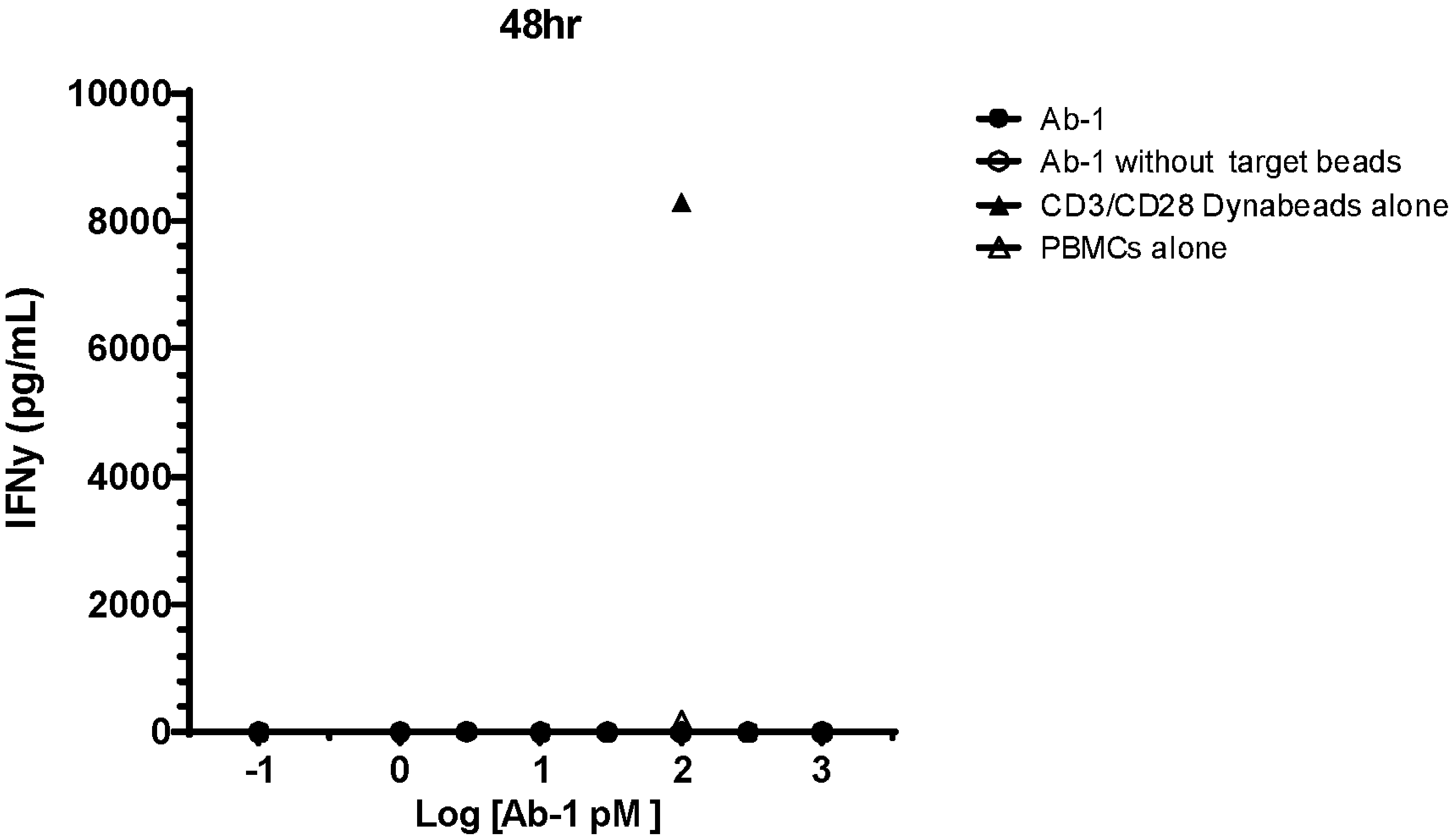

48hr
IFNy (pg/mL)
10000
8000
6000
4000
2000
0
-1
0
1
2
3
Log [Ab-1 pM]
Ab-1
Ab-1 without target beads
CD3/CD28 Dynabeads alone
PBMCs alone

Fig. 3A

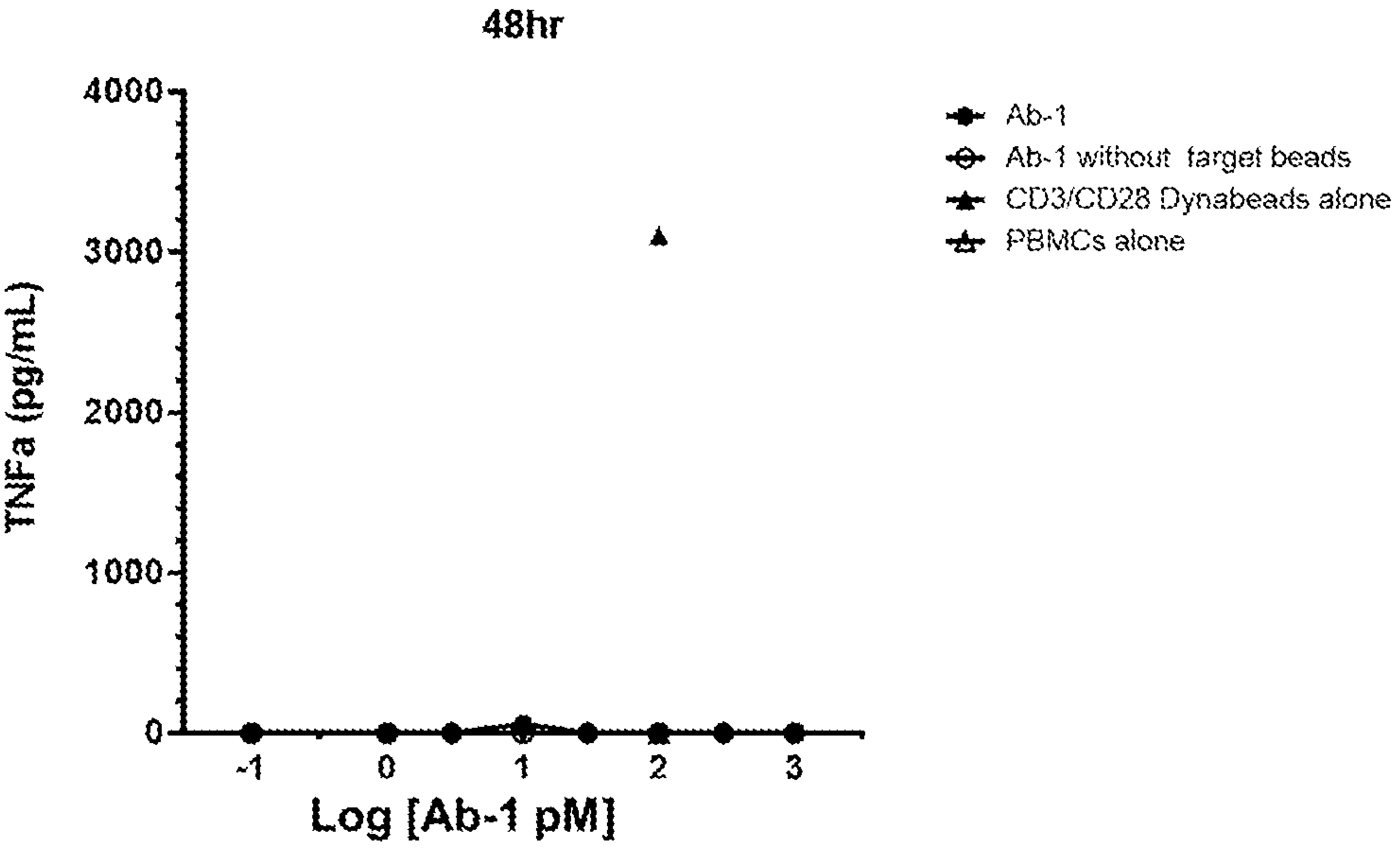

48hr
TNFa (pg/mL)
4000
3000
2000
1000
0
-1
0
1
2
3
Log [Ab-1 pM]
Ab-1
Ab-1 without target beads
CD3/CD28 Dynabeads alone
PBMCs alone

Fig. 3B

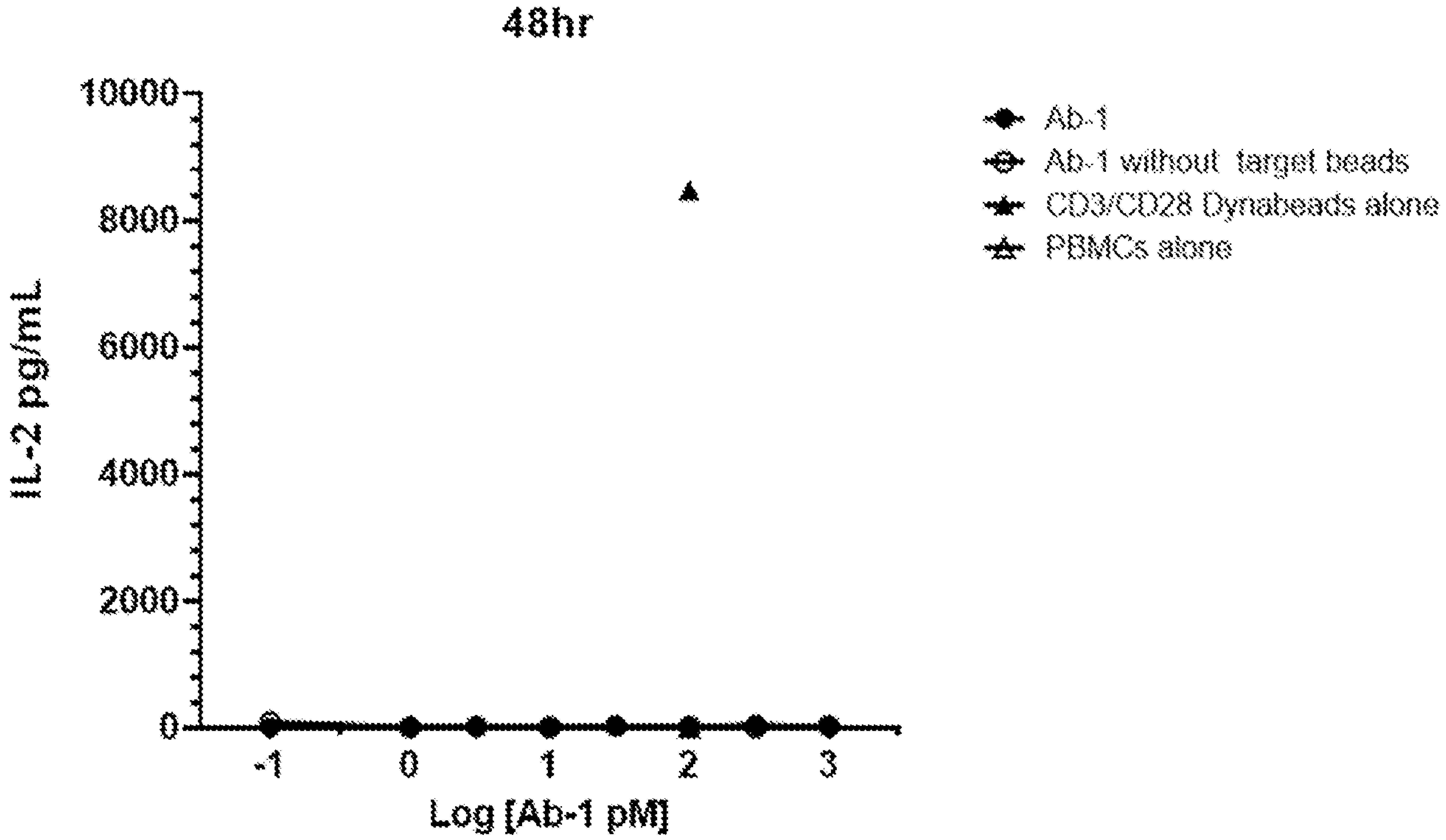

48hr
IL-2 pg/mL
10000
8000
6000
4000
2000
0
-1
0
1
2
3
Log [Ab-1 pM]
Ab-1
Ab-1 without target beads
CD3/CD28 Dynabeads alone
PBMCs alone

Fig. 3C

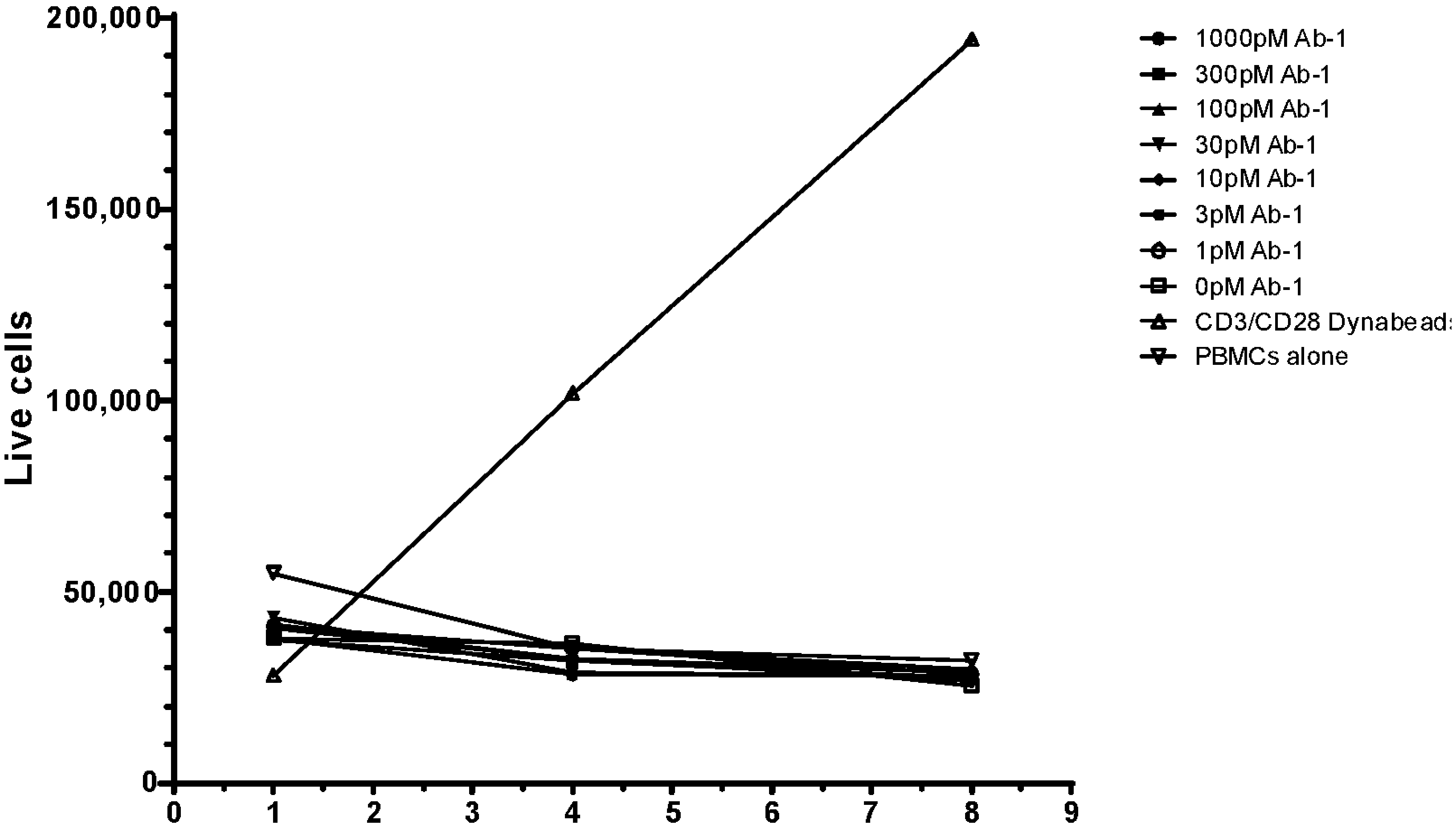

Live cells
200,000
150,000
100,000
50,000
0
0
1
2
3
4
5
6
7
8
9
1000pM Ab-1
300pM Ab-1
100pM Ab-1
30pM Ab-1
10pM Ab-1
3pM Ab-1
1pM Ab-1
0pM Ab-1
CD3/CD28 Dynabeads
PBMCs alone

Fig. 4A

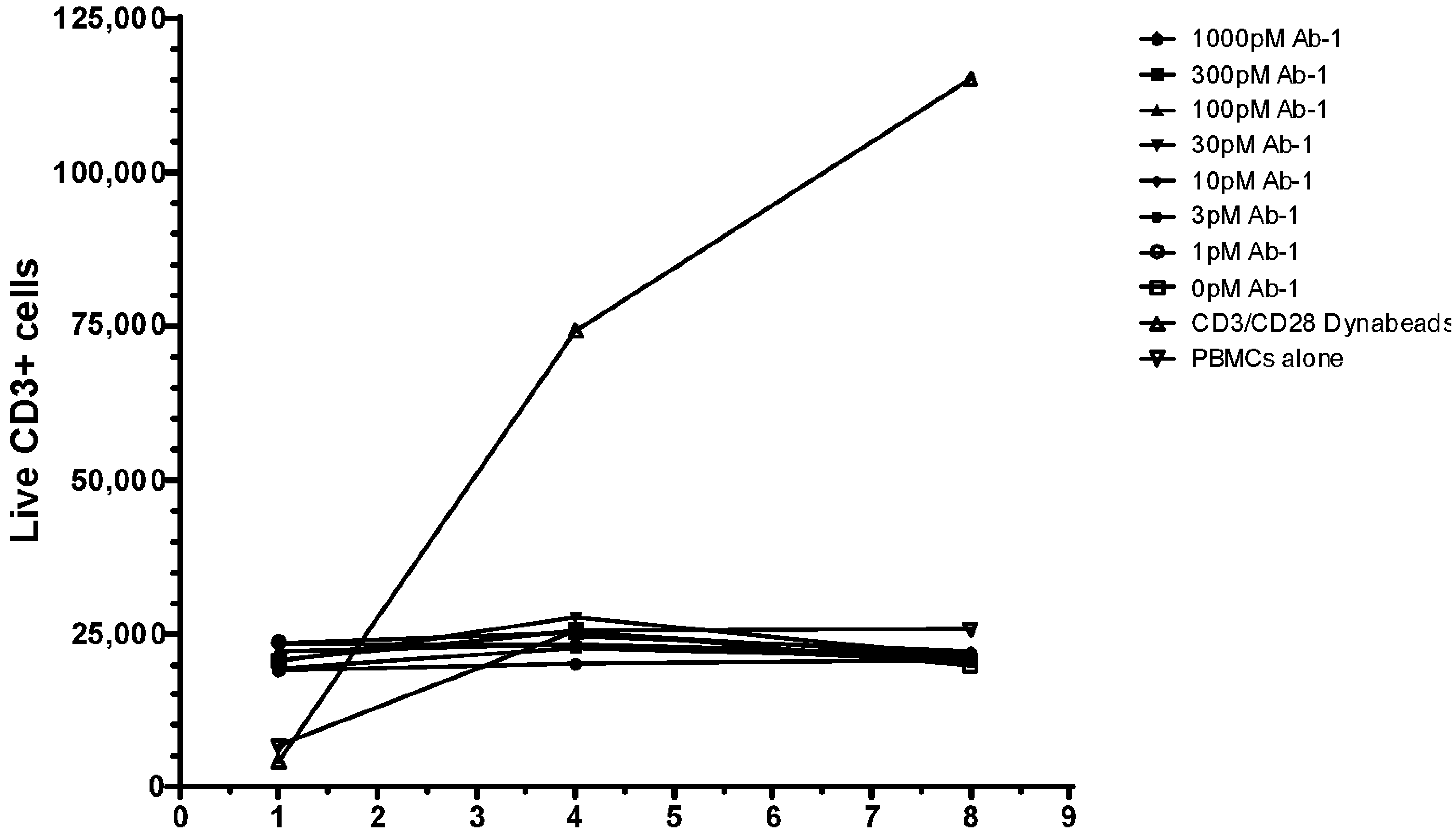

Live CD3+ cells
125,000
100,000
75,000
50,000
25,000
0
0
1
2
3
4
5
6
7
8
9
1000pM Ab-1
300pM Ab-1
100pM Ab-1
30pM Ab-1
10pM Ab-1
3pM Ab-1
1pM Ab-1
0pM Ab-1
CD3/CD28 Dynabeads
PBMCs alone

Fig. 4B

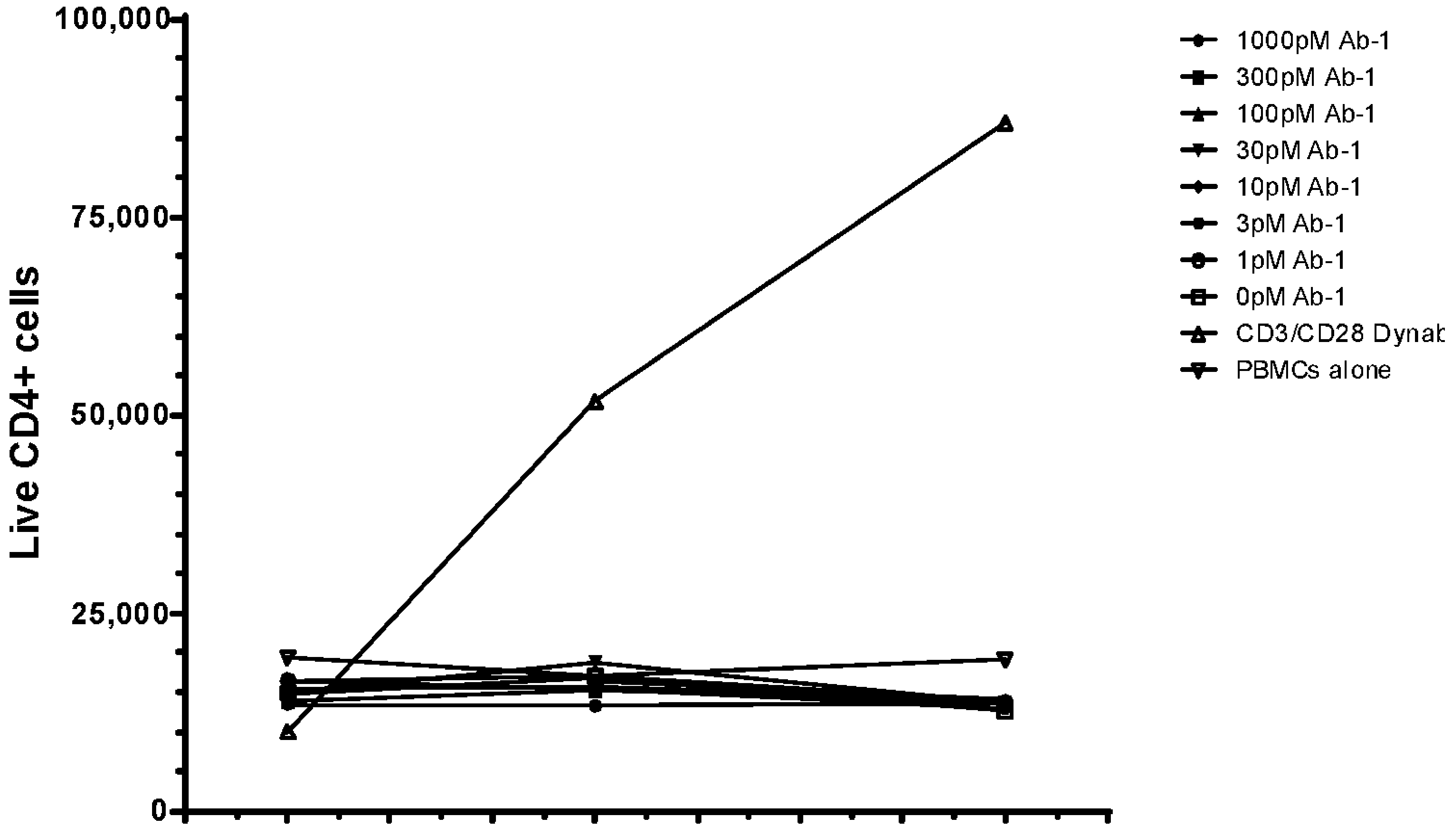

100,000
75,000
50,000
25,000
0
Live CD4+ cells
1000pM Ab-1
300pM Ab-1
100pM Ab-1
30pM Ab-1
10pM Ab-1
3pM Ab-1
1pM Ab-1
0pM Ab-1
CD3/CD28 Dynat
PBMCs alone

Fig. 4C

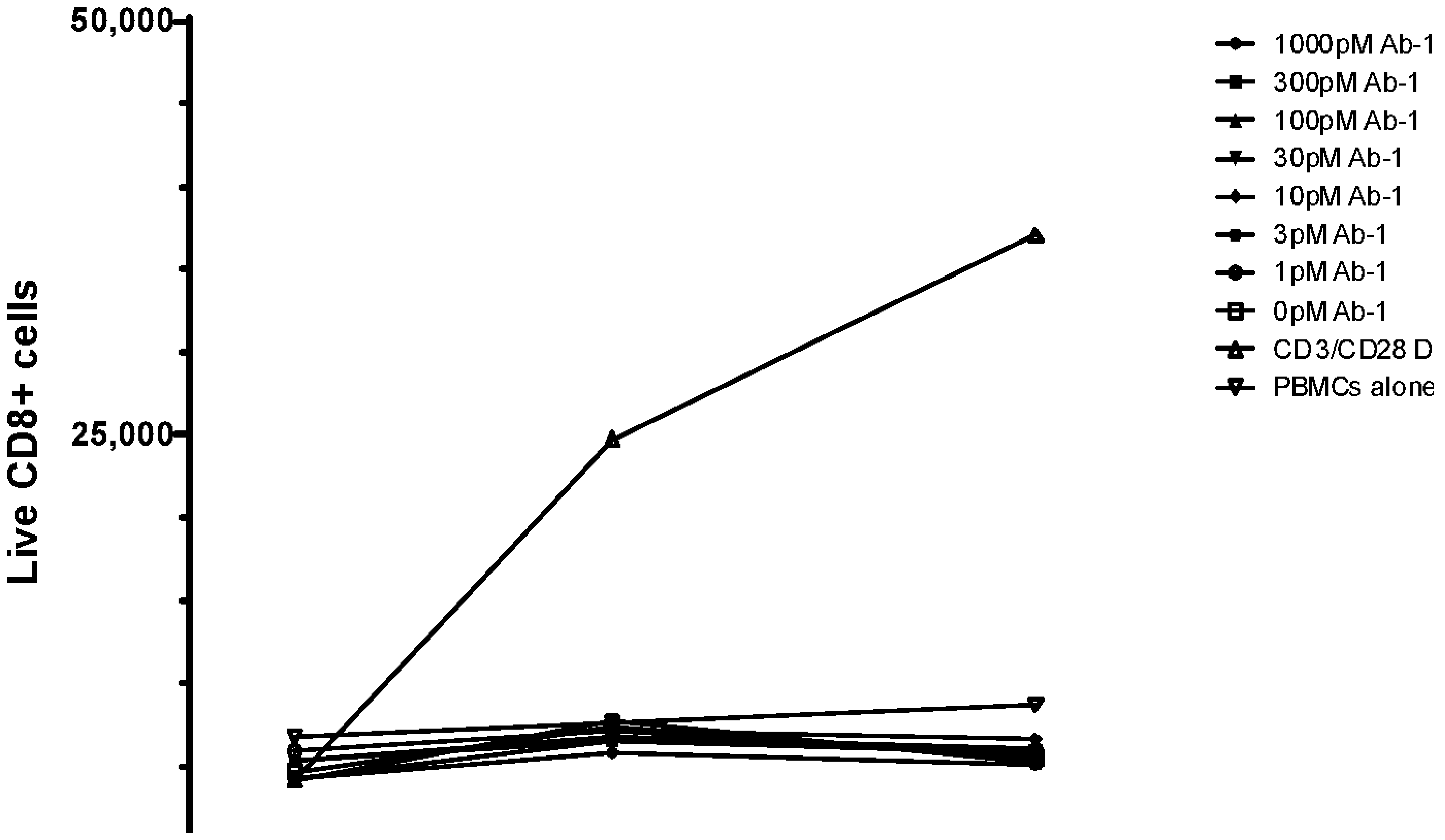

50,000
25,000
Live CD8+ cells
1000pM Ab-1
300pM Ab-1
100pM Ab-1
30pM Ab-1
10pM Ab-1
3pM Ab-1
1pM Ab-1
0pM Ab-1
CD3/CD28 D
PBMCs alone

Fig. 4D

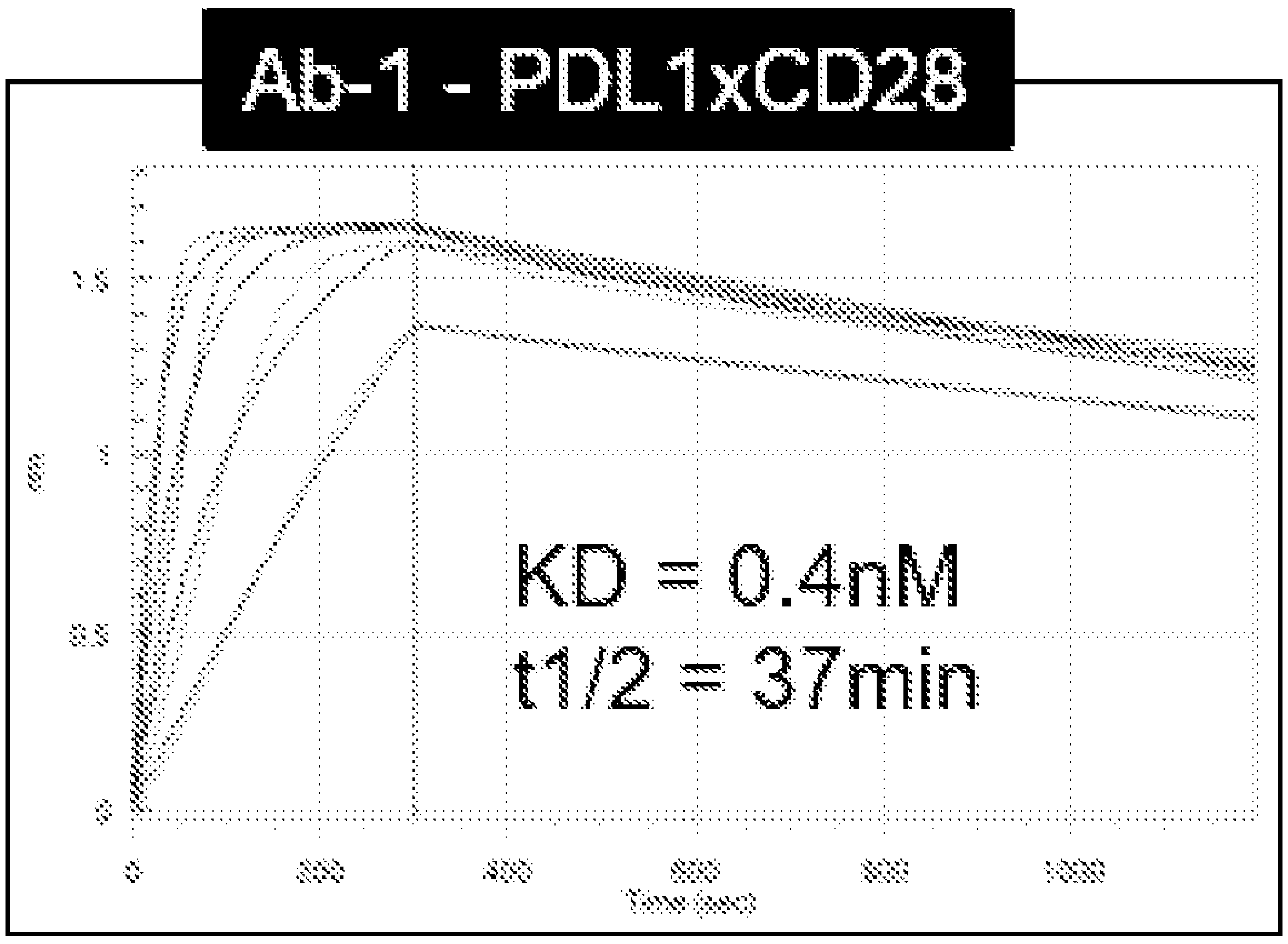

Ab-1 - PDL1xCD28
KD = 0.4nM
t1/2 = 37min
1.5
1
0.5
0
0
200
400
600
800
1000
Time (sec)

Fig. 5A

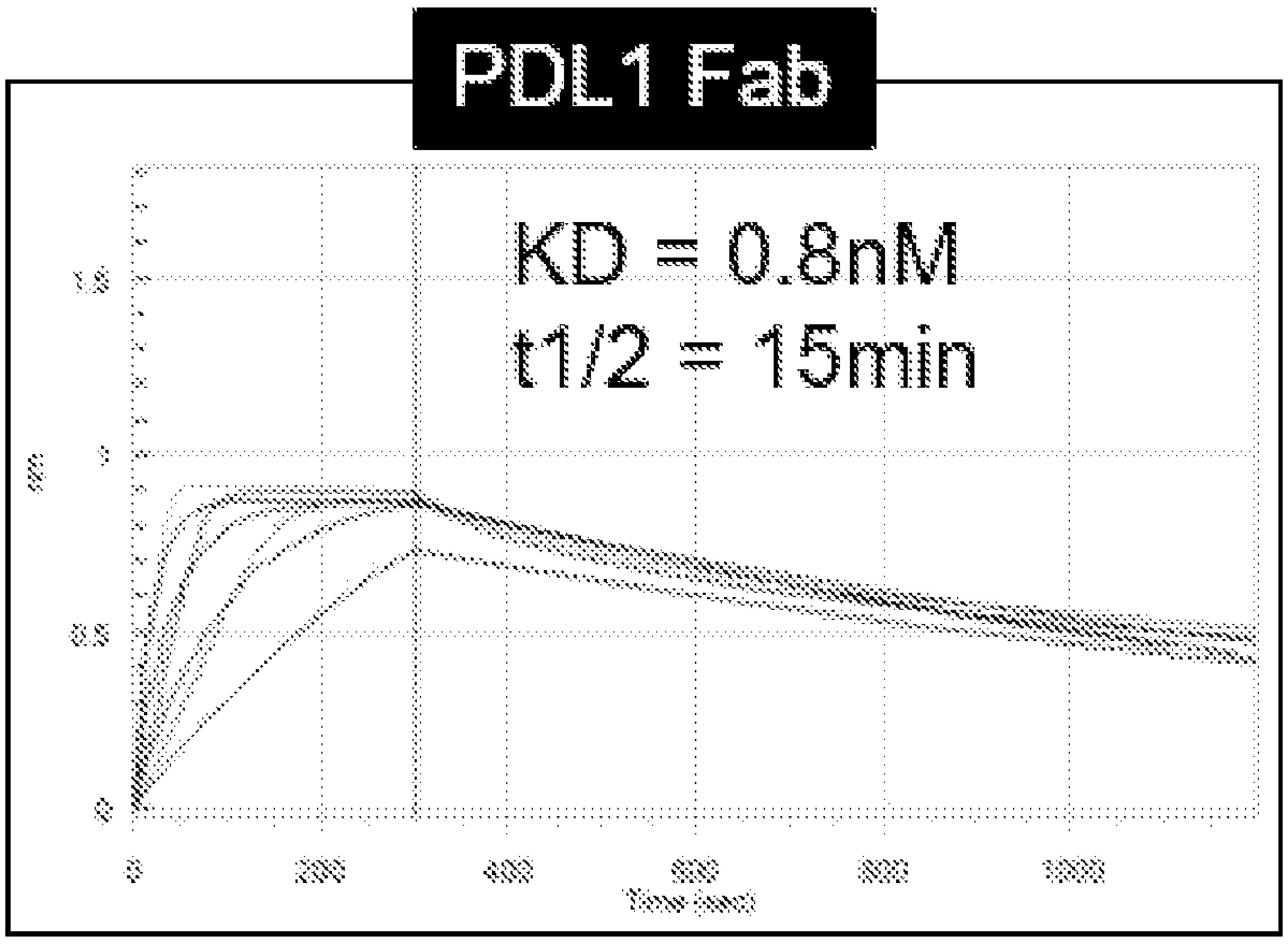

PDL1 Fab
KD = 0.8nM
t1/2 = 15min
1.5
1
0.5
0
0
200
400
600
800
1000
Time (sec)

Fig. 5B

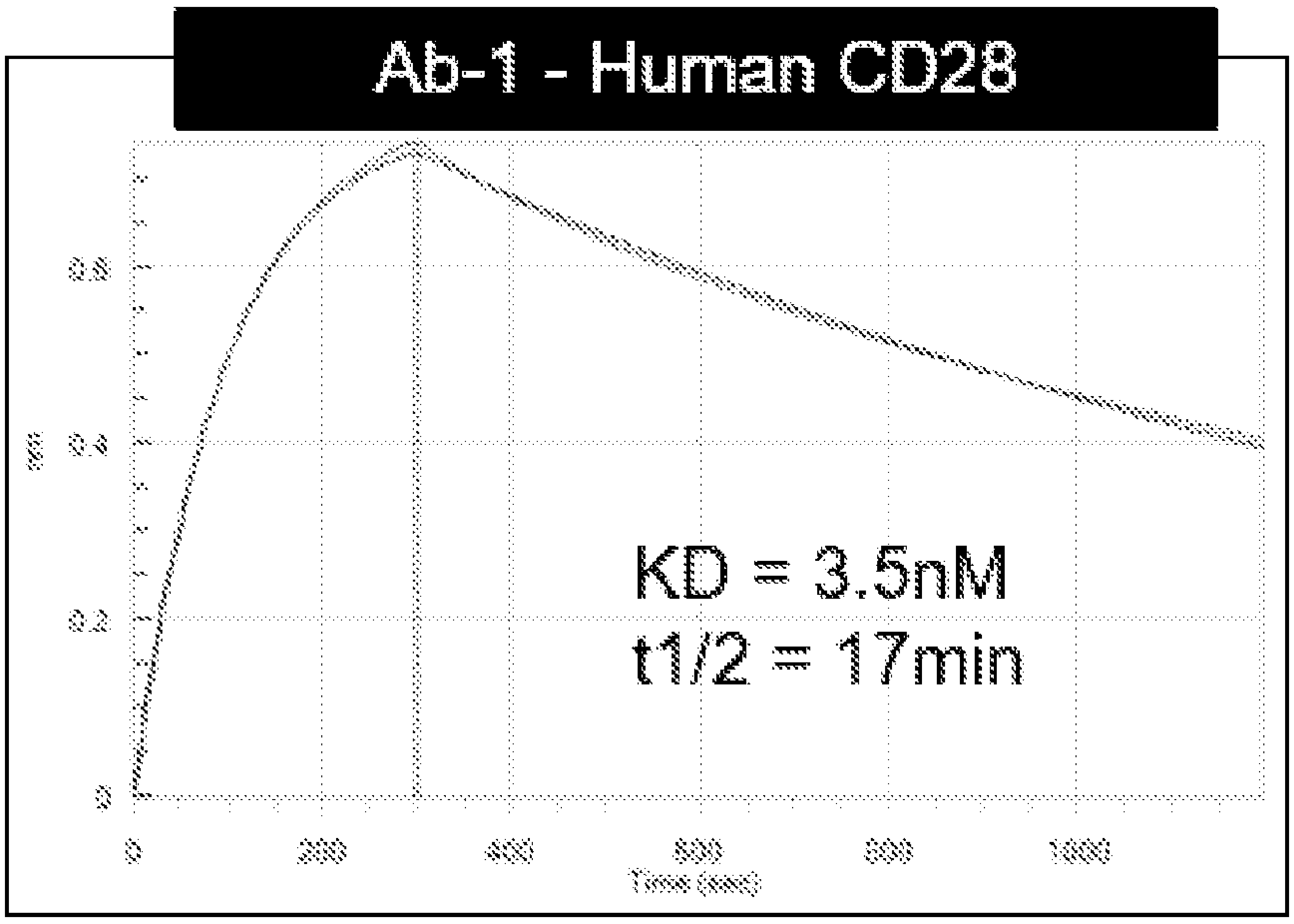

Ab-1 - Human CD28
0.6
0.4
0.2
0
0
200
400
600
800
1000
Time (sec)
KD = 3.5nM
t1/2 = 17min

Fig. 6A

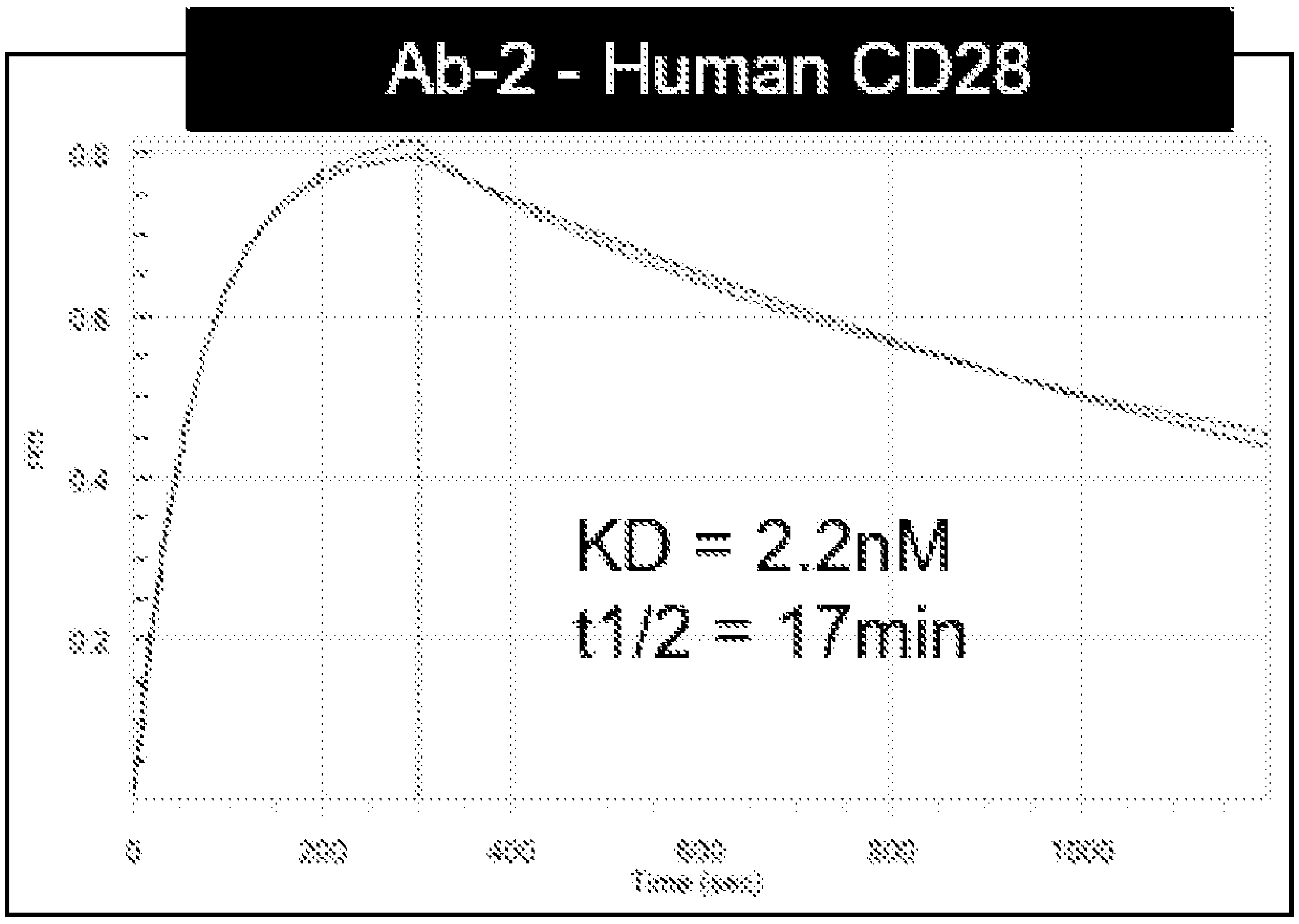

Ab-2 - Human CD28
0.8
0.6
0.4
0.2
0
200
400
600
800
1000
Time (sec)
KD = 2.2nM
t1/2 = 17min

Fig. 6B

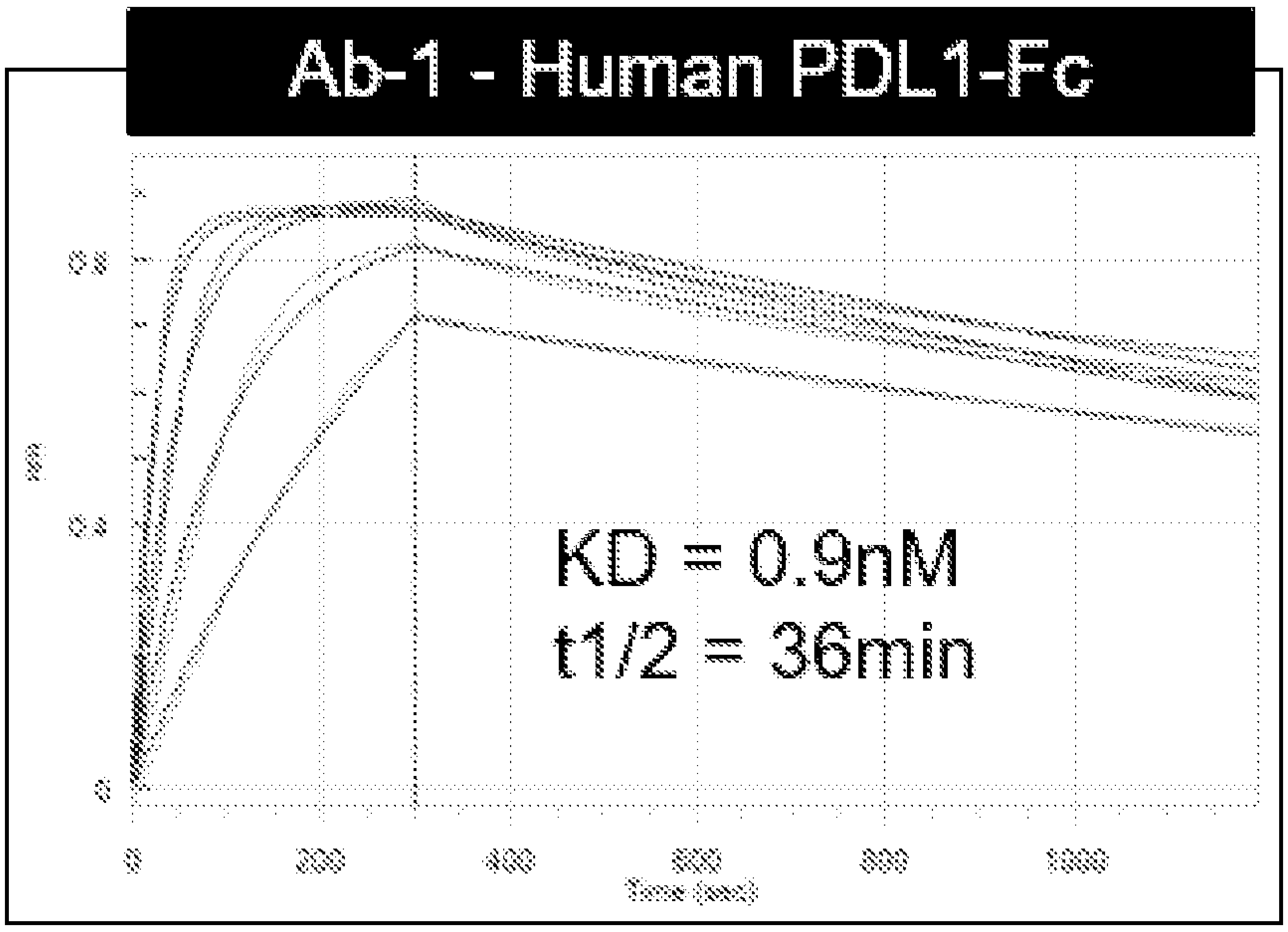

Ab-1 - Human PDL1-Fc
KD = 0.9nM
t1/2 = 36min
0.8
0.4
0
0
200
400
600
800
1000
Time (sec)

Fig. 7A

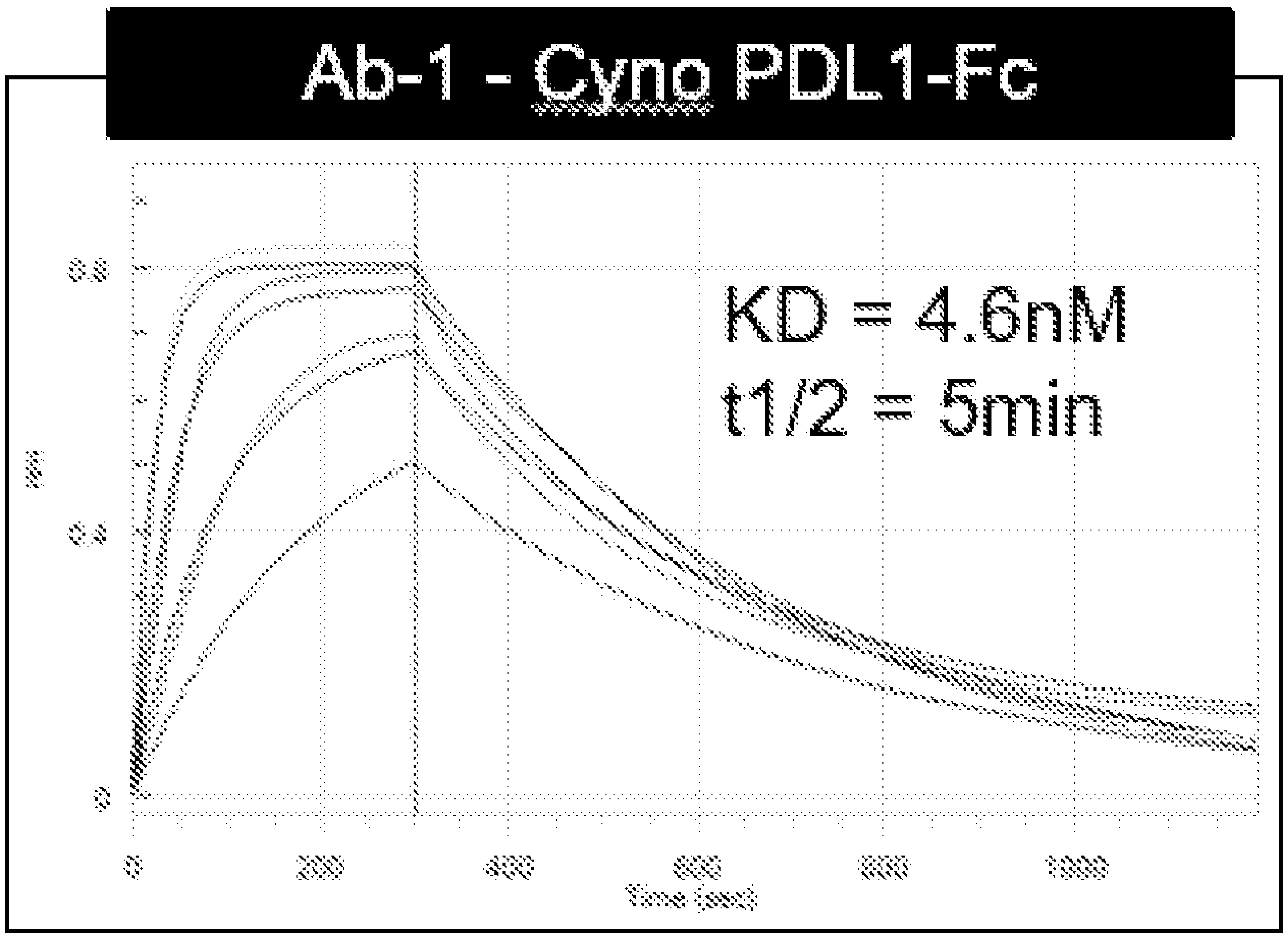

Ab-1 - Cyno PDL1-Fc
KD = 4.6nM
t1/2 = 5min
0.8
0.4
0
0
200
400
600
800
1000
Time (sec)

Fig. 7B

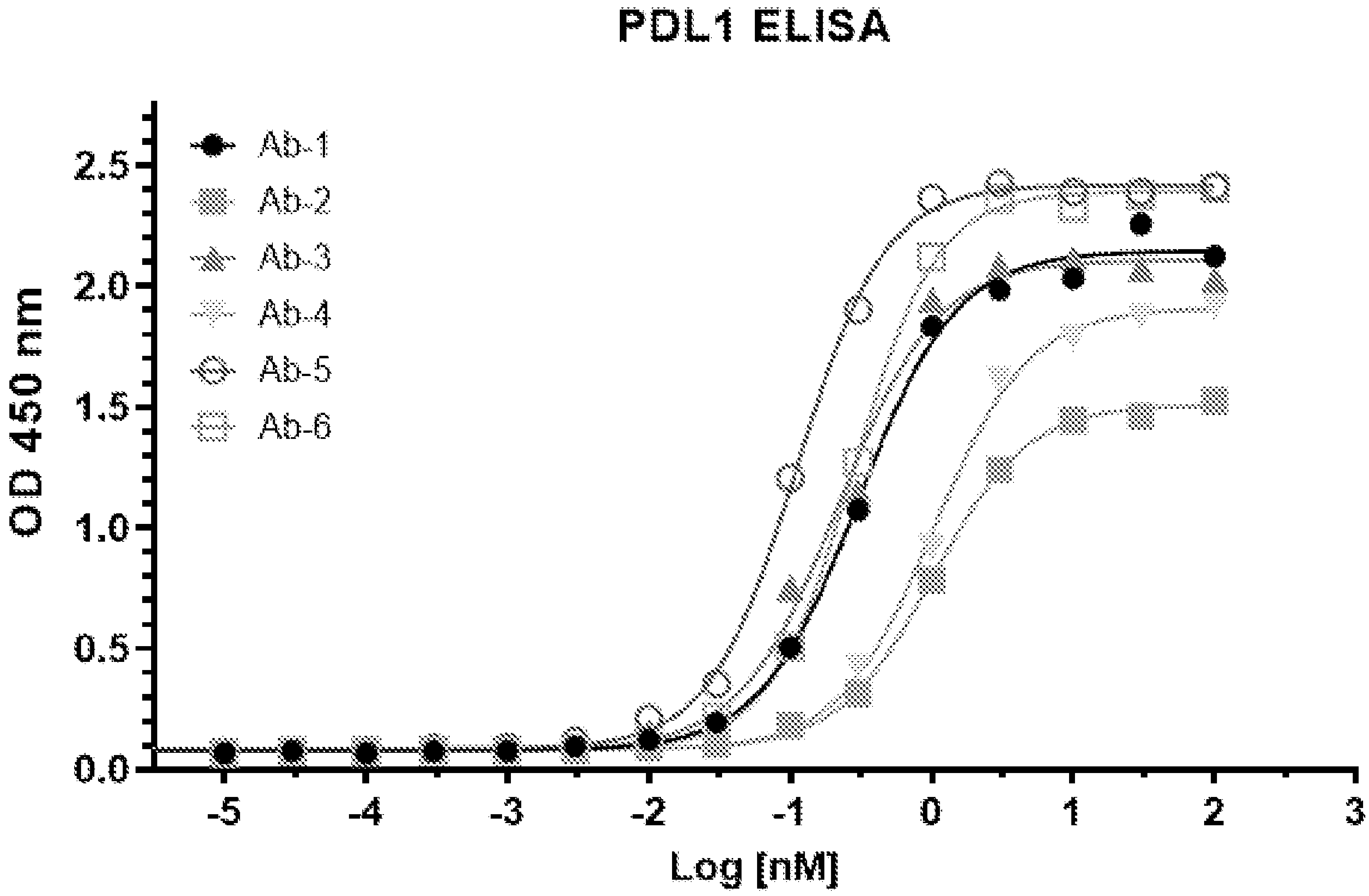

PDL1 ELISA
OD 450 nm
0.0
0.5
1.0
1.5
2.0
2.5
-5
-4
-3
-2
-1
0
1
2
3
Log [nM]
Ab-1
Ab-2
Ab-3
Ab-4
Ab-5
Ab-6

Fig. 8A

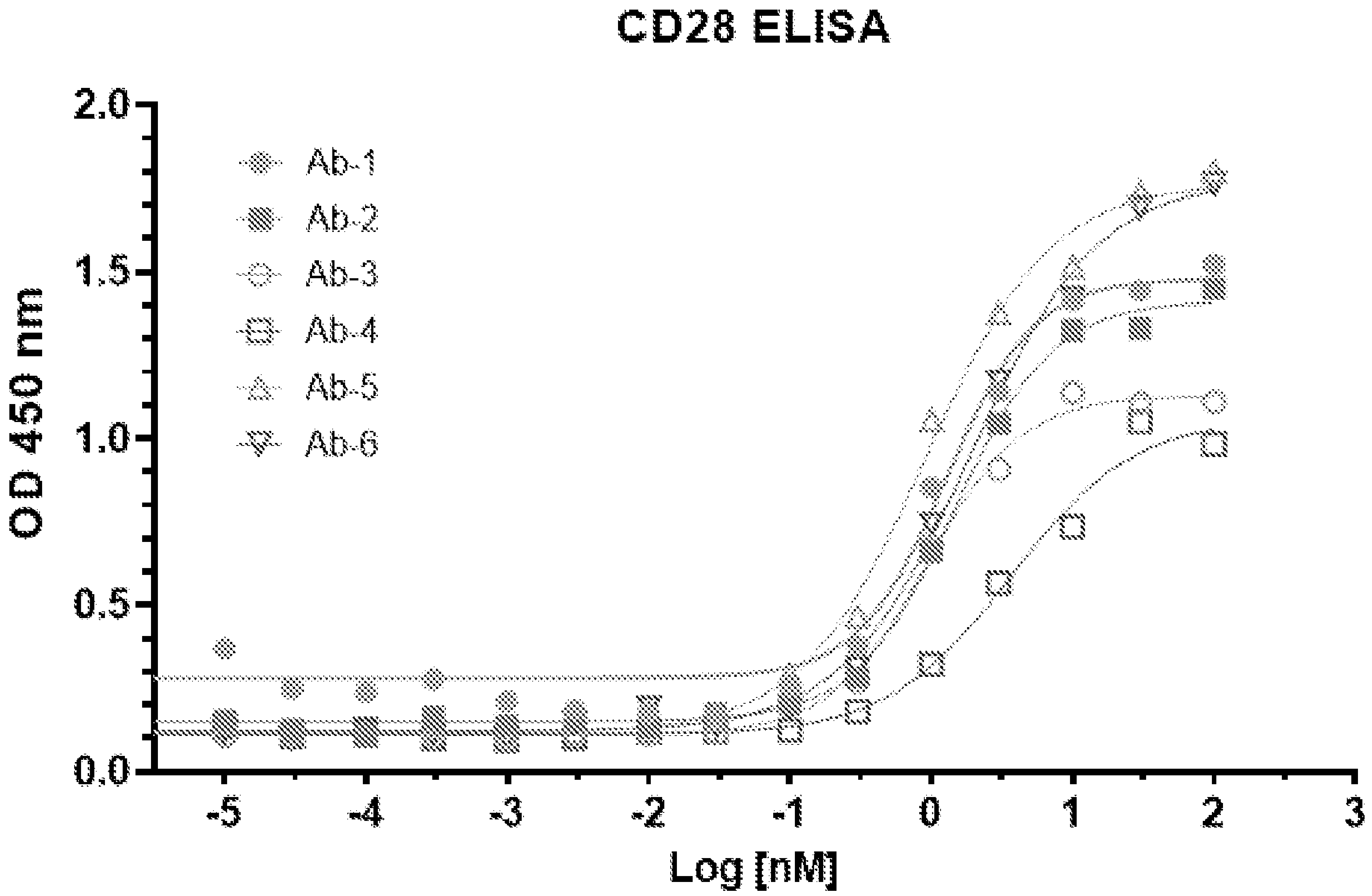

CD28 ELISA
OD 450 nm
Log [nM]
Ab-1
Ab-2
Ab-3
Ab-4
Ab-5
Ab-6
2.0
1.5
1.0
0.5
0.0
-5
-4
-3
-2
-1
0
1
2
3

Fig. 8B

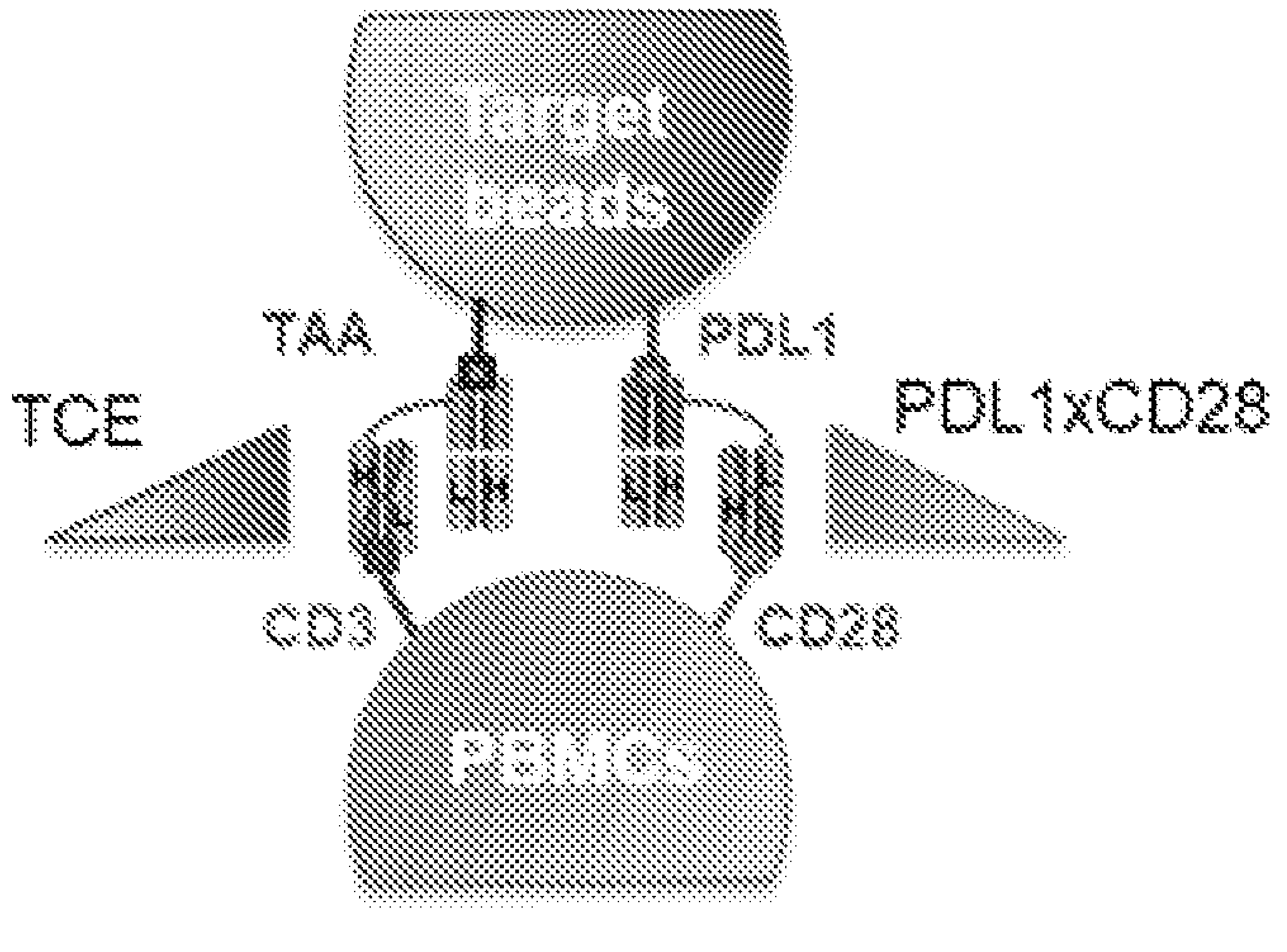

Target beads
TAA
PDL1
TCE
PDL1xCD28
VH
VL
CD3
CD28
PBMCs

Fig. 9A

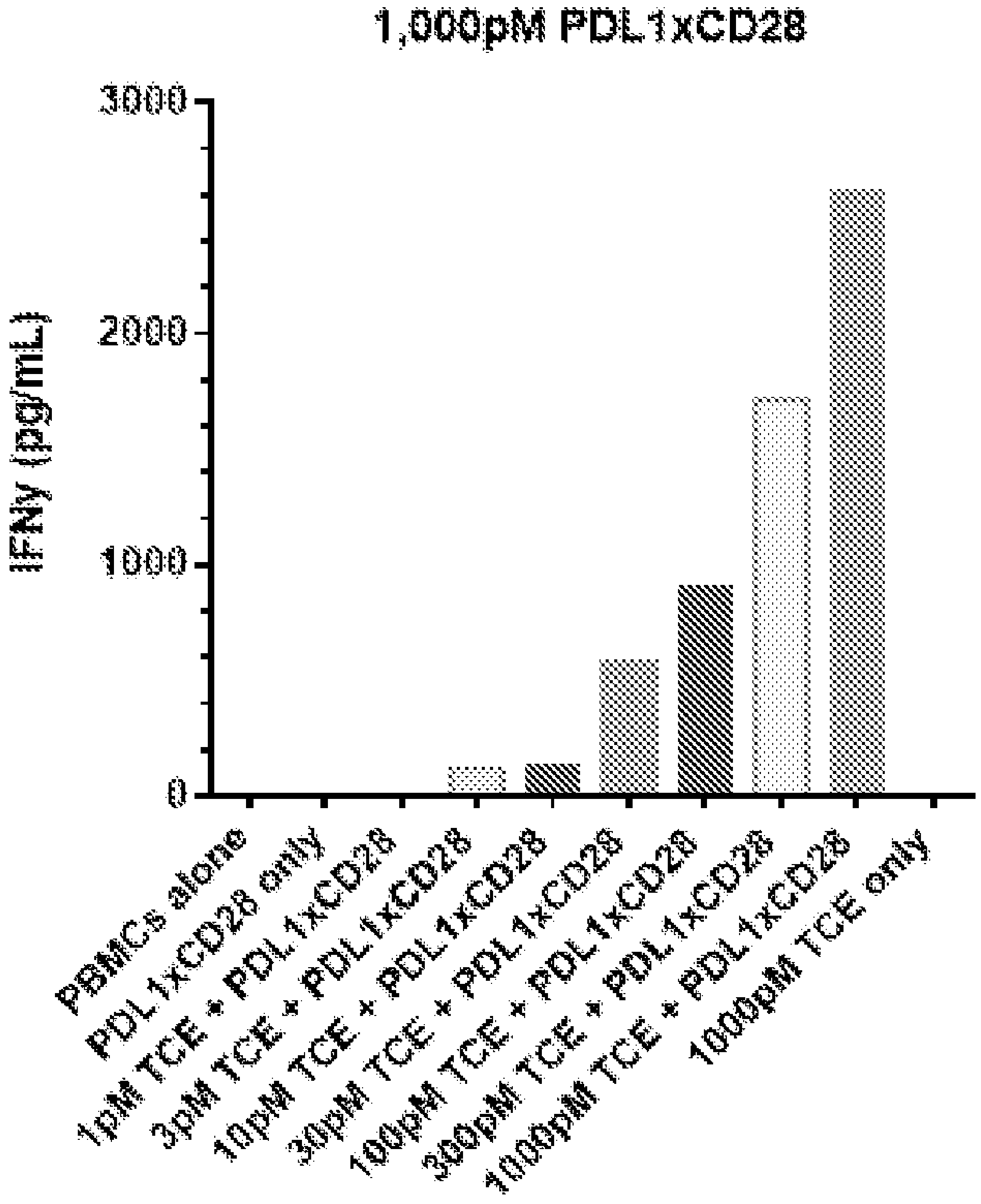

1,000pM PDL1xCD28
IFNy (pg/mL)
3000
2000
1000
0
PBMCs alone
PDL1xCD28 only
1pM TCE + PDL1xCD28
3pM TCE + PDL1xCD28
10pM TCE + PDL1xCD28
30pM TCE + PDL1xCD28
100pM TCE + PDL1xCD28
300pM TCE + PDL1xCD28
1000pM TCE + PDL1xCD28
1000pM TCE only

Fig. 9B

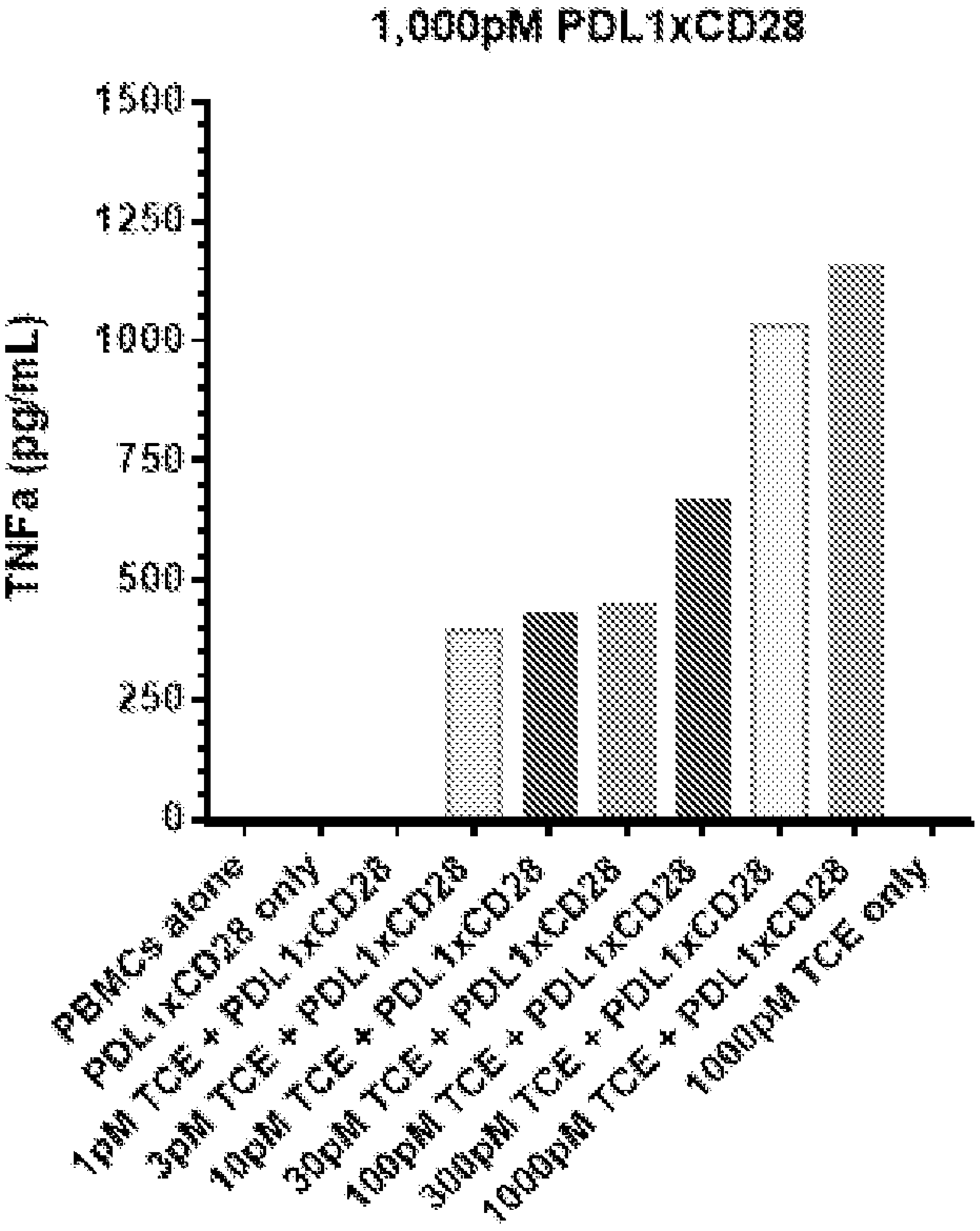

1,000pM PDL1xCD28
TNFa (pg/mL)
1500
1250
1000
750
500
250
0
PBMCs alone
PDL1xCD28 only
1pM TCE + PDL1xCD28
3pM TCE + PDL1xCD28
10pM TCE + PDL1xCD28
30pM TCE + PDL1xCD28
100pM TCE + PDL1xCD28
300pM TCE + PDL1xCD28
1000pM TCE + PDL1xCD28
1000pM TCE only

Fig. 9C

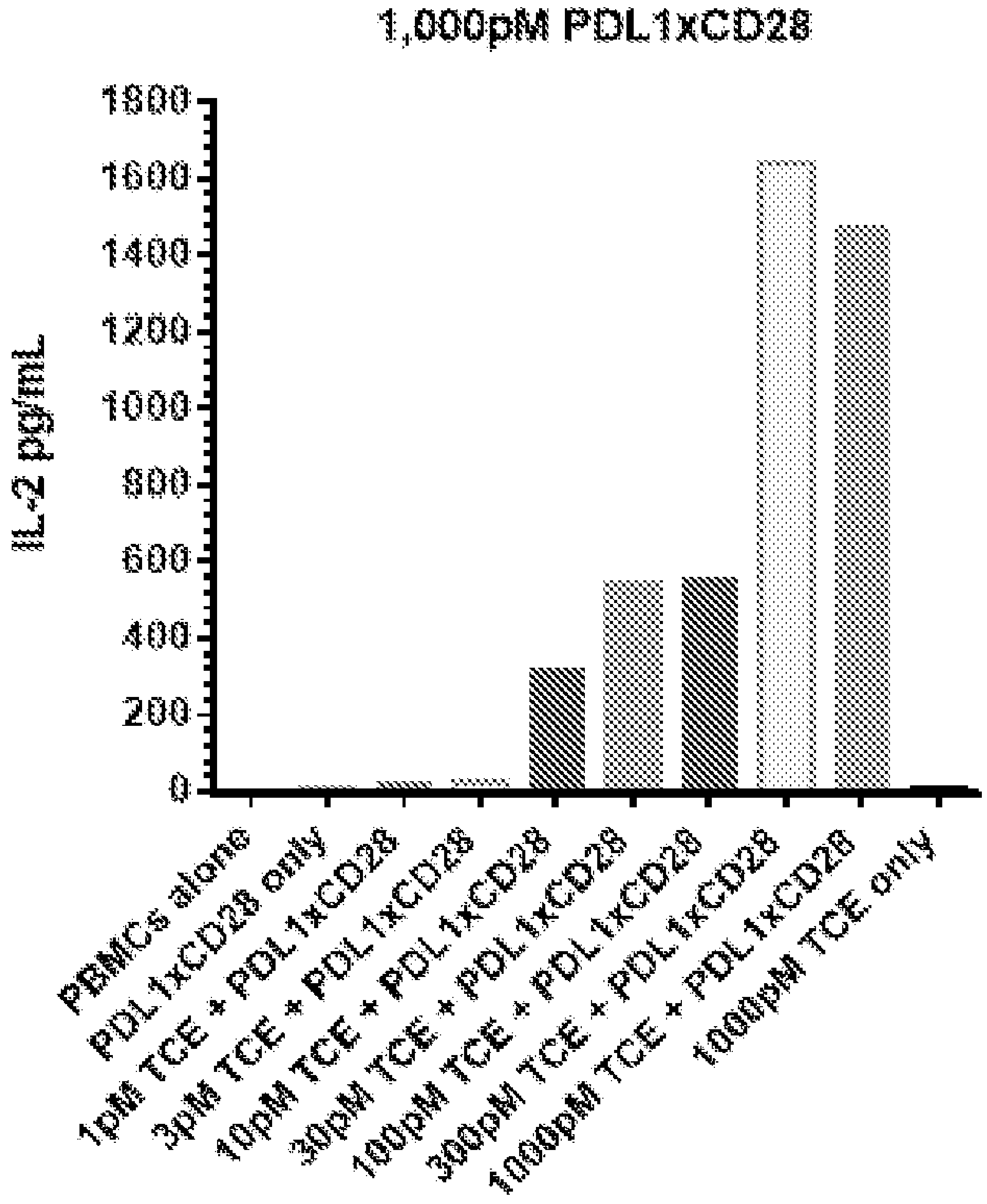

1,000pM PDL1xCD28
IL-2 pg/mL
1800
1600
1400
1200
1000
800
600
400
200
0
PBMCs alone
PDL1xCD28 only
1pM TCE + PDL1xCD28
3pM TCE + PDL1xCD28
10pM TCE + PDL1xCD28
30pM TCE + PDL1xCD28
100pM TCE + PDL1xCD28
300pM TCE + PDL1xCD28
1000pM TCE + PDL1xCD28
1000pM TCE only

Fig. 9D

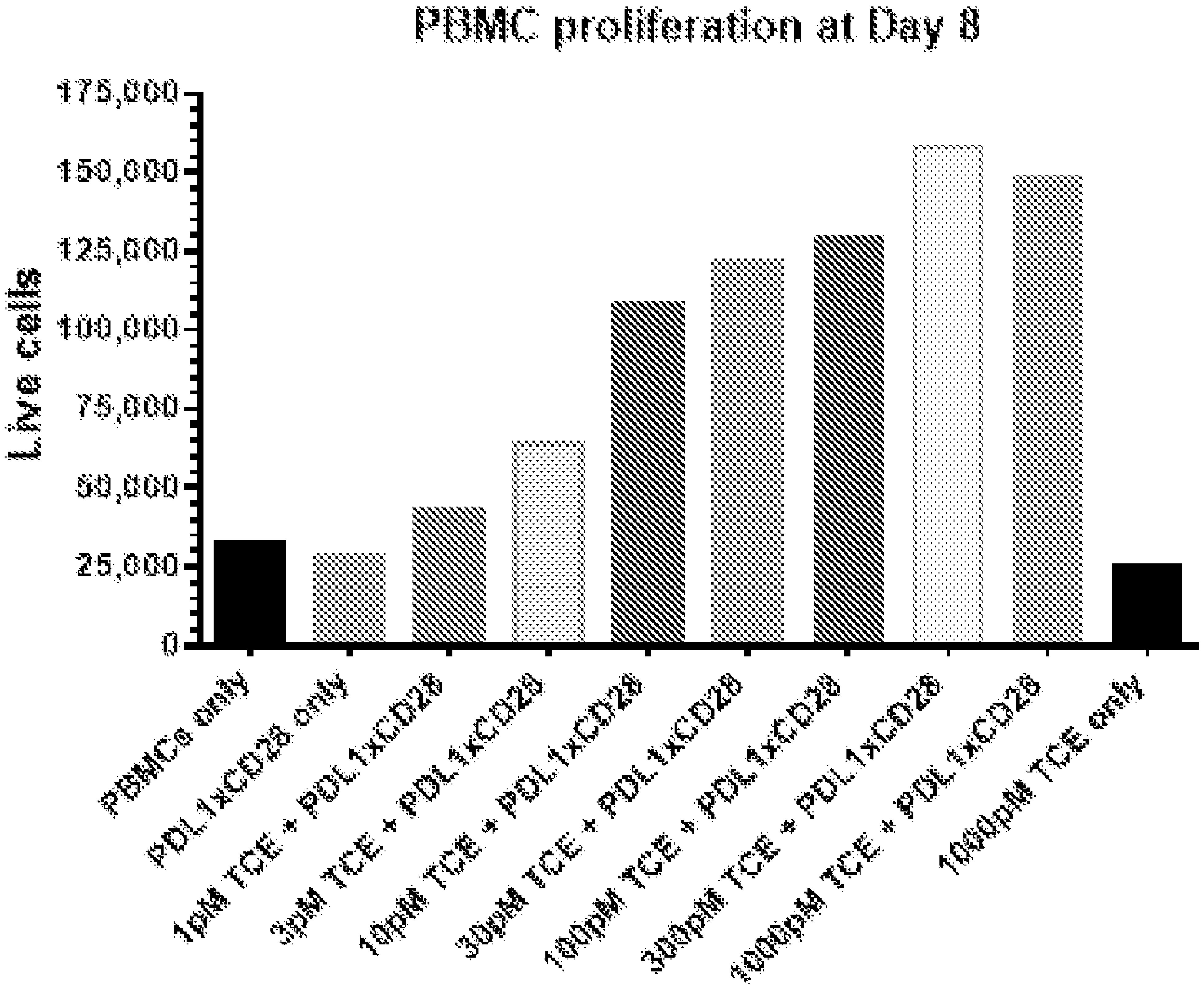

PBMC proliferation at Day 8
Live cells
175,000
150,000
125,000
100,000
75,000
50,000
25,000
0
PBMCs only
PDL1xCD28 only
1pM TCE + PDL1xCD28
3pM TCE + PDL1xCD28
10pM TCE + PDL1xCD28
30pM TCE + PDL1xCD28
100pM TCE + PDL1xCD28
300pM TCE + PDL1xCD28
1000pM TCE + PDL1xCD28
1000pM TCE only

Fig. 9E

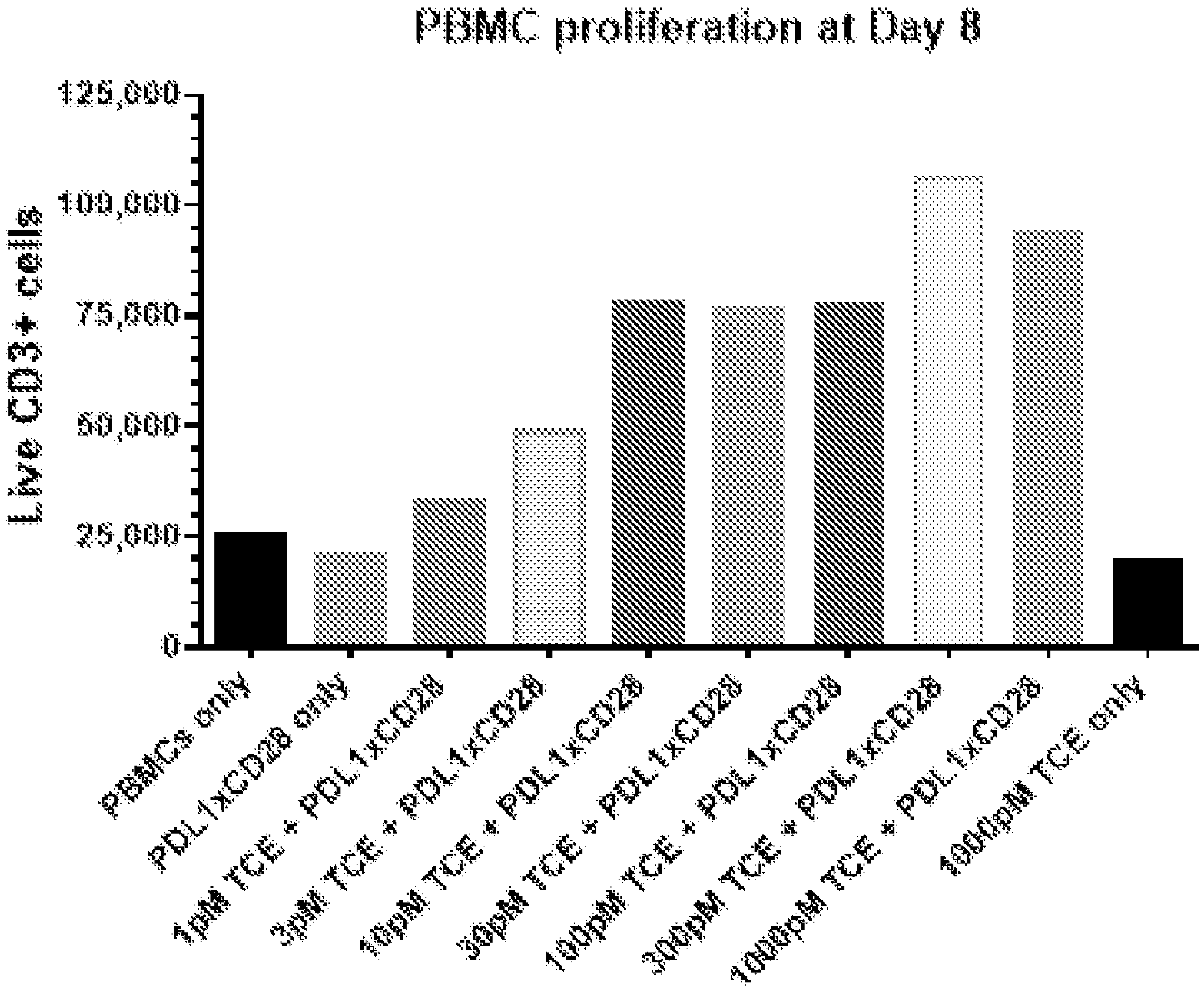

PBMC proliferation at Day 8
Live CD3+ cells
125,000
100,000
75,000
50,000
25,000
0
PBMCs only
PDL1xCD28 only
1pM TCE + PDL1xCD28
3pM TCE + PDL1xCD28
10pM TCE + PDL1xCD28
30pM TCE + PDL1xCD28
100pM TCE + PDL1xCD28
300pM TCE + PDL1xCD28
1000pM TCE + PDL1xCD28
1000pM TCE only

Fig. 9F

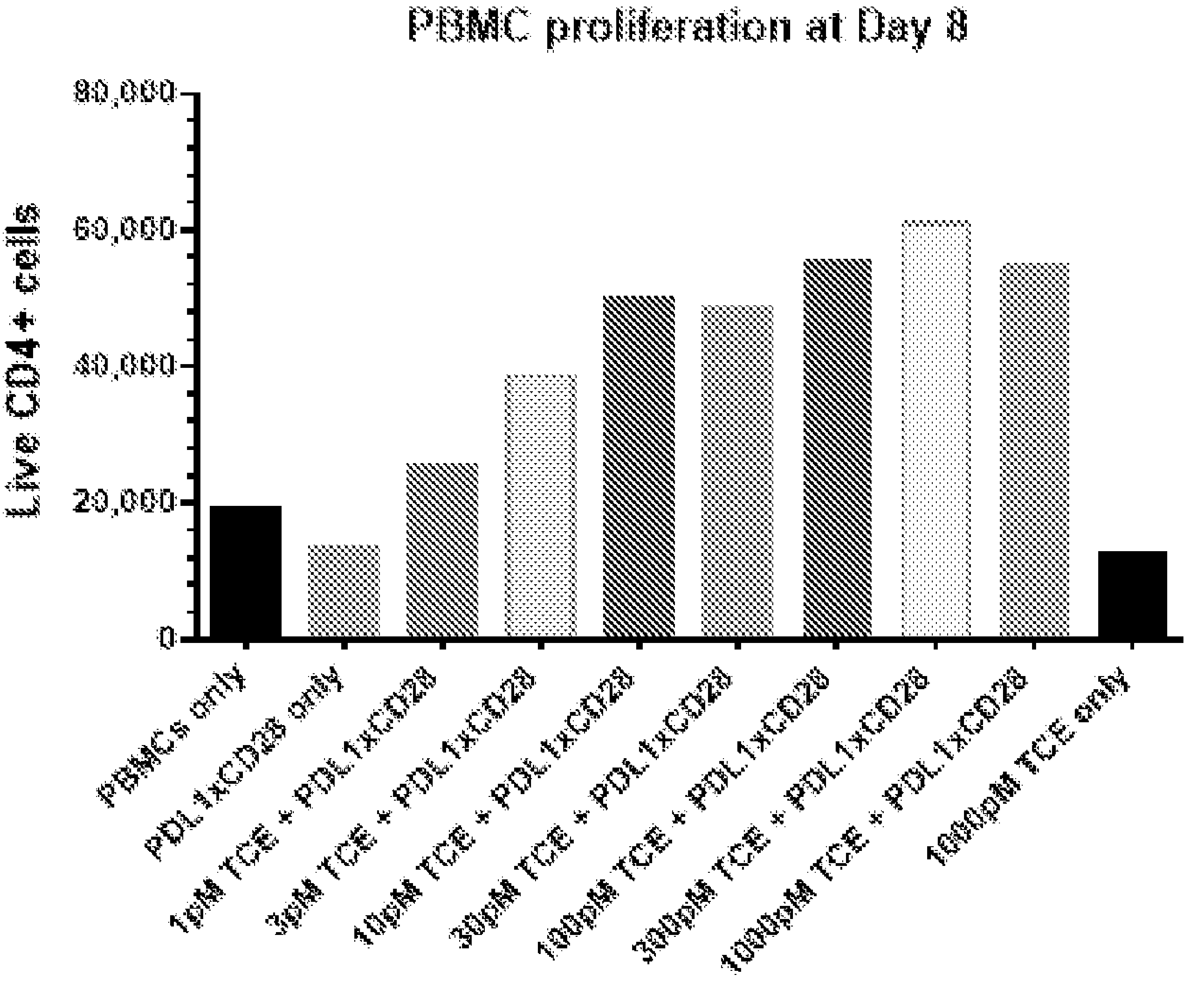

PBMC proliferation at Day 8
Live CD4+ cells
80,000
60,000
40,000
20,000
0
PBMCs only
PDL1xCD28 only
1pM TCE + PDL1xCD28
3pM TCE + PDL1xCD28
10pM TCE + PDL1xCD28
30pM TCE + PDL1xCD28
100pM TCE + PDL1xCD28
300pM TCE + PDL1xCD28
1000pM TCE + PDL1xCD28
1000pM TCE only

Fig. 9G

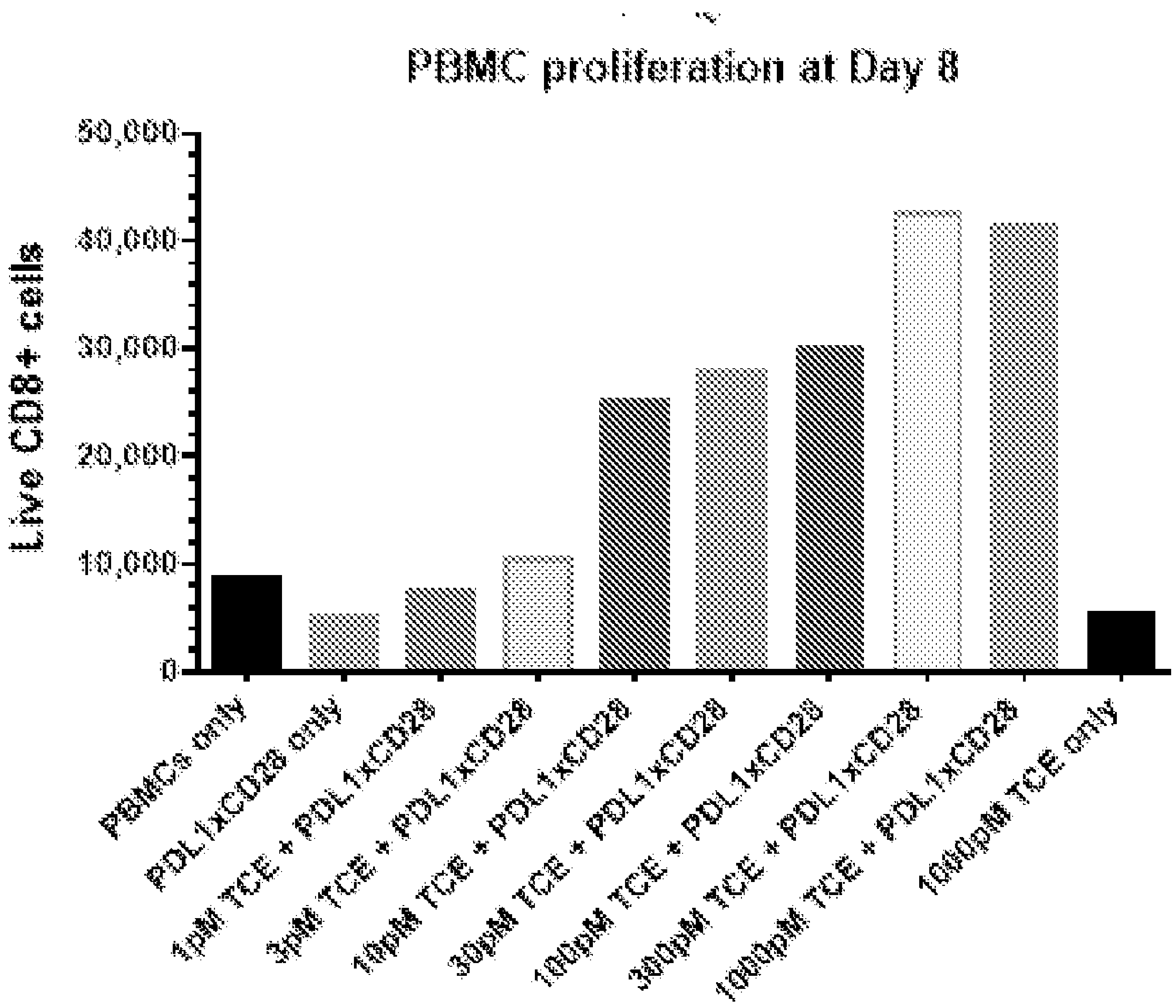

PBMC proliferation at Day 8
Live CD8+ cells
50,000
40,000
30,000
20,000
10,000
0
PBMCs only
PDL1xCD28 only
1pM TCE + PDL1xCD28
3pM TCE + PDL1xCD28
10pM TCE + PDL1xCD28
30pM TCE + PDL1xCD28
100pM TCE + PDL1xCD28
300pM TCE + PDL1xCD28
1000pM TCE + PDL1xCD28
1000pM TCE only

Fig. 9H

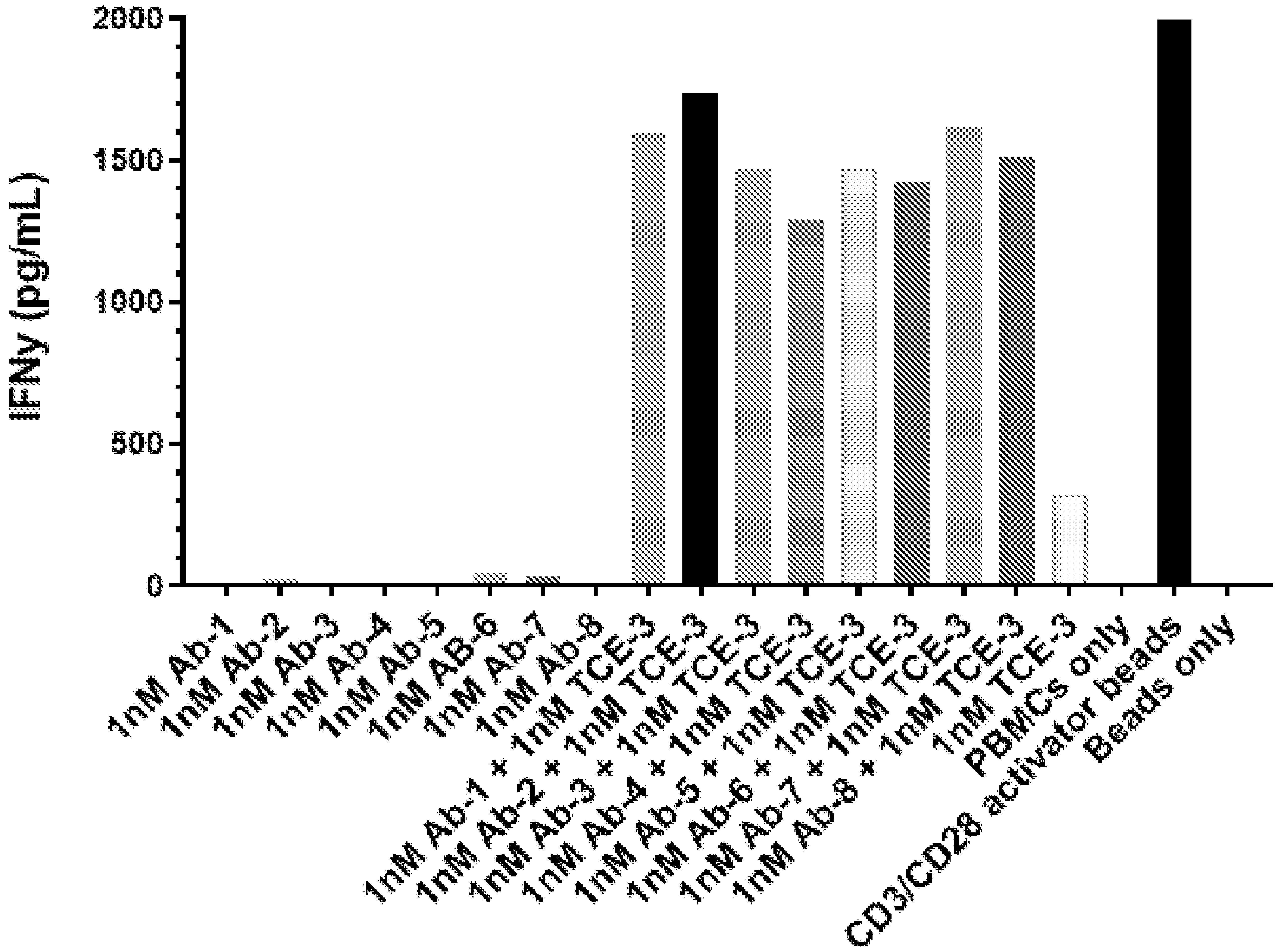

IFNy (pg/mL)
2000
1500
1000
500
0
1nM Ab-1
1nM Ab-2
1nM Ab-3
1nM Ab-4
1nM Ab-5
1nM AB-6
1nM Ab-7
1nM Ab-8
1nM Ab-1 + 1nM TCE-3
1nM Ab-2 + 1nM TCE-3
1nM Ab-3 + 1nM TCE-3
1nM Ab-4 + 1nM TCE-3
1nM Ab-5 + 1nM TCE-3
1nM Ab-6 + 1nM TCE-3
1nM Ab-7 + 1nM TCE-3
1nM Ab-8 + 1nM TCE-3
1nM TCE-3
PBMCs only
CD3/CD28 activator beads
Beads only

Fig. 9I

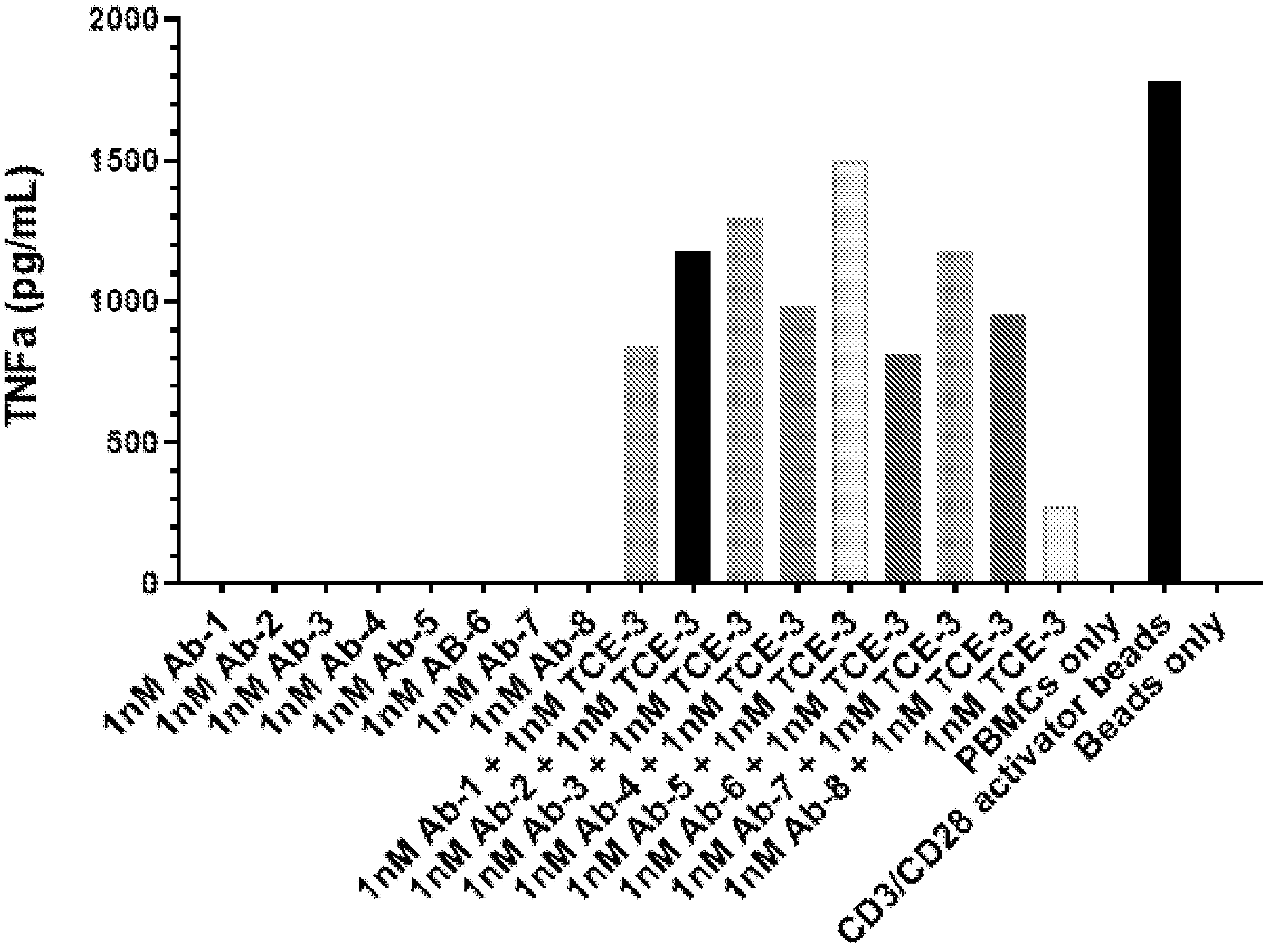

TNFa (pg/mL)
2000
1500
1000
500
0
1nM Ab-1
1nM Ab-2
1nM Ab-3
1nM Ab-4
1nM Ab-5
1nM AB-6
1nM Ab-7
1nM Ab-8
1nM Ab-1 + 1nM TCE-3
1nM Ab-2 + 1nM TCE-3
1nM Ab-3 + 1nM TCE-3
1nM Ab-4 + 1nM TCE-3
1nM Ab-5 + 1nM TCE-3
1nM Ab-6 + 1nM TCE-3
1nM Ab-7 + 1nM TCE-3
1nM Ab-8 + 1nM TCE-3
1nM TCE-3
PBMCs only
CD3/CD28 activator beads
Beads only

Fig. 9J

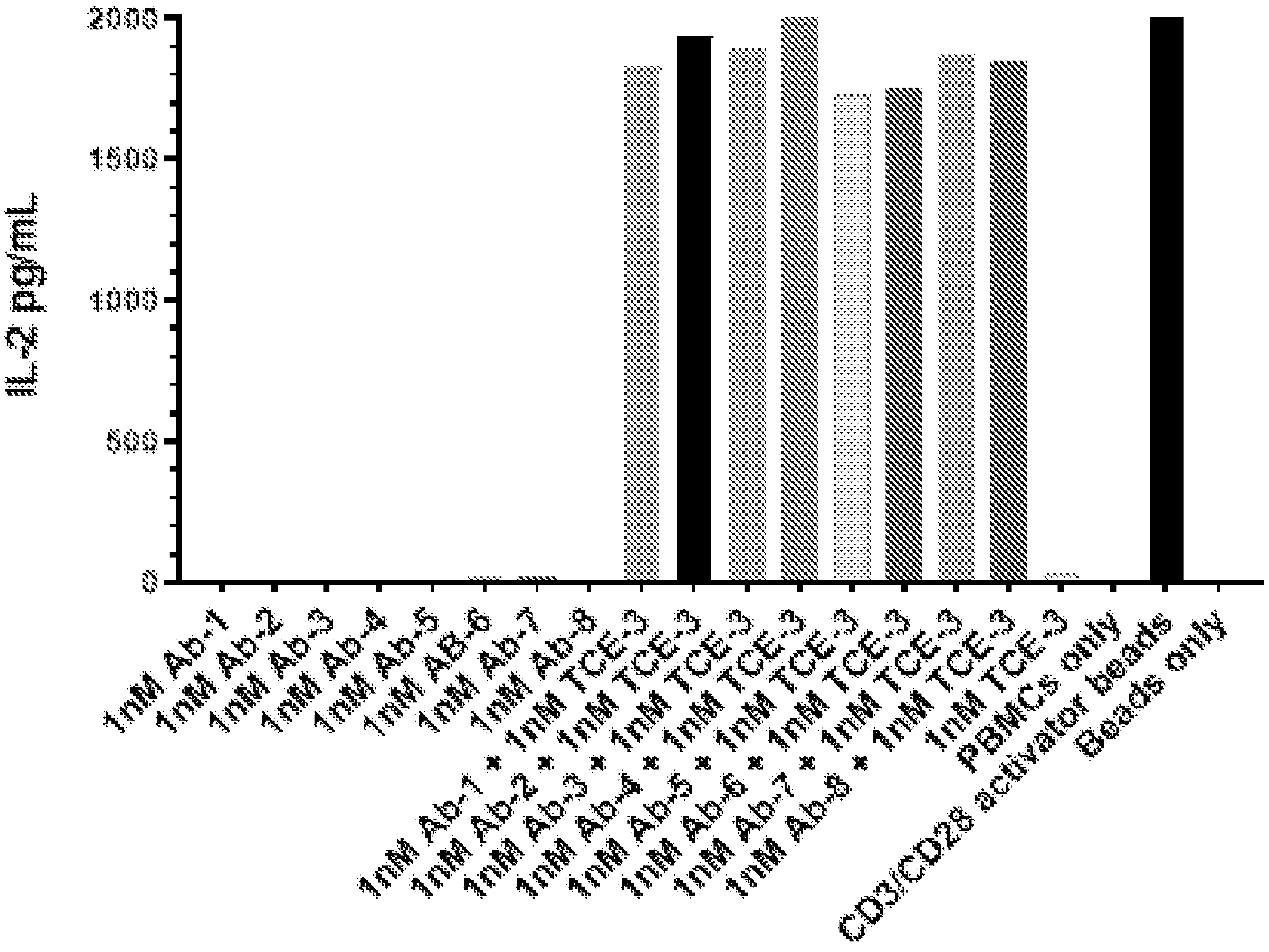

IL-2 pg/mL
2000
1500
1000
500
0
1nM Ab-1
1nM Ab-2
1nM Ab-3
1nM Ab-4
1nM Ab-5
1nM AB-6
1nM Ab-7
1nM Ab-8
1nM Ab-1 + 1nM TCE-3
1nM Ab-2 + 1nM TCE-3
1nM Ab-3 + 1nM TCE-3
1nM Ab-4 + 1nM TCE-3
1nM Ab-5 + 1nM TCE-3
1nM Ab-6 + 1nM TCE-3
1nM Ab-7 + 1nM TCE-3
1nM Ab-8 + 1nM TCE-3
1nM TCE-3
PBMCs only
CD3/CD28 activator beads
Beads only

Fig. 9K

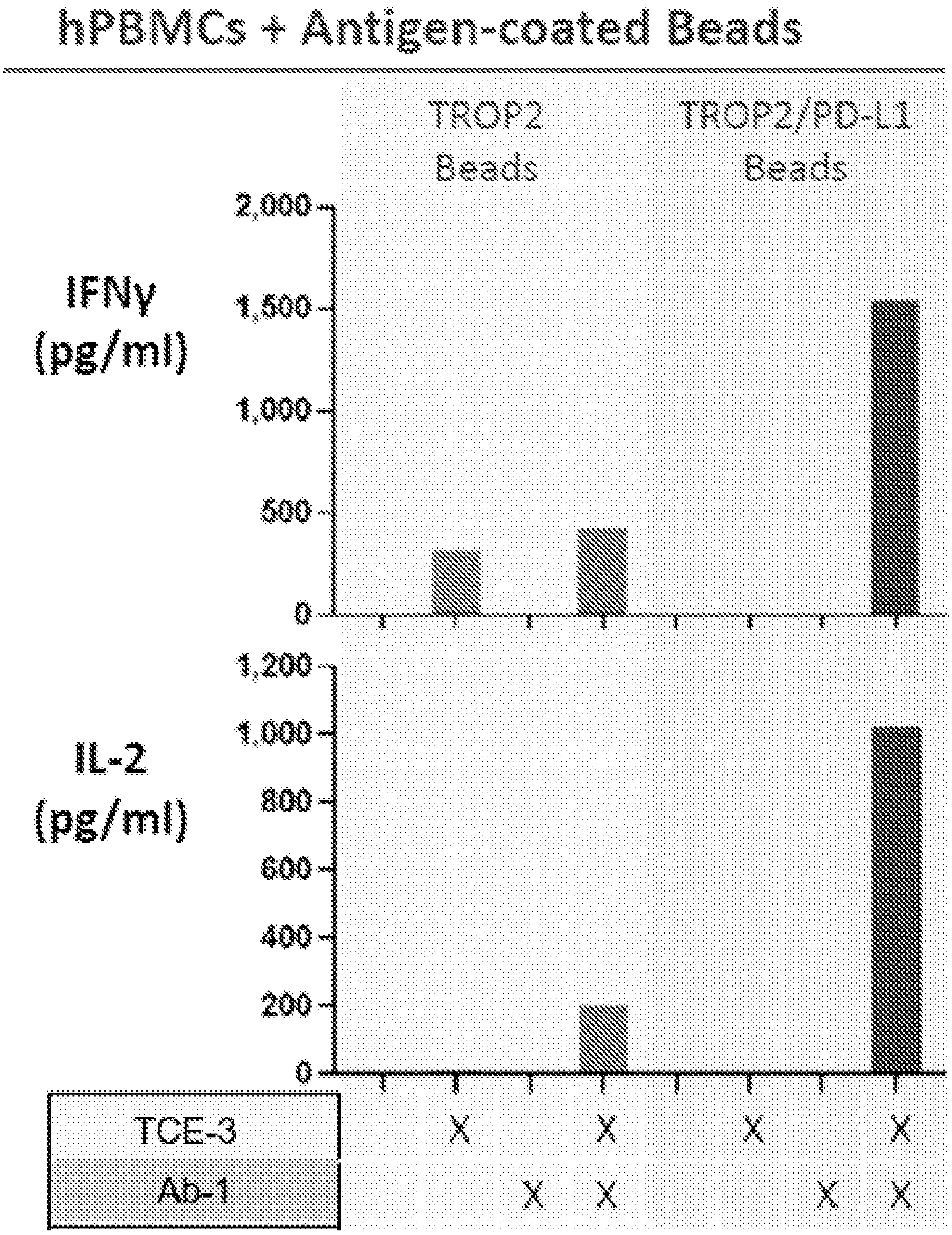

hPBMCs + Antigen-coated Beads
TROP2 Beads
TROP2/PD-L1 Beads
IFNγ (pg/ml)
2,000
1,500
1,000
500
0
IL-2 (pg/ml)
1,200
1,000
800
600
400
200
0
TCE-3
X
X
X
X
Ab-1
X
X
X
X

Fig. 9L

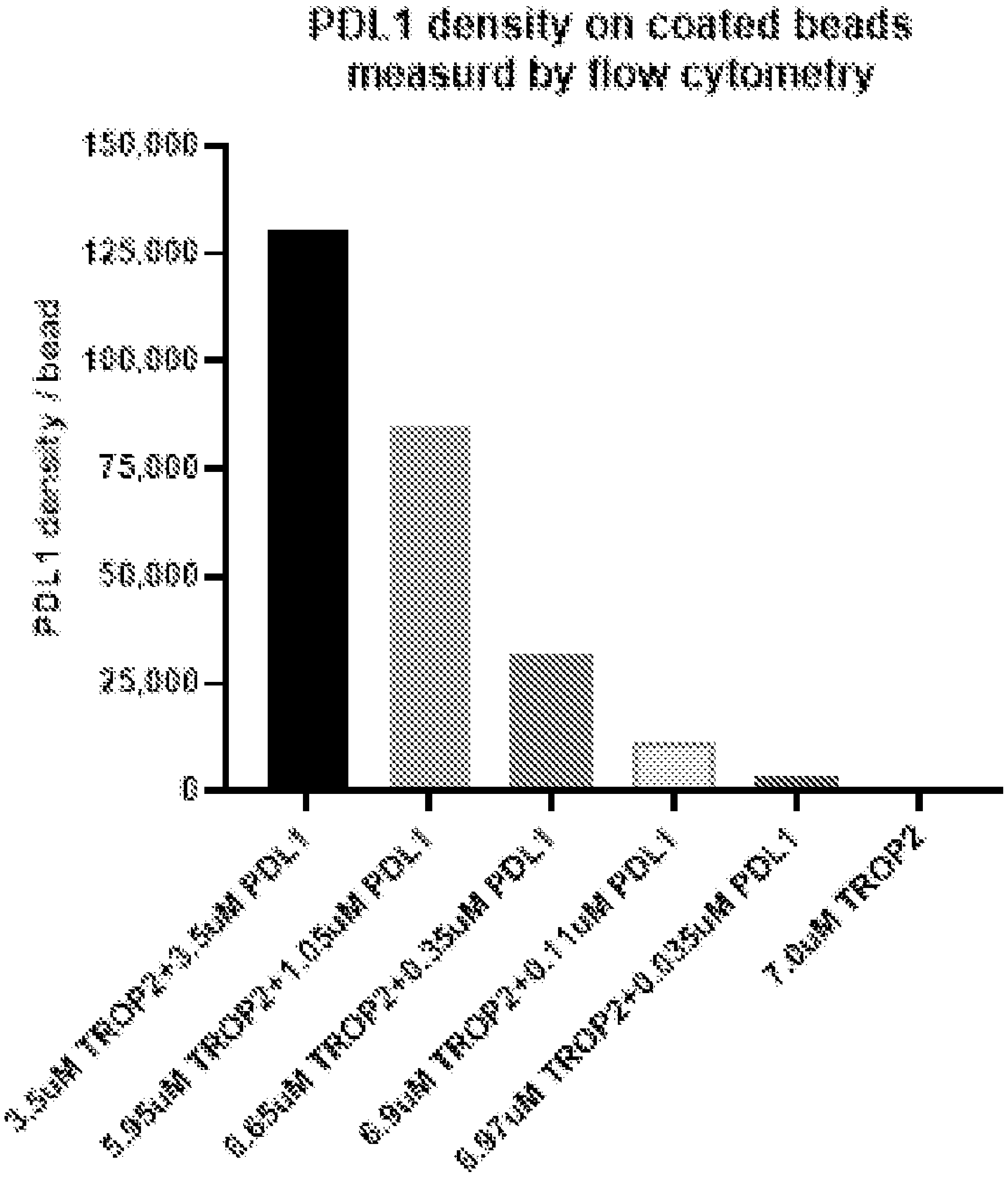

PDL1 density on coated beads
measurd by flow cytometry
PDL1 density / bead
150,000
125,000
100,000
75,000
50,000
25,000
0
3.5uM TROP2+3.5uM PDL1
5.95uM TROP2+1.05uM PDL1
6.65uM TROP2+0.35uM PDL1
6.9uM TROP2+0.11uM PDL1
6.97uM TROP2+0.035uM PDL1
7.0uM TROP2

Fig. 9M

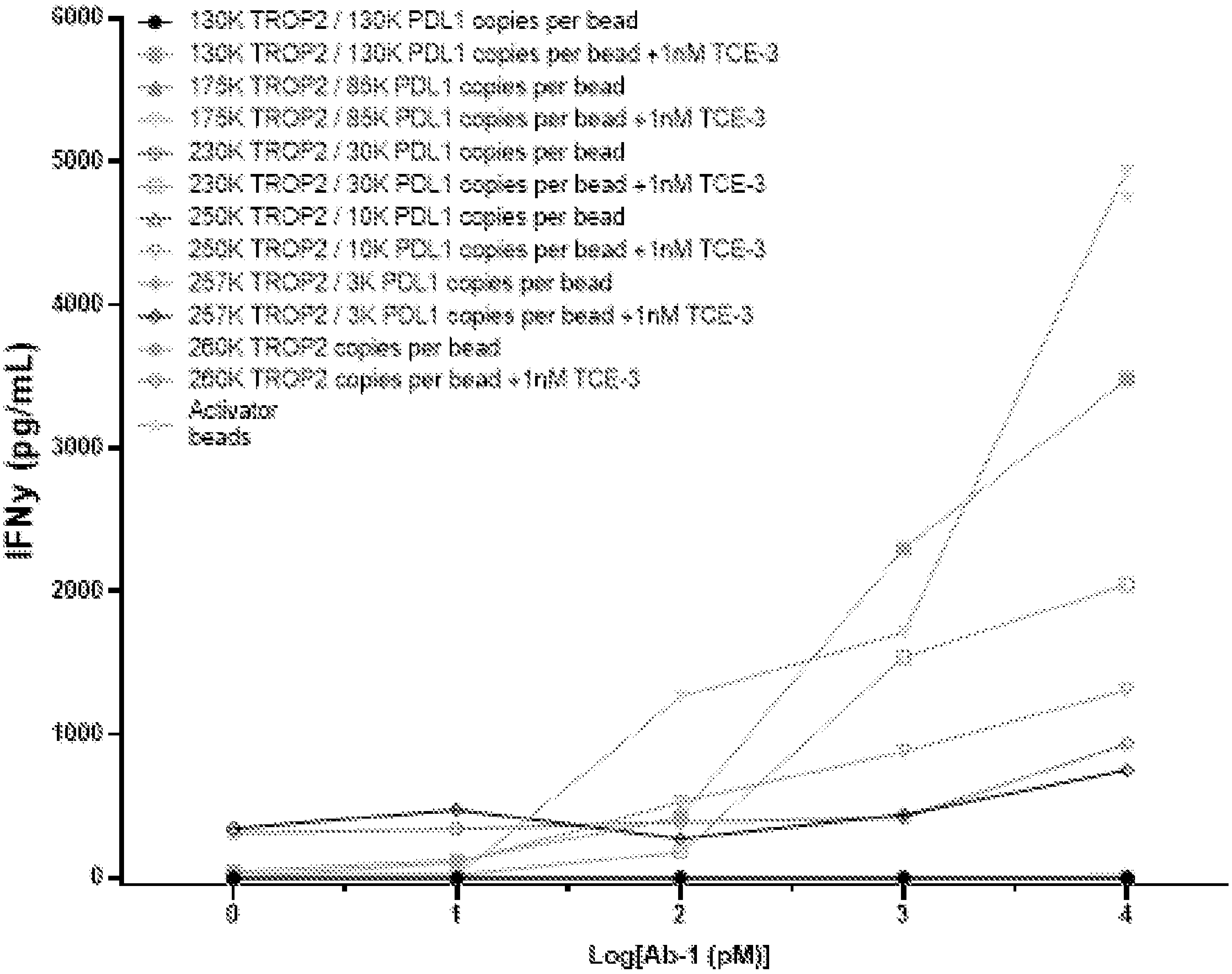

6000
5000
4000
3000
2000
1000
0
IFNγ (pg/mL)
0
1
2
3
4
Log[Ab-1 (pM)]
130K TROP2 / 130K PDL1 copies per bead
130K TROP2 / 130K PDL1 copies per bead +1nM TCE-3
175K TROP2 / 85K PDL1 copies per bead
175K TROP2 / 85K PDL1 copies per bead +1nM TCE-3
230K TROP2 / 30K PDL1 copies per bead
230K TROP2 / 30K PDL1 copies per bead +1nM TCE-3
250K TROP2 / 10K PDL1 copies per bead
250K TROP2 / 10K PDL1 copies per bead +1nM TCE-3
257K TROP2 / 3K PDL1 copies per bead
257K TROP2 / 3K PDL1 copies per bead +1nM TCE-3
260K TROP2 copies per bead
260K TROP2 copies per bead +1nM TCE-3
Activator beads

Fig. 9N

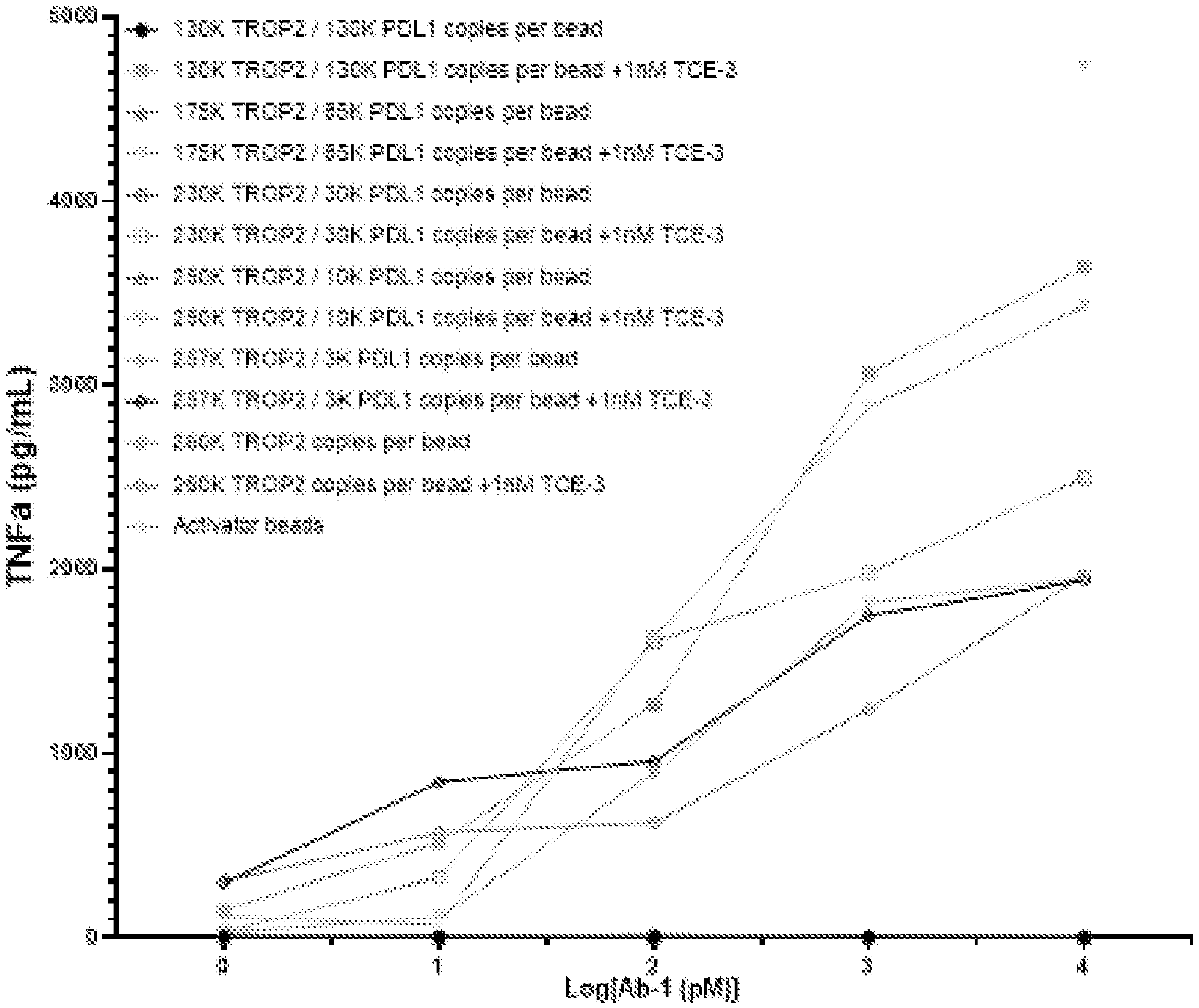

5000
4000
3000
2000
1000
0
TNFa (pg/mL)
130K TROP2 / 130K PDL1 copies per bead
130K TROP2 / 130K PDL1 copies per bead +1nM TCE-3
175K TROP2 / 85K PDL1 copies per bead
175K TROP2 / 85K PDL1 copies per bead +1nM TCE-3
230K TROP2 / 30K PDL1 copies per bead
230K TROP2 / 30K PDL1 copies per bead +1nM TCE-3
250K TROP2 / 10K PDL1 copies per bead
250K TROP2 / 10K PDL1 copies per bead +1nM TCE-3
257K TROP2 / 3K PDL1 copies per bead
257K TROP2 / 3K PDL1 copies per bead +1nM TCE-3
260K TROP2 copies per bead
260K TROP2 copies per bead +1nM TCE-3
Activator beads
0
1
2
3
4
Log[Ab-1 (pM)]

Fig. 9O

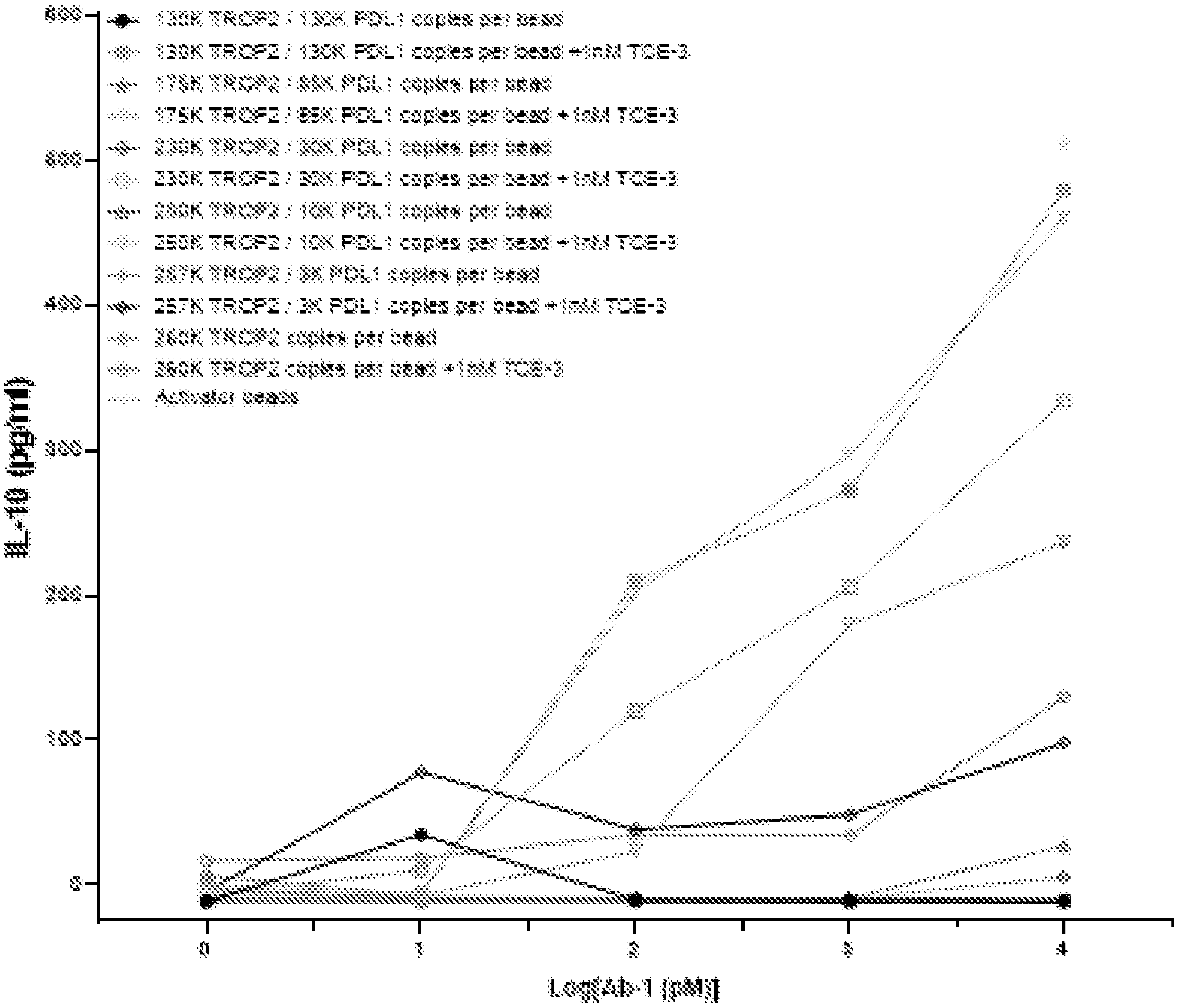

600
500
400
300
200
100
0
IL-10 (pg/ml)
0
1
2
3
4
Log[Ab-1 (pM)]
130K TROP2 / 130K PDL1 copies per bead
130K TROP2 / 130K PDL1 copies per bead +1nM TCE-3
175K TROP2 / 85K PDL1 copies per bead
175K TROP2 / 85K PDL1 copies per bead +1nM TCE-3
230K TROP2 / 30K PDL1 copies per bead
230K TROP2 / 30K PDL1 copies per bead +1nM TCE-3
250K TROP2 / 10K PDL1 copies per bead
250K TROP2 / 10K PDL1 copies per bead +1nM TCE-3
257K TROP2 / 3K PDL1 copies per bead
257K TROP2 / 3K PDL1 copies per bead +1nM TCE-3
260K TROP2 copies per bead
260K TROP2 copies per bead +1nM TCE-3
Activator beads

Fig. 9P

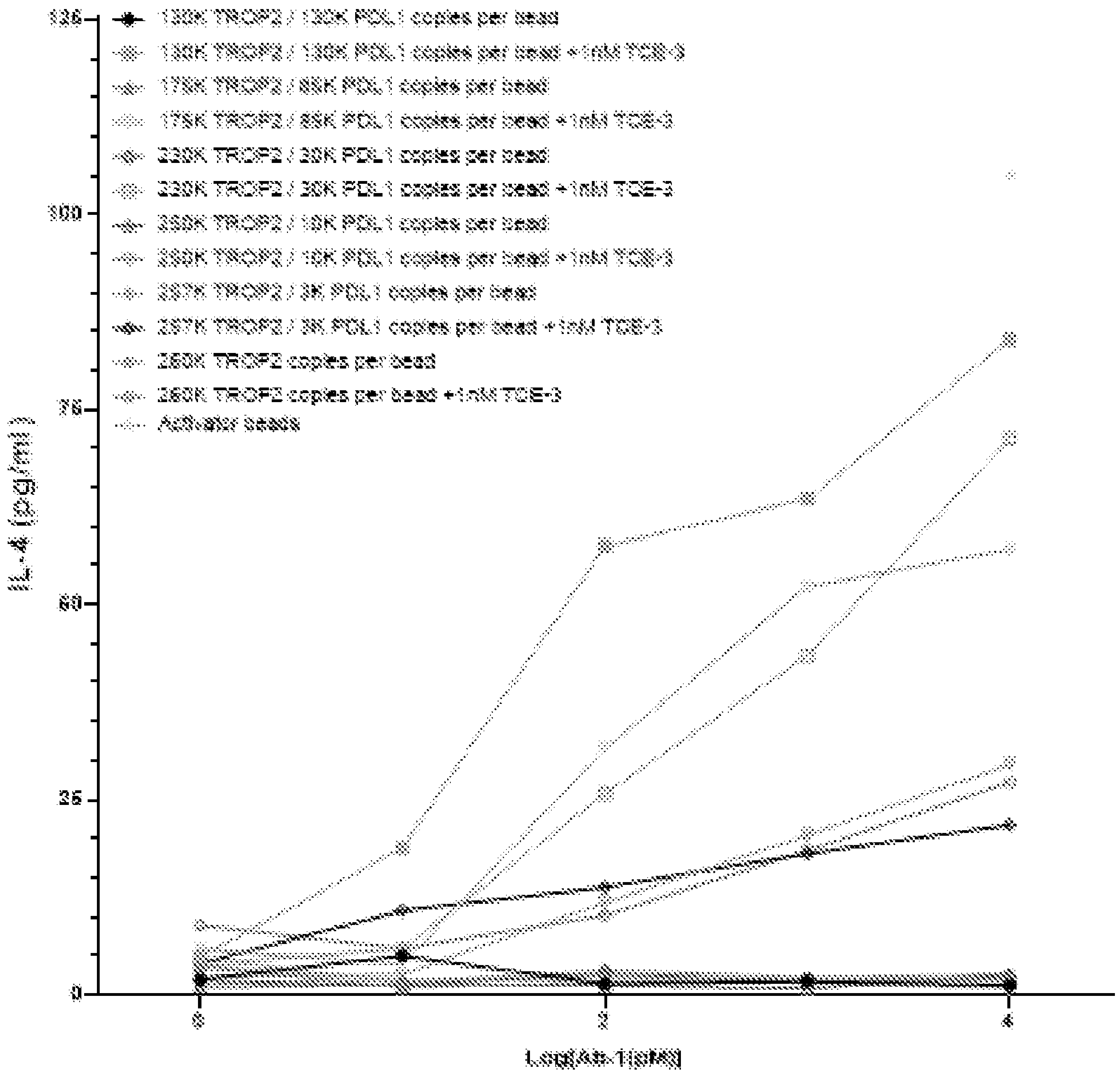

125
100
75
50
25
0
IL-4 (pg/ml)
130K TROP2 / 130K PDL1 copies per bead
130K TROP2 / 130K PDL1 copies per bead +1nM TCE-3
175K TROP2 / 85K PDL1 copies per bead
175K TROP2 / 85K PDL1 copies per bead +1nM TCE-3
230K TROP2 / 30K PDL1 copies per bead
230K TROP2 / 30K PDL1 copies per bead +1nM TCE-3
250K TROP2 / 10K PDL1 copies per bead
250K TROP2 / 10K PDL1 copies per bead +1nM TCE-3
257K TROP2 / 3K PDL1 copies per bead
257K TROP2 / 3K PDL1 copies per bead +1nM TCE-3
260K TROP2 copies per bead
260K TROP2 copies per bead +1nM TCE-3
Activator beads
0
2
4
Log[Ab-1](pM)

Fig. 9Q

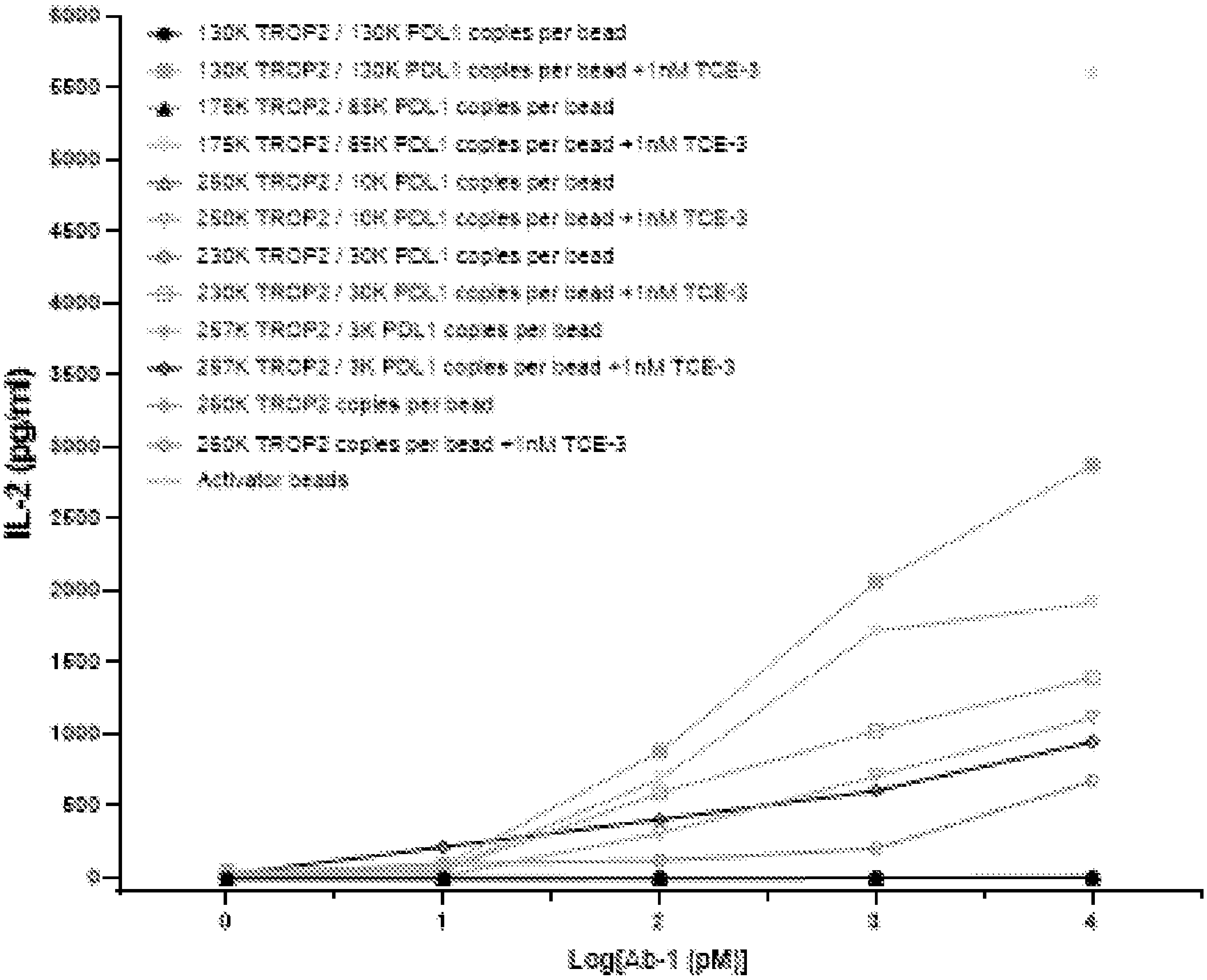

6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
IL-2 (pg/ml)
130K TROP2 / 130K PDL1 copies per bead
130K TROP2 / 130K PDL1 copies per bead +1nM TCE-3
175K TROP2 / 85K PDL1 copies per bead
175K TROP2 / 85K PDL1 copies per bead +1nM TCE-3
250K TROP2 / 10K PDL1 copies per bead
250K TROP2 / 10K PDL1 copies per bead +1nM TCE-3
230K TROP2 / 30K PDL1 copies per bead
230K TROP2 / 30K PDL1 copies per bead +1nM TCE-3
257K TROP2 / 3K PDL1 copies per bead
257K TROP2 / 3K PDL1 copies per bead +1nM TCE-3
260K TROP2 copies per bead
260K TROP2 copies per bead +1nM TCE-3
Activator beads
0
1
2
3
4
Log[Ab-1 (pM)]

Fig. 9R

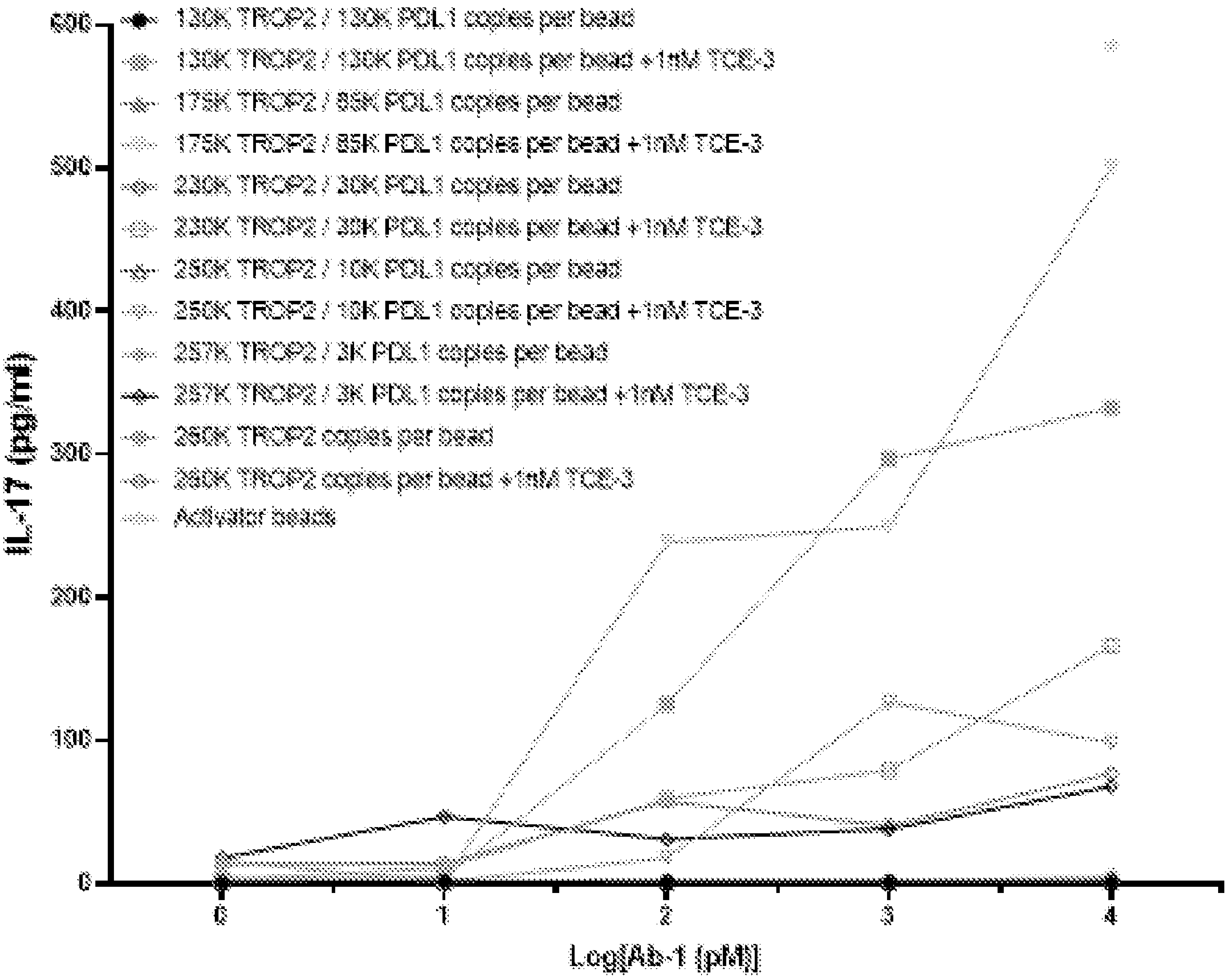

130K TROP2 / 130K PDL1 copies per bead
130K TROP2 / 130K PDL1 copies per bead +1nM TCE-3
175K TROP2 / 85K PDL1 copies per bead
175K TROP2 / 85K PDL1 copies per bead +1nM TCE-3
230K TROP2 / 30K PDL1 copies per bead
230K TROP2 / 30K PDL1 copies per bead +1nM TCE-3
250K TROP2 / 10K PDL1 copies per bead
250K TROP2 / 10K PDL1 copies per bead +1nM TCE-3
257K TROP2 / 3K PDL1 copies per bead
257K TROP2 / 3K PDL1 copies per bead +1nM TCE-3
260K TROP2 copies per bead
260K TROP2 copies per bead +1nM TCE-3
Activator beads
IL-17 (pg/ml)
600
500
400
300
200
100
0
0
1
2
3
4
Log[Ab-1 (pM)]

Fig. 9S

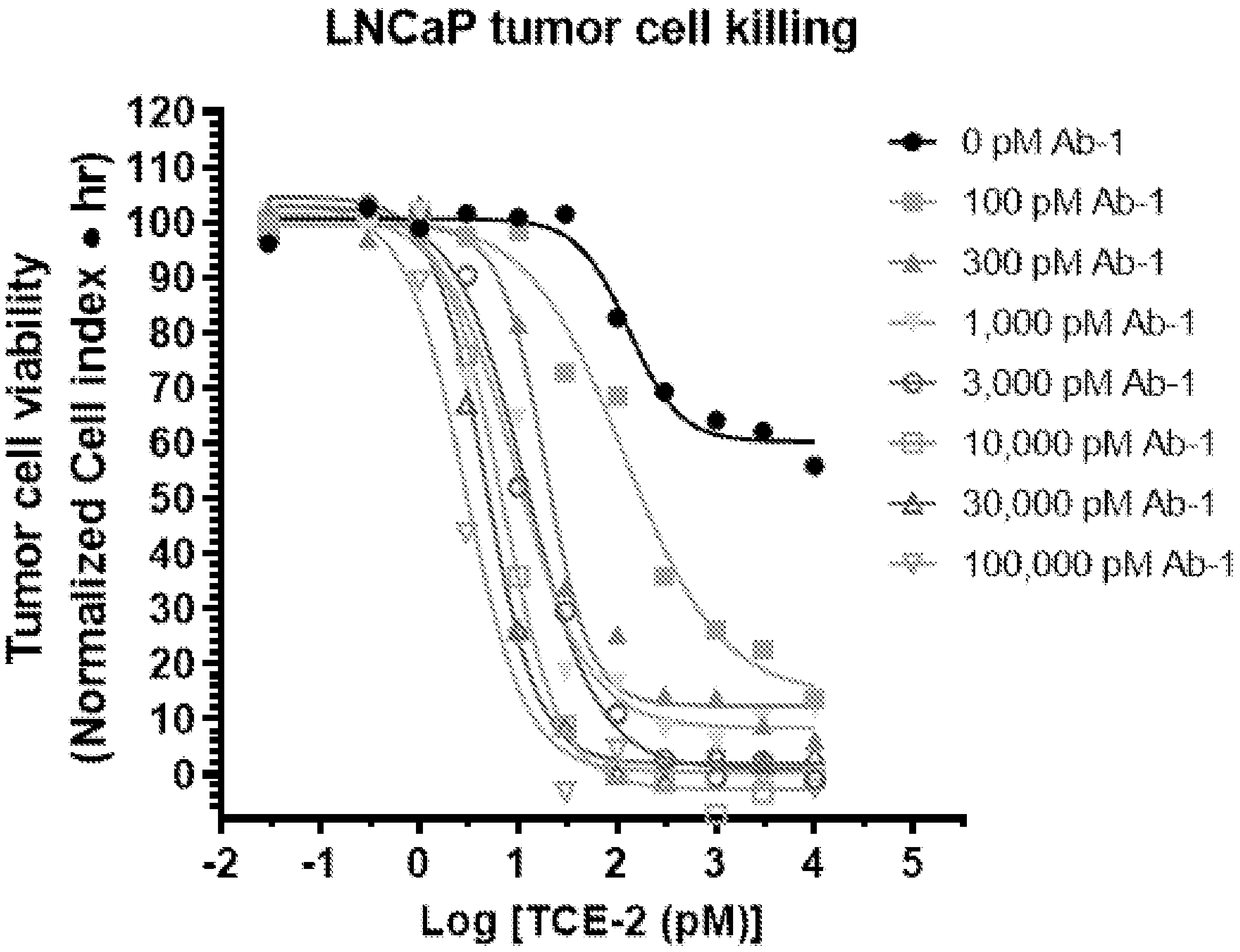

LNCaP tumor cell killing
Tumor cell viability
(Normalized Cell index • hr)
120
110
100
90
80
70
60
50
40
30
20
10
0
-2
-1
0
1
2
3
4
5
Log [TCE-2 (pM)]
0 pM Ab-1
100 pM Ab-1
300 pM Ab-1
1,000 pM Ab-1
3,000 pM Ab-1
10,000 pM Ab-1
30,000 pM Ab-1
100,000 pM Ab-1

Fig. 10A

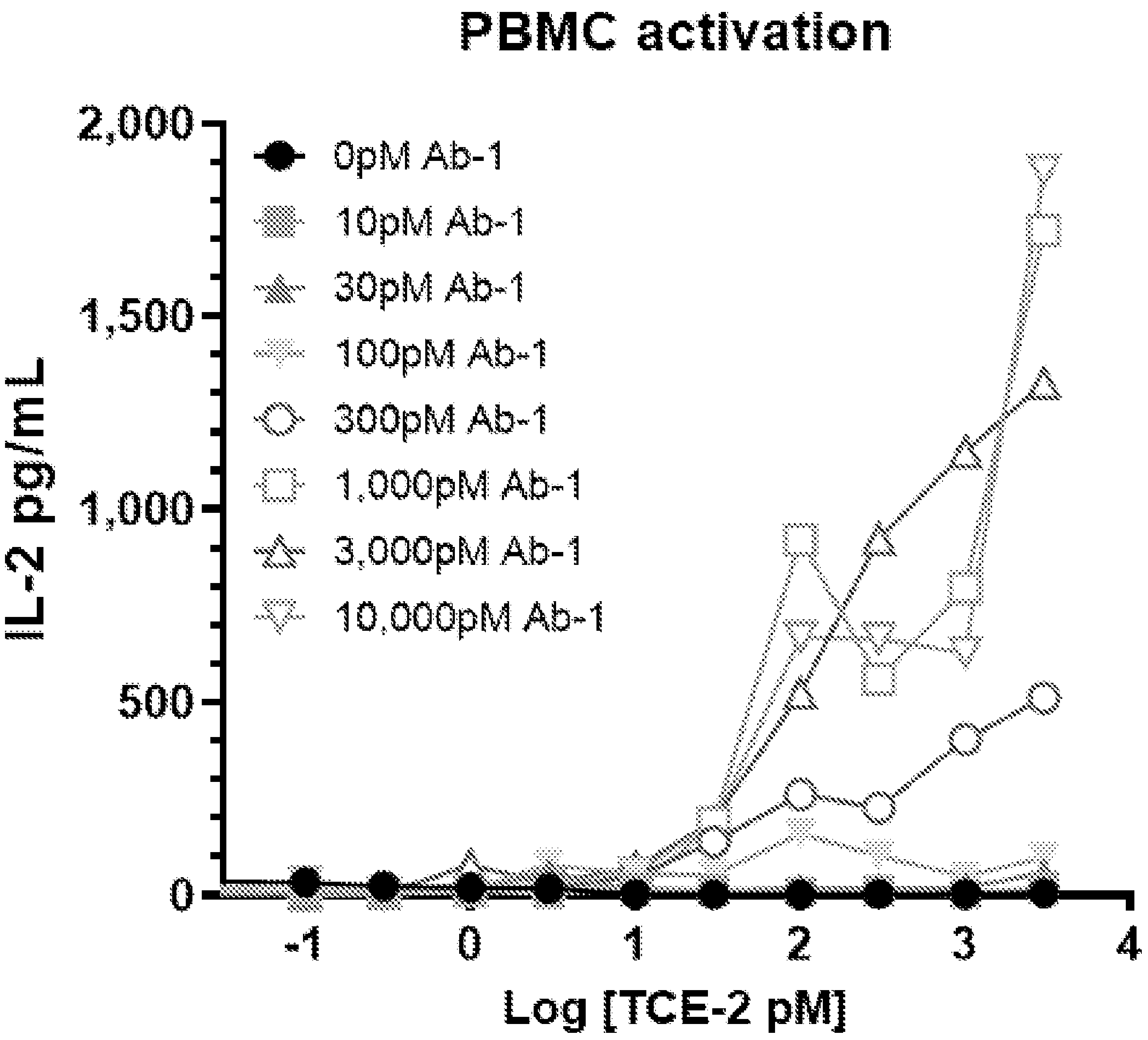

PBMC activation
IL-2 pg/mL
2,000
1,500
1,000
500
0
-1
0
1
2
3
4
Log [TCE-2 pM]
0pM Ab-1
10pM Ab-1
30pM Ab-1
100pM Ab-1
300pM Ab-1
1,000pM Ab-1
3,000pM Ab-1
10,000pM Ab-1

Fig. 10B

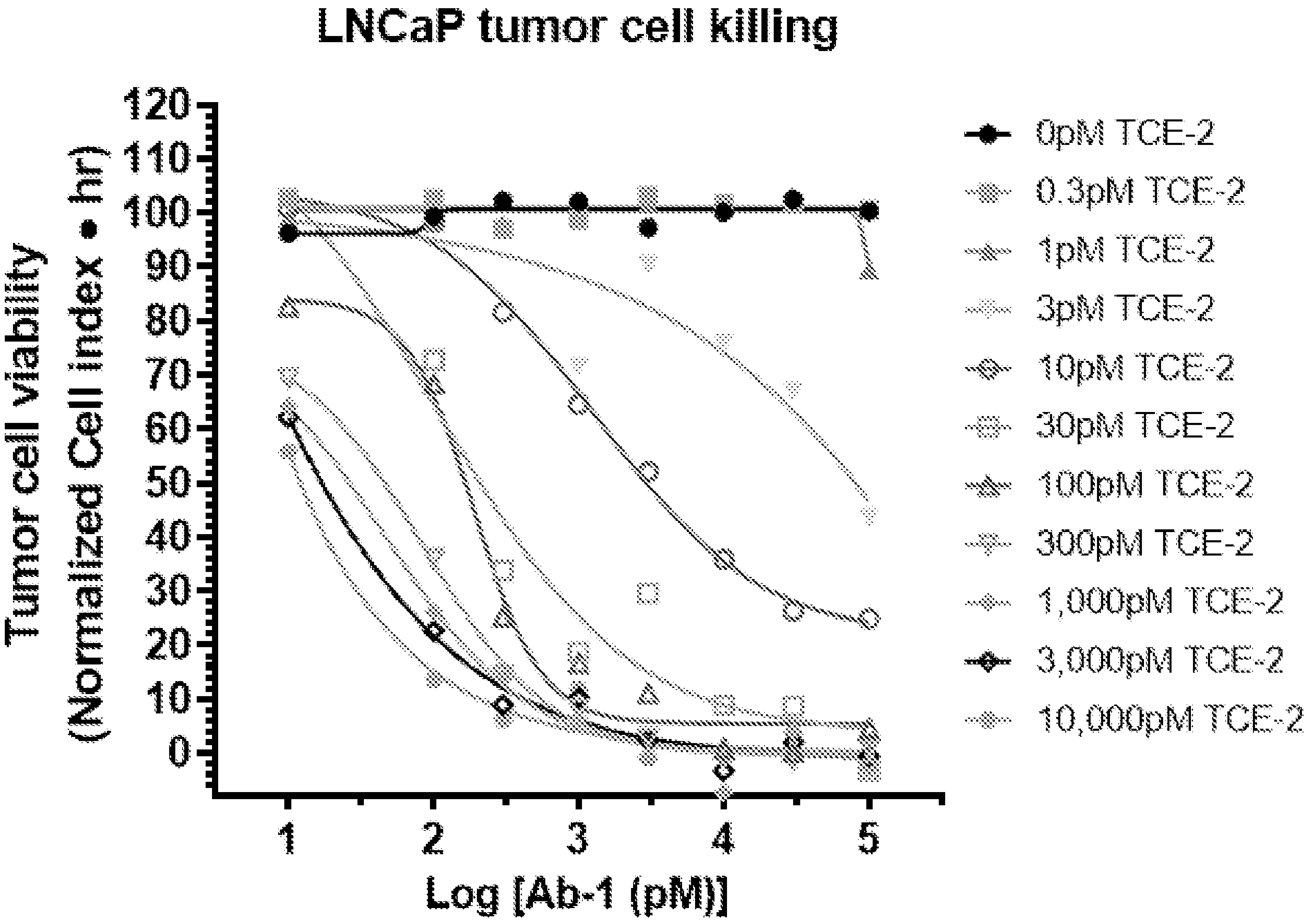

LNCaP tumor cell killing
Tumor cell viability
(Normalized Cell index • hr)
120
110
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
Log [Ab-1 (pM)]
0pM TCE-2
0.3pM TCE-2
1pM TCE-2
3pM TCE-2
10pM TCE-2
30pM TCE-2
100pM TCE-2
300pM TCE-2
1,000pM TCE-2
3,000pM TCE-2
10,000pM TCE-2

Fig. 10C

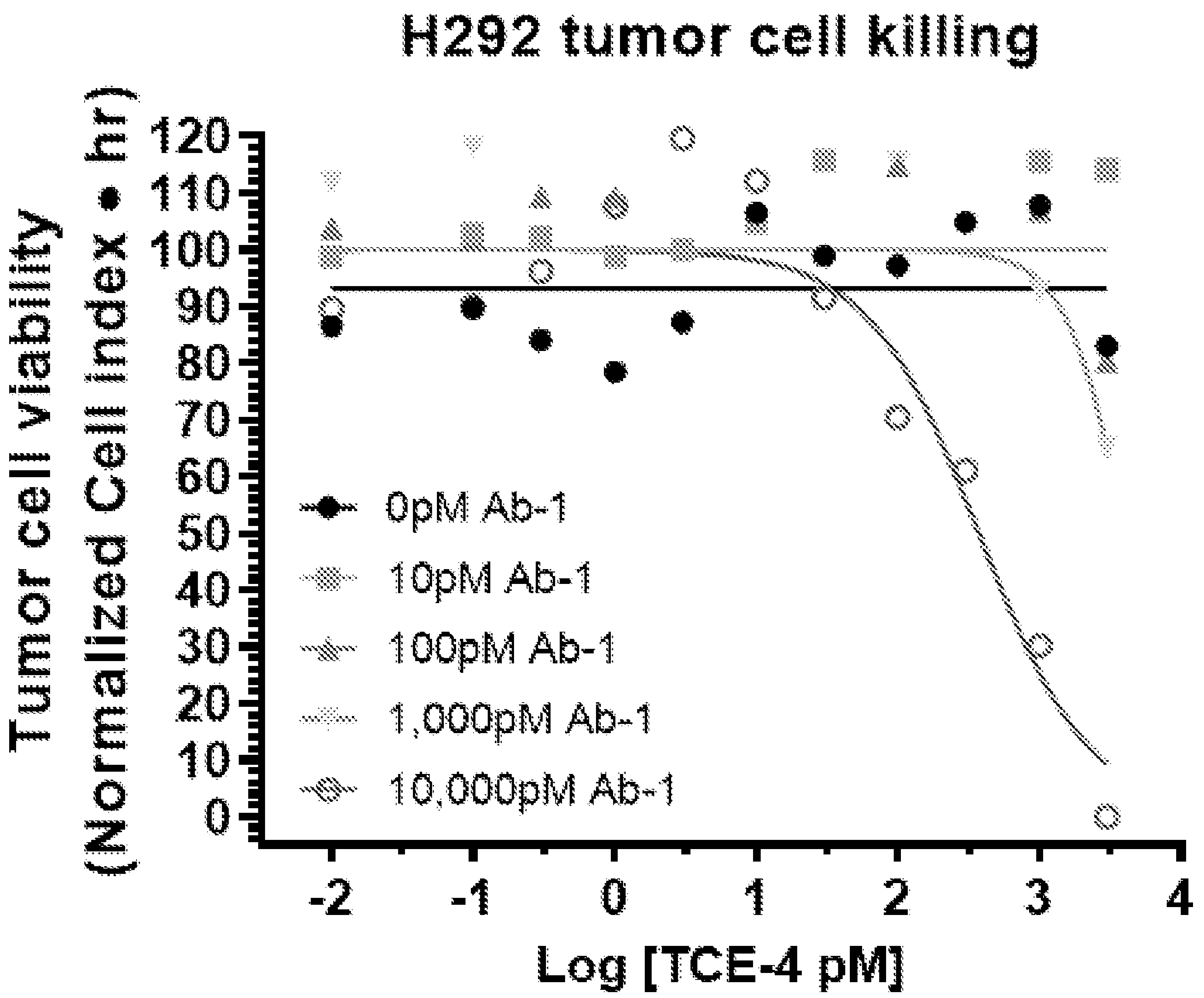

H292 tumor cell killing
Tumor cell viability
(Normalized Cell index • hr)
120
110
100
90
80
70
60
50
40
30
20
10
0
-2
-1
0
1
2
3
4
Log [TCE-4 pM]
0pM Ab-1
10pM Ab-1
100pM Ab-1
1,000pM Ab-1
10,000pM Ab-1

Fig. 10D

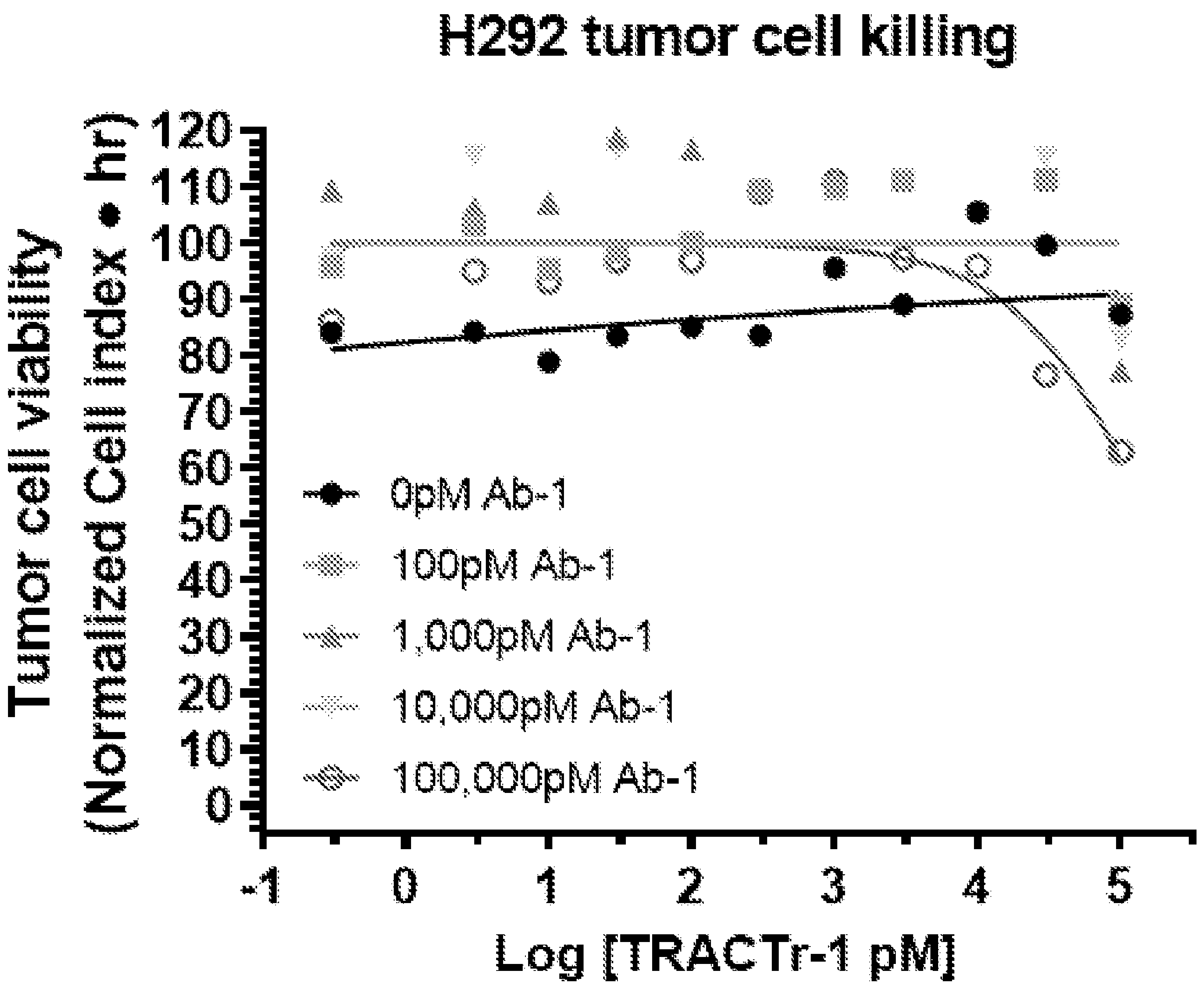

H292 tumor cell killing
Tumor cell viability
(Normalized Cell index • hr)
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
0
1
2
3
4
5
Log [TRACTr-1 pM]
0pM Ab-1
100pM Ab-1
1,000pM Ab-1
10,000pM Ab-1
100,000pM Ab-1

Fig. 10E

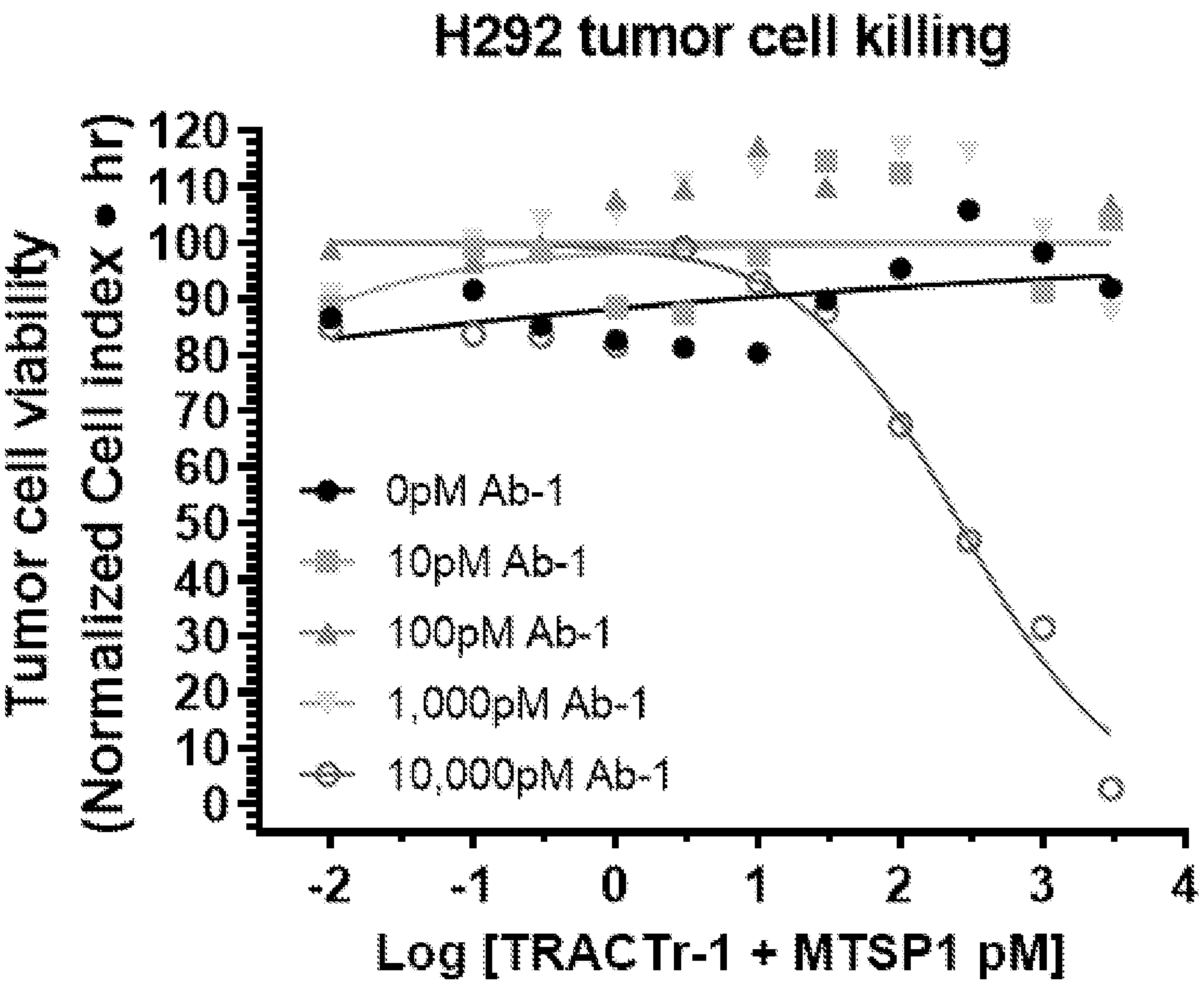

H292 tumor cell killing
Tumor cell viability
(Normalized Cell index • hr)
120
110
100
90
80
70
60
50
40
30
20
10
0
-2
-1
0
1
2
3
4
Log [TRACTr-1 + MTSP1 pM]
0pM Ab-1
10pM Ab-1
100pM Ab-1
1,000pM Ab-1
10,000pM Ab-1

Fig. 10F

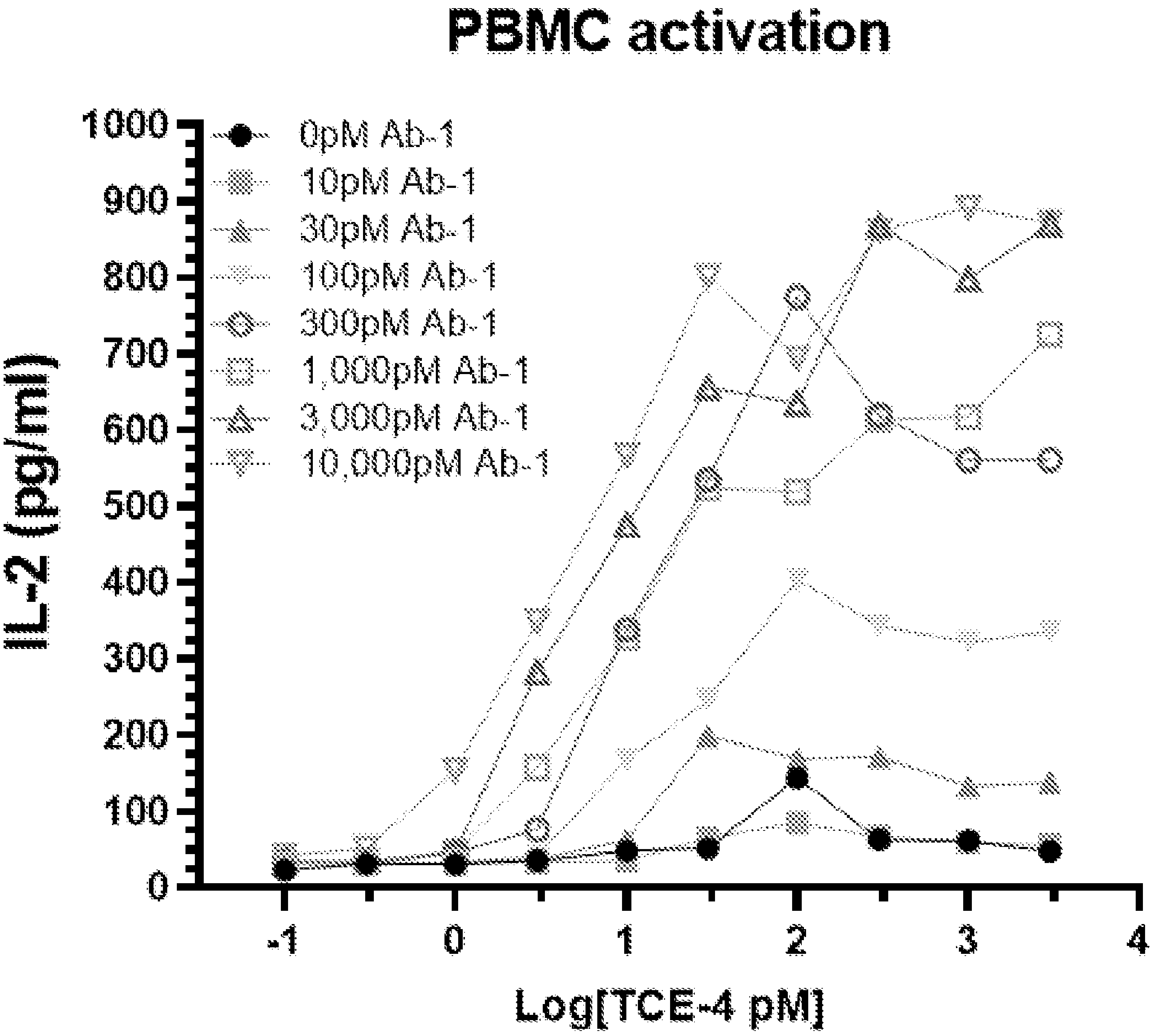

PBMC activation
IL-2 (pg/ml)
1000
900
800
700
600
500
400
300
200
100
0
-1
0
1
2
3
4
Log[TCE-4 pM]
0pM Ab-1
10pM Ab-1
30pM Ab-1
100pM Ab-1
300pM Ab-1
1,000pM Ab-1
3,000pM Ab-1
10,000pM Ab-1

Fig. 10G

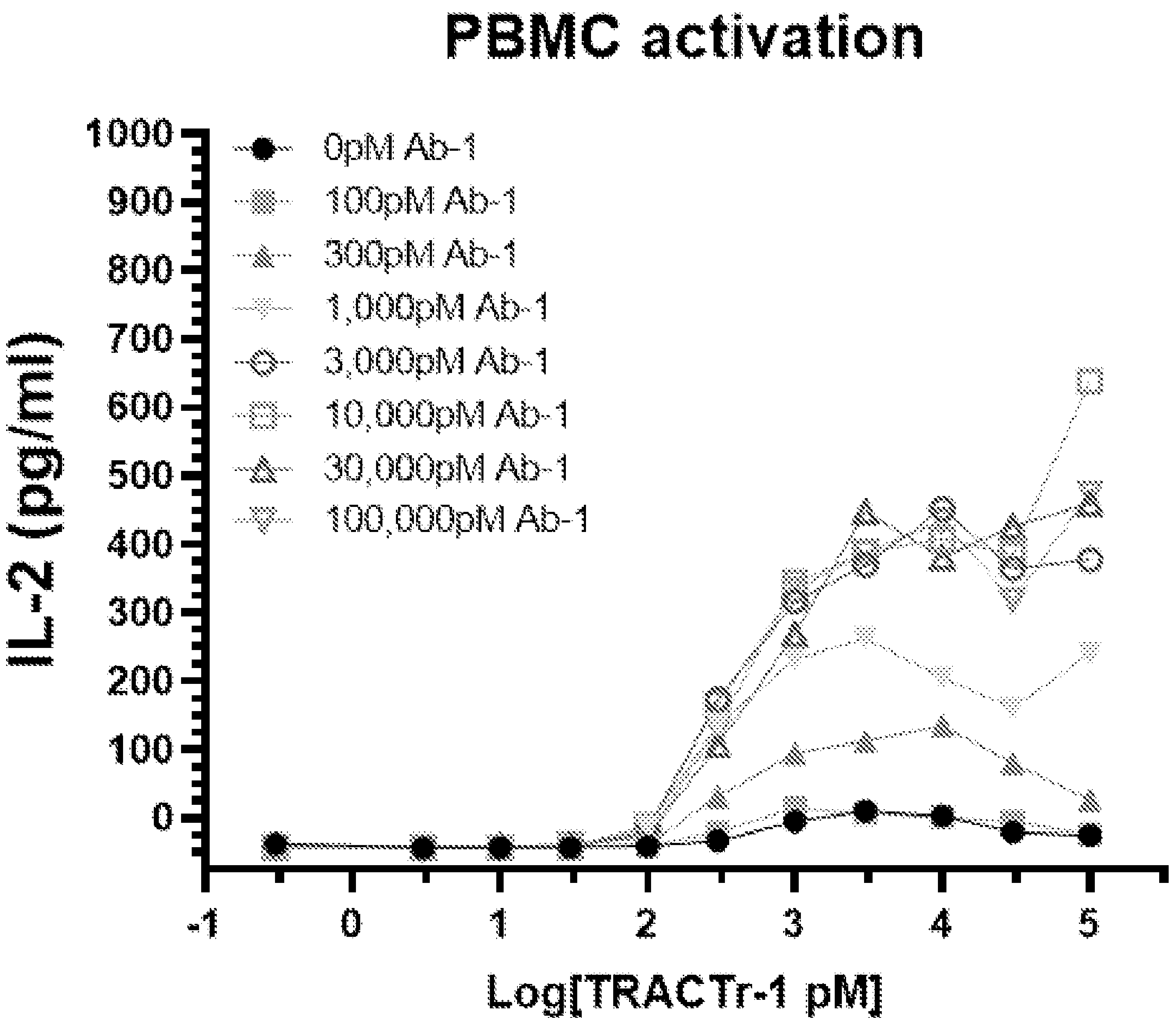

PBMC activation
IL-2 (pg/ml)
1000
900
800
700
600
500
400
300
200
100
0
-1
0
1
2
3
4
5
Log[TRACTr-1 pM]
0pM Ab-1
100pM Ab-1
300pM Ab-1
1,000pM Ab-1
3,000pM Ab-1
10,000pM Ab-1
30,000pM Ab-1
100,000pM Ab-1

Fig. 10H

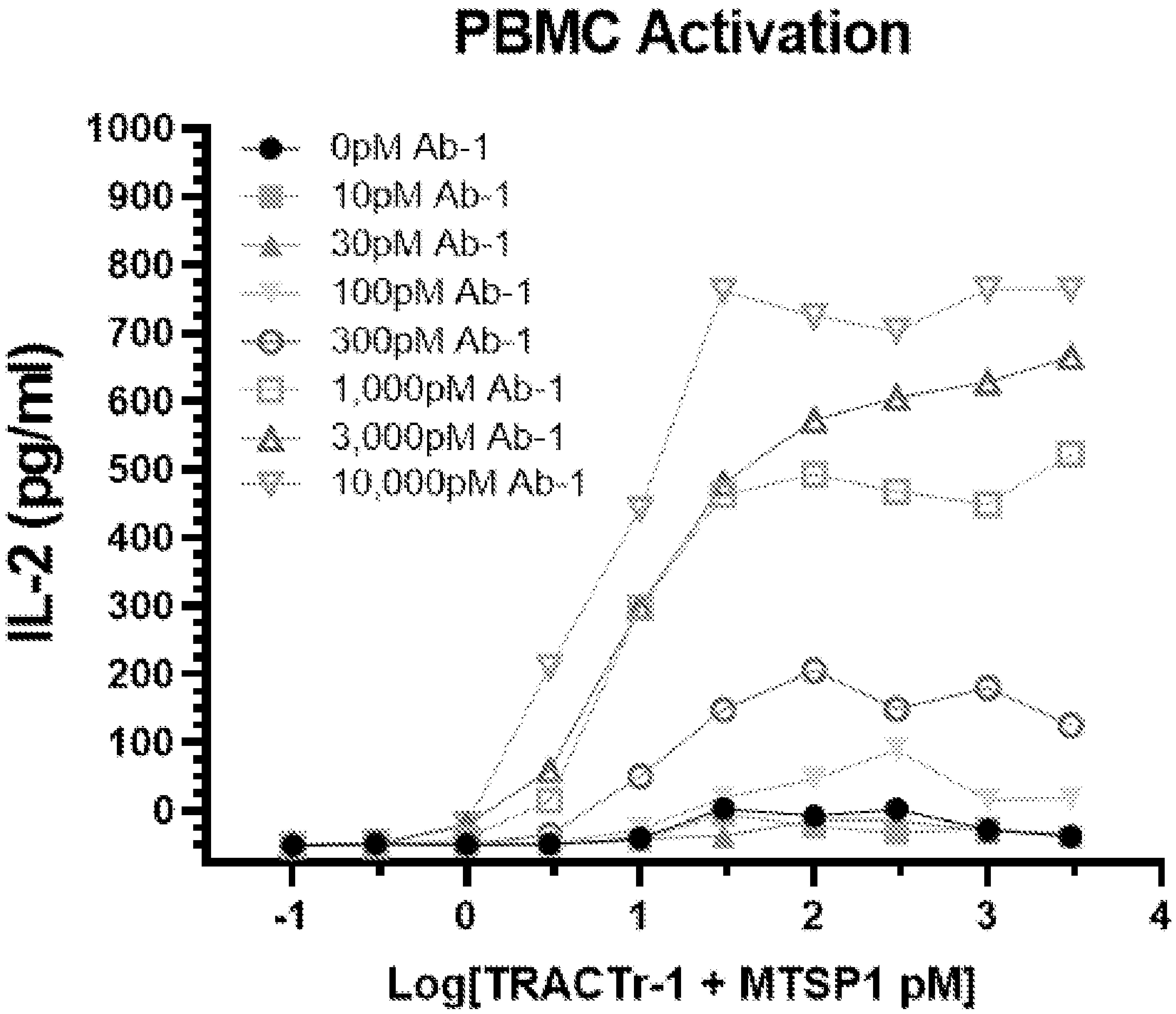

PBMC Activation
IL-2 (pg/ml)
1000
900
800
700
600
500
400
300
200
100
0
0pM Ab-1
10pM Ab-1
30pM Ab-1
100pM Ab-1
300pM Ab-1
1,000pM Ab-1
3,000pM Ab-1
10,000pM Ab-1
-1
0
1
2
3
4
Log[TRACTr-1 + MTSP1 pM]

Fig. 10I

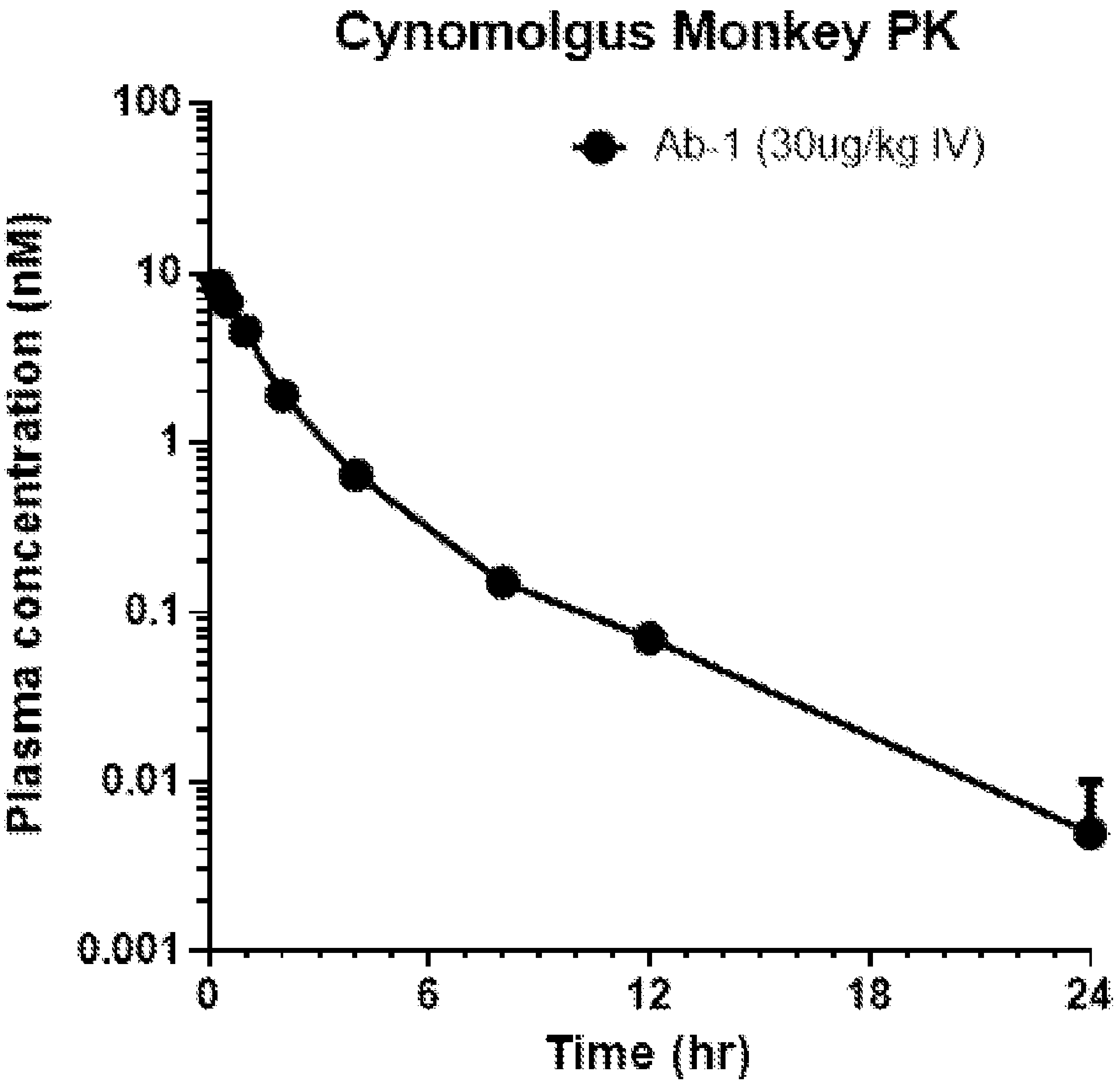

Cynomolgus Monkey PK
Ab-1 (30ug/kg IV)
Plasma concentration (nM)
100
10
1
0.1
0.01
0.001
0
6
12
18
24
Time (hr)

Fig. 11

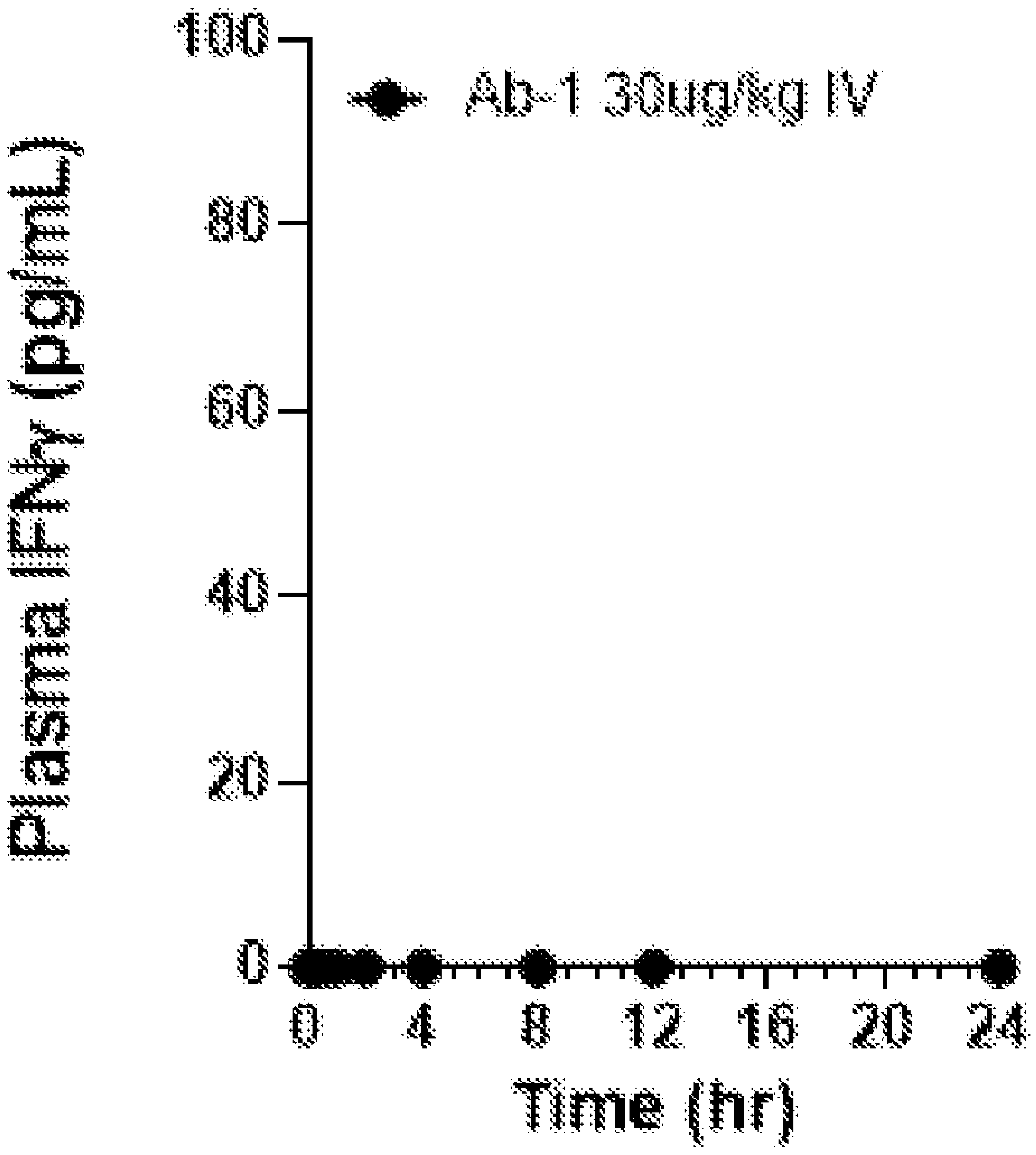


Fig. 12A

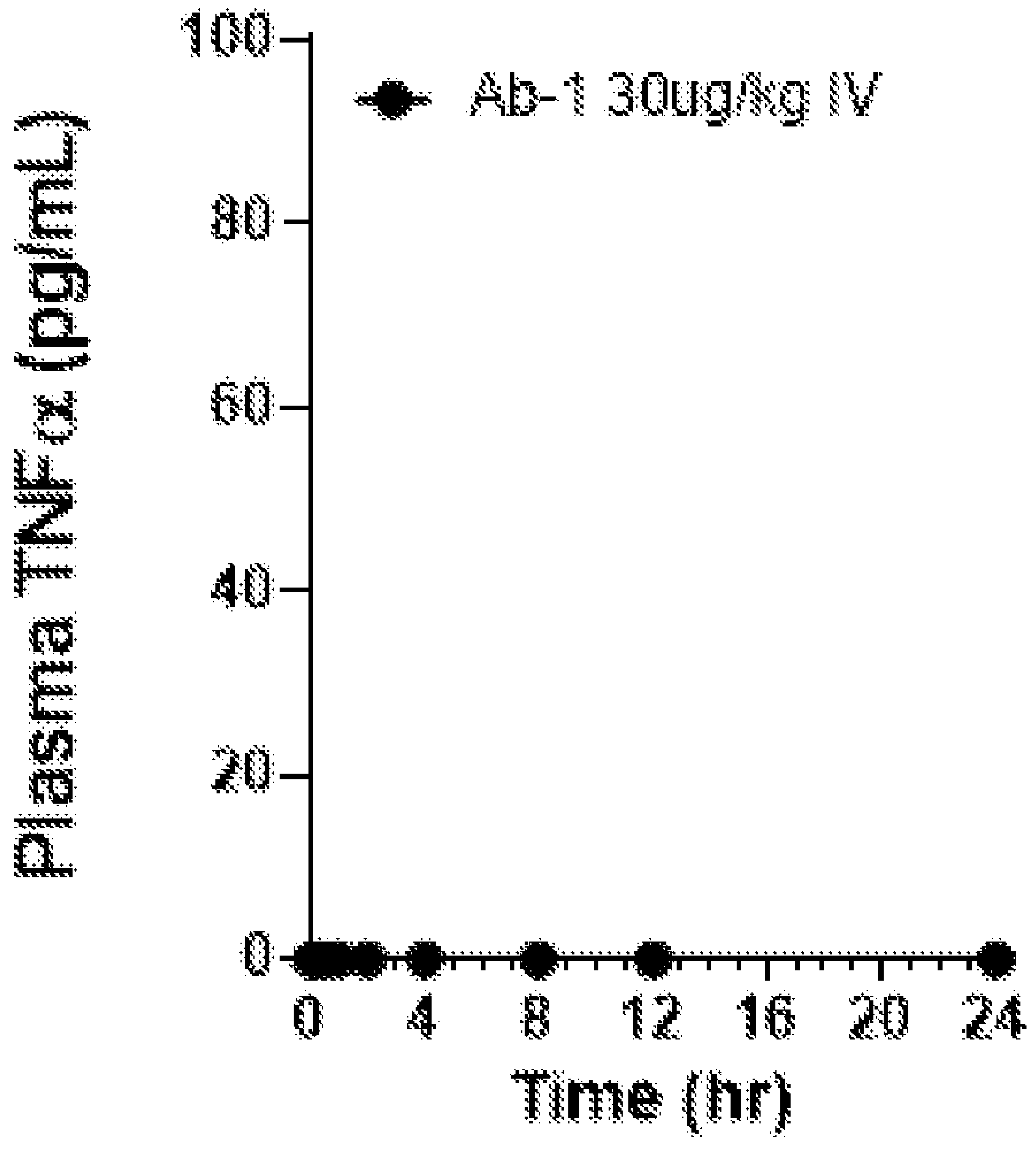


Fig. 12B

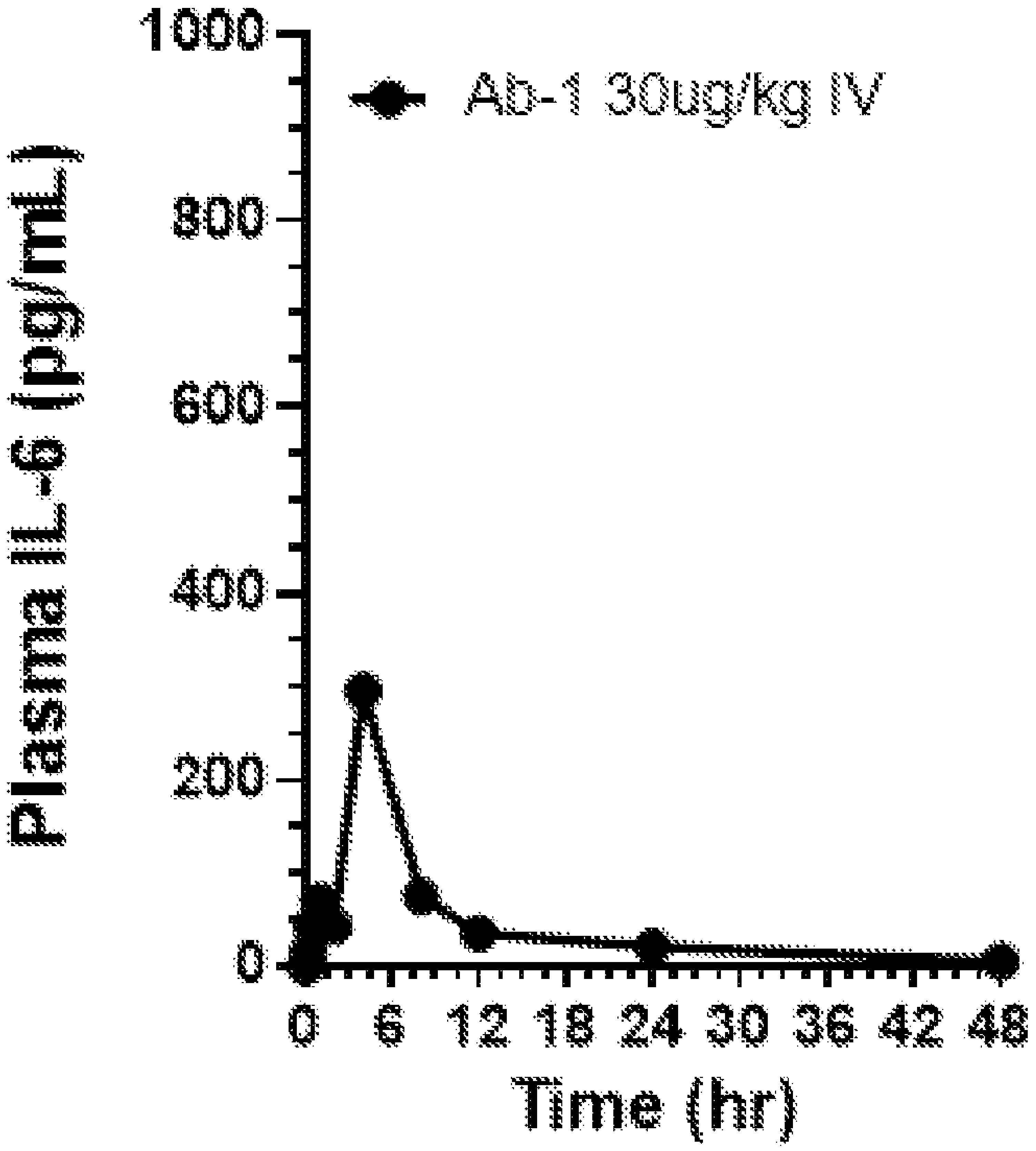

Ab-1 30ug/kg IV
Plasma IL-6 (pg/mL)
1000
800
600
400
200
0
0
6
12
18
24
30
36
42
48
Time (hr)

Fig. 12C

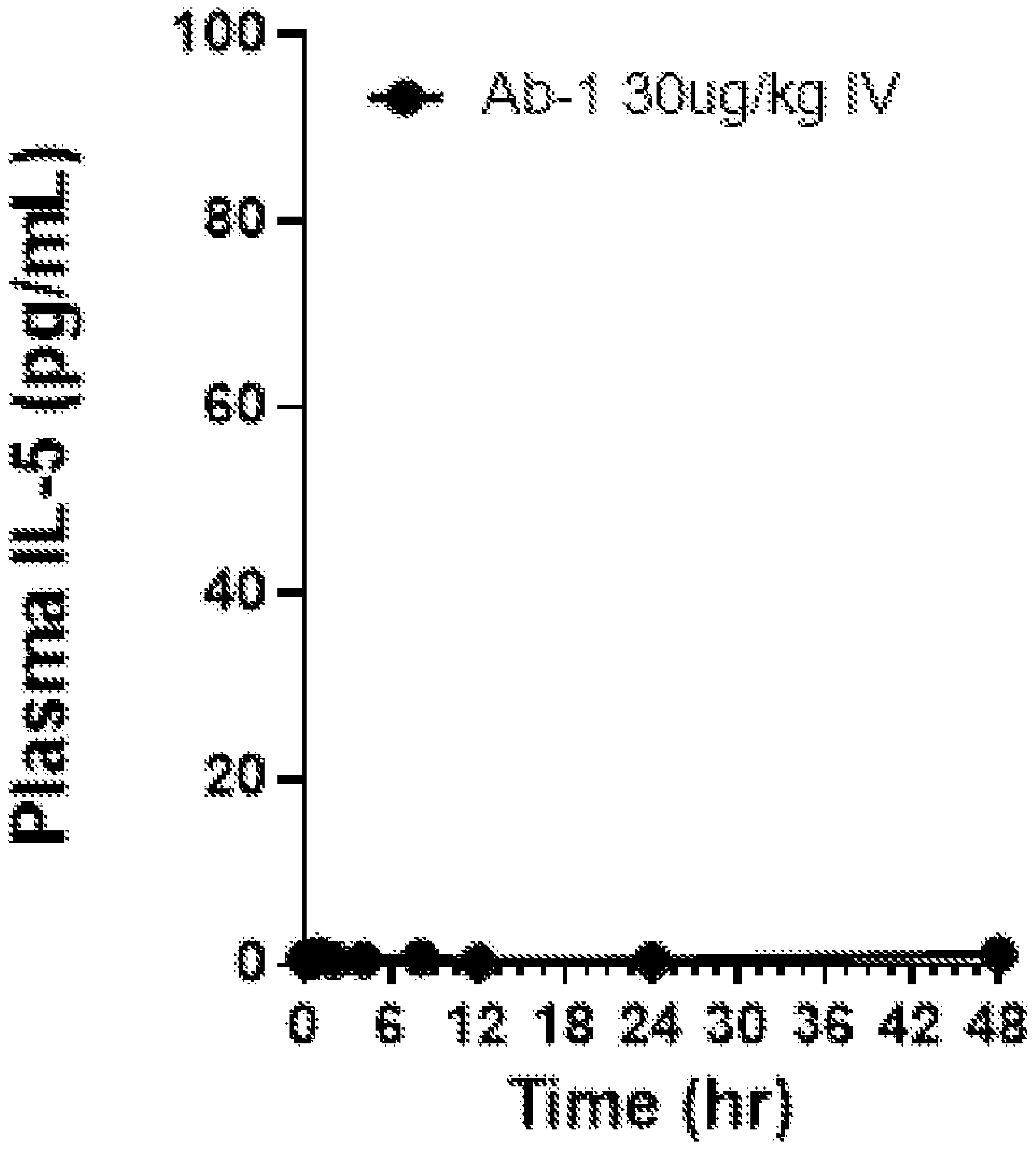


Fig. 12D

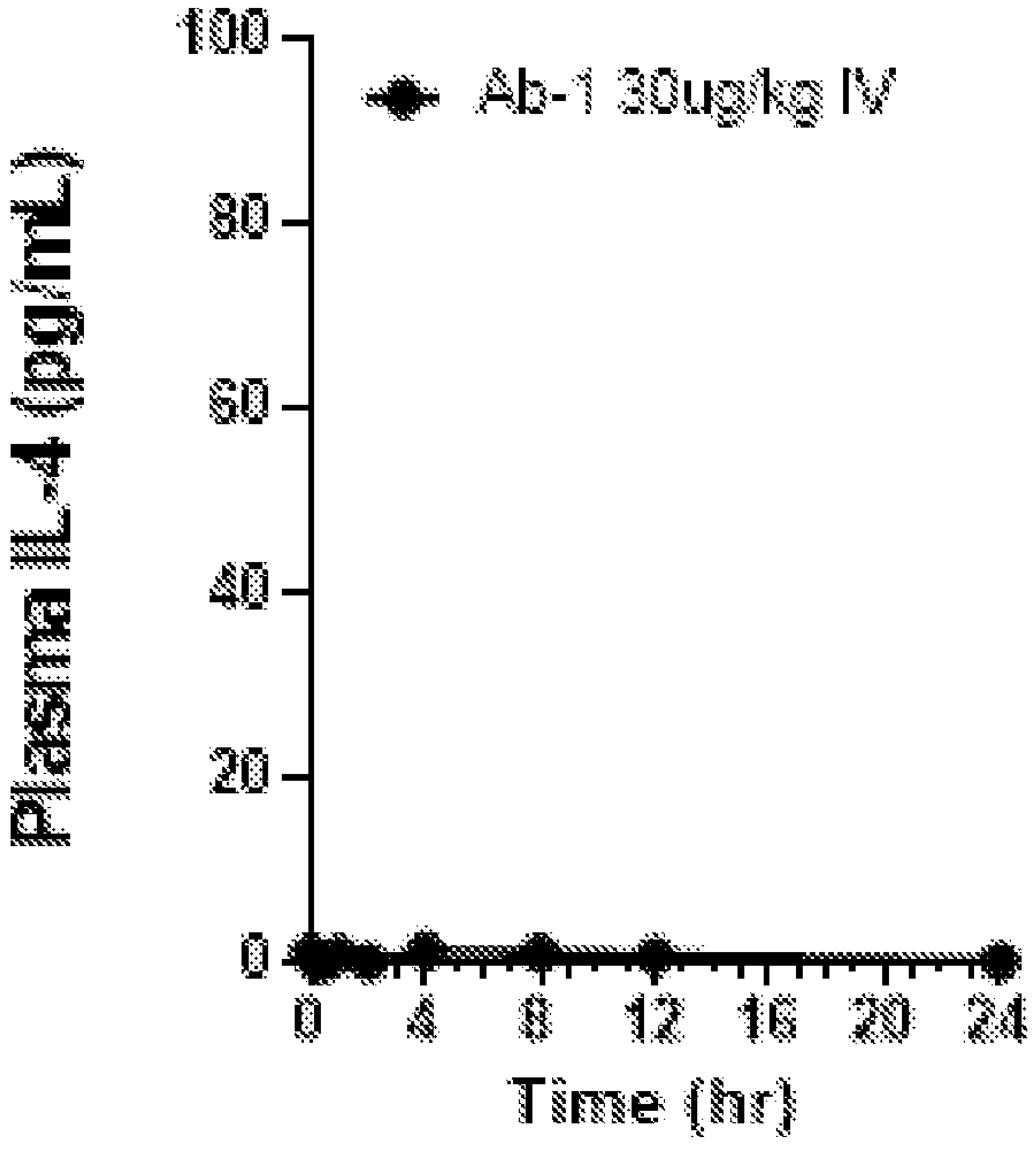


Fig. 12E

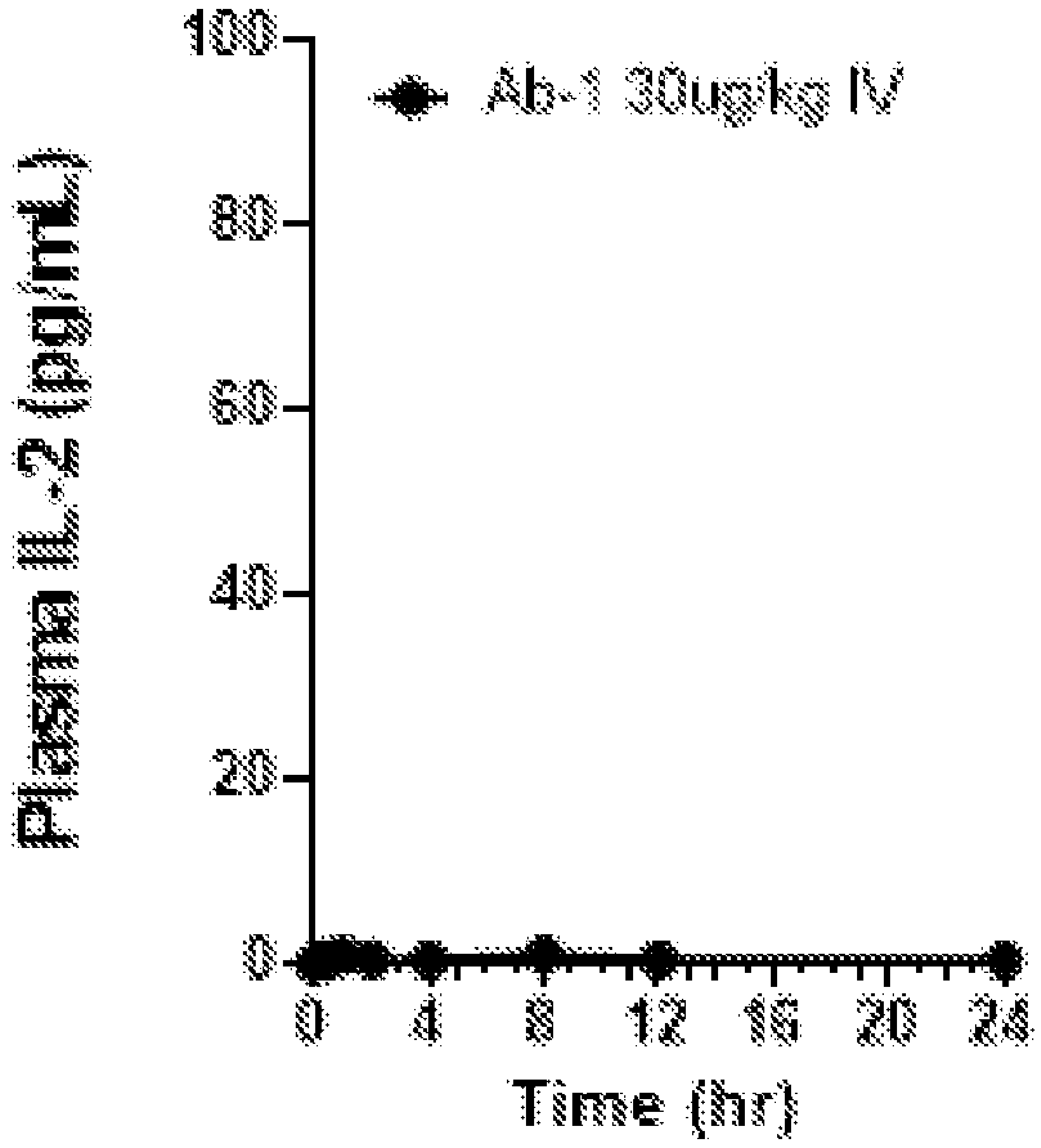


Fig. 12F

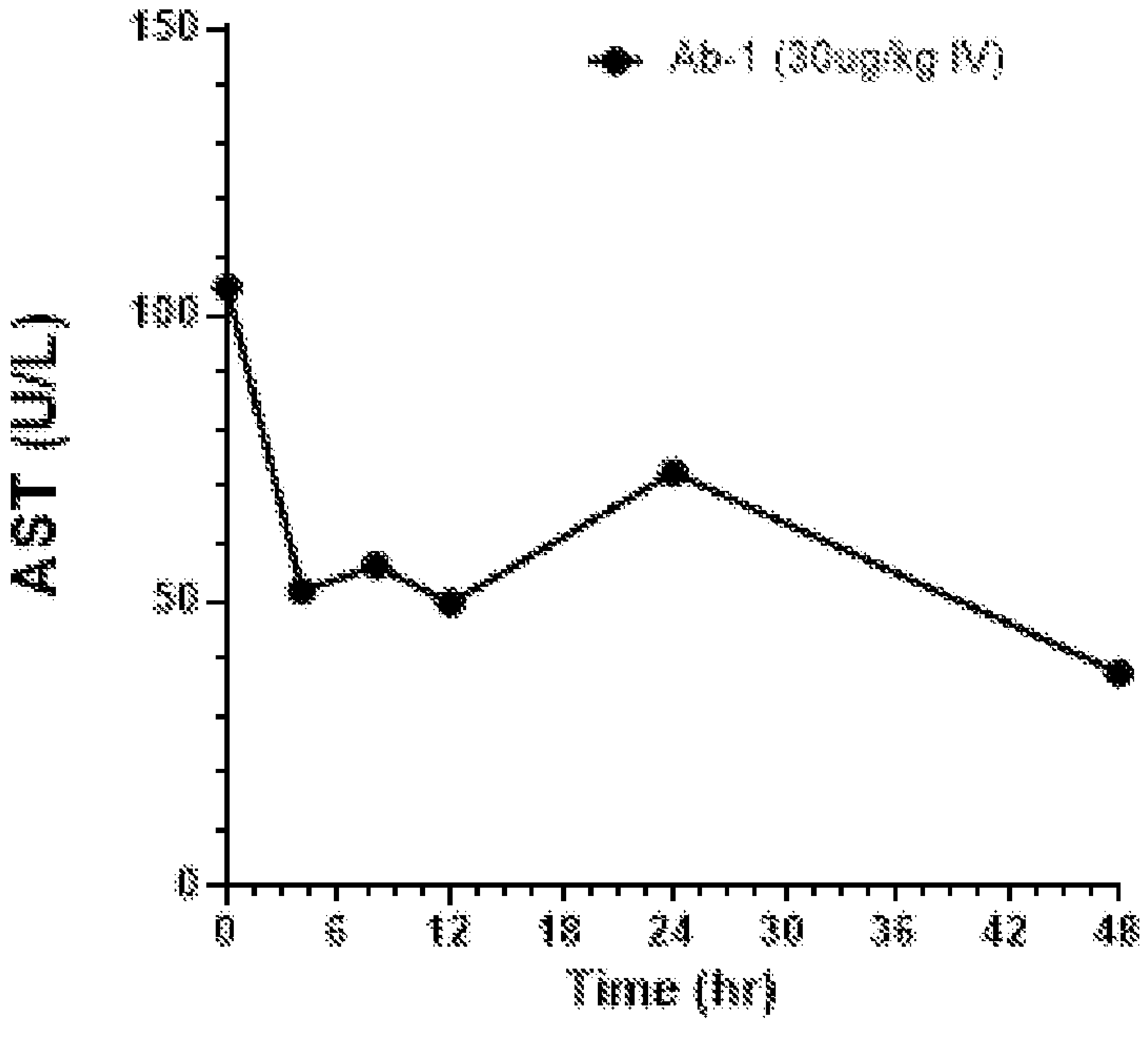


Fig. 13A

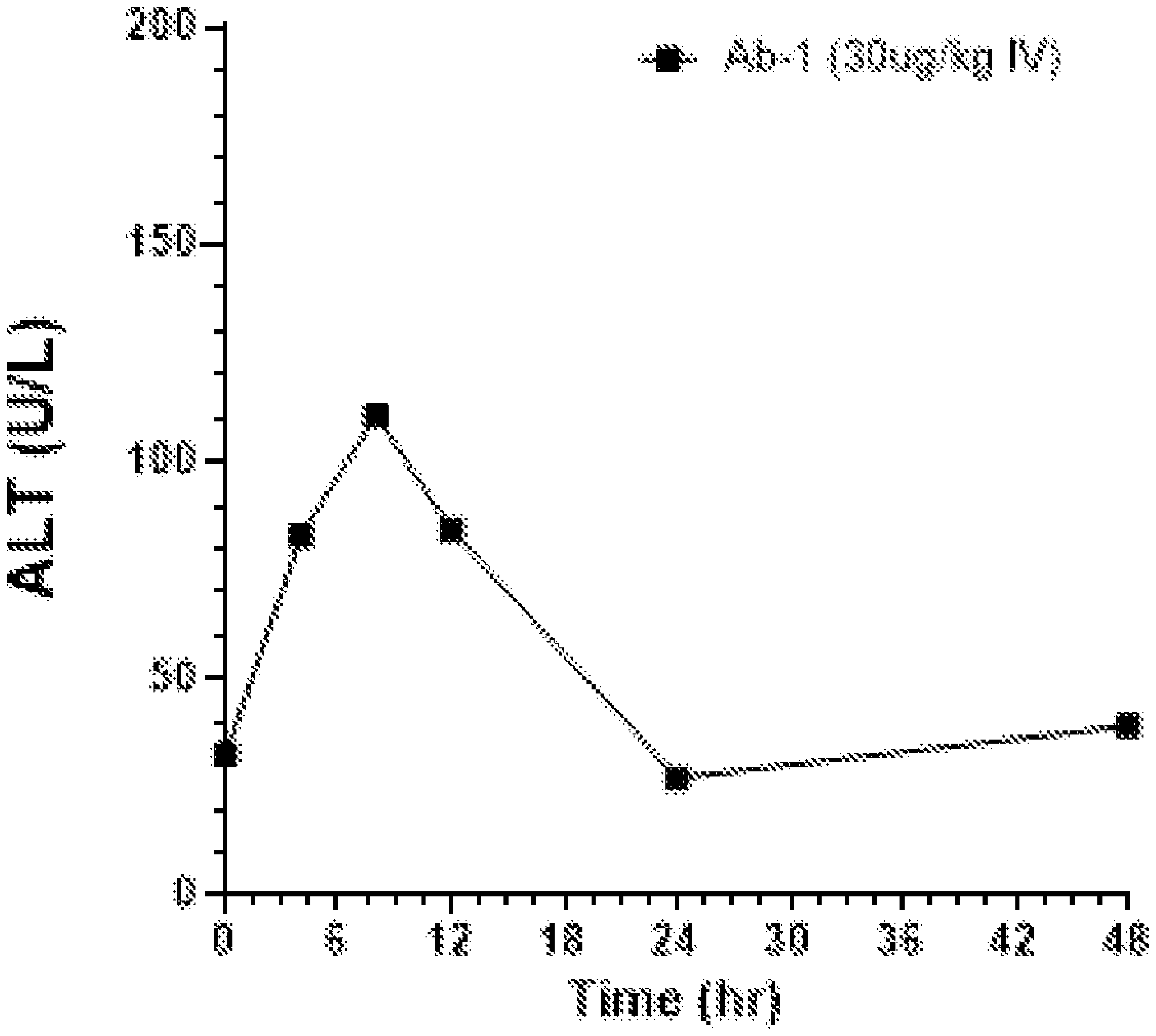


Fig. 13B

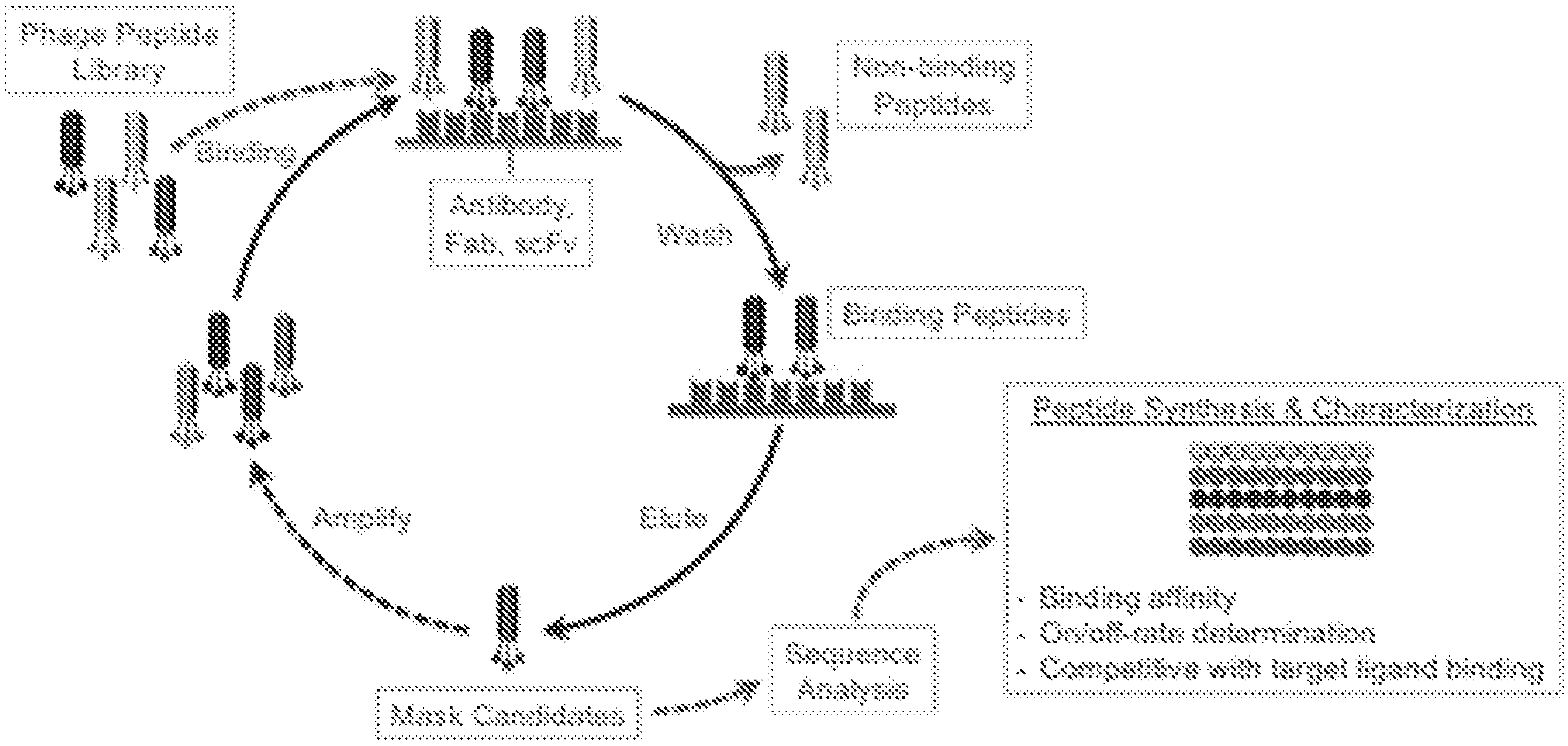


Fig. 14

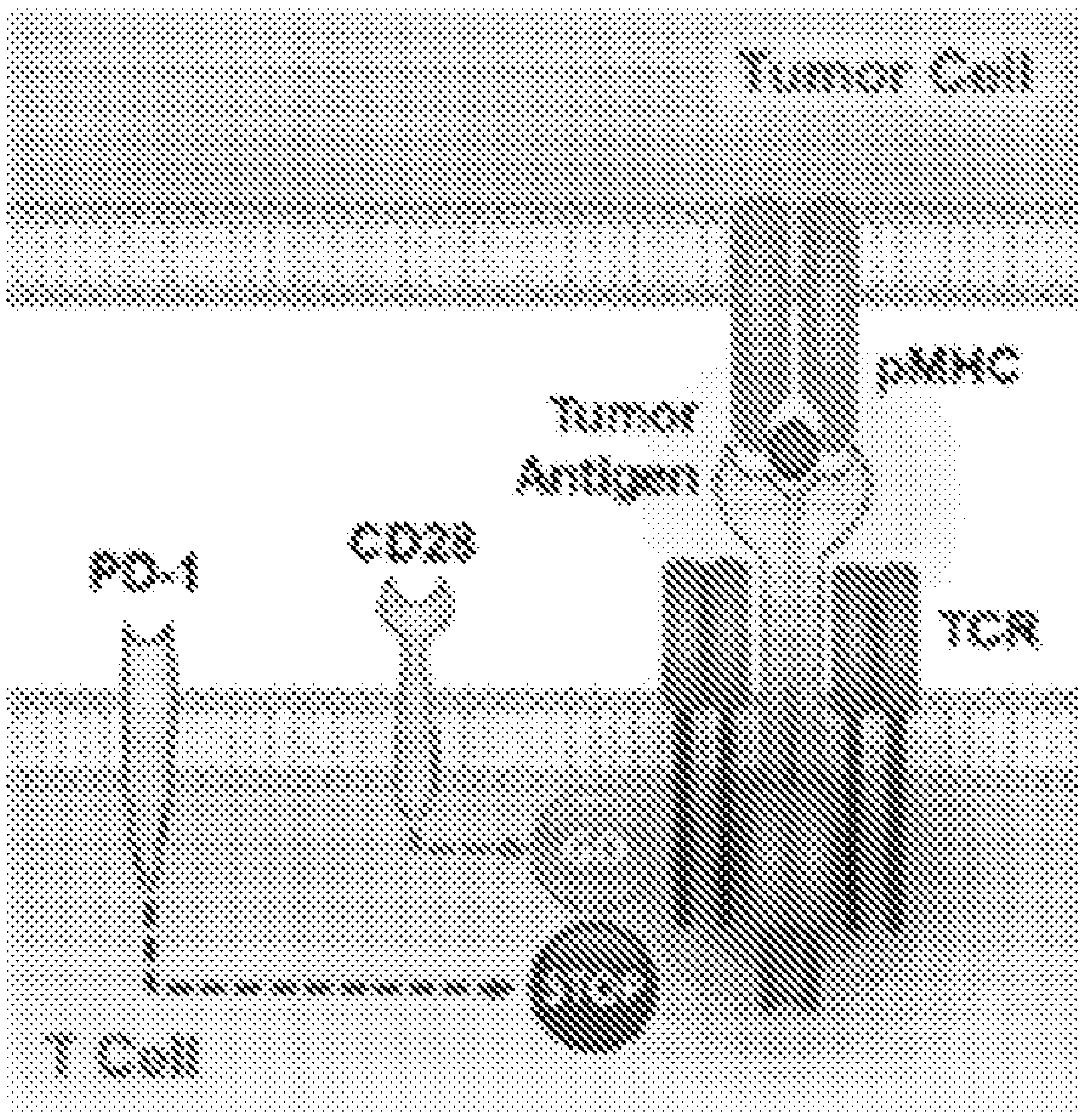


Fig. 15A

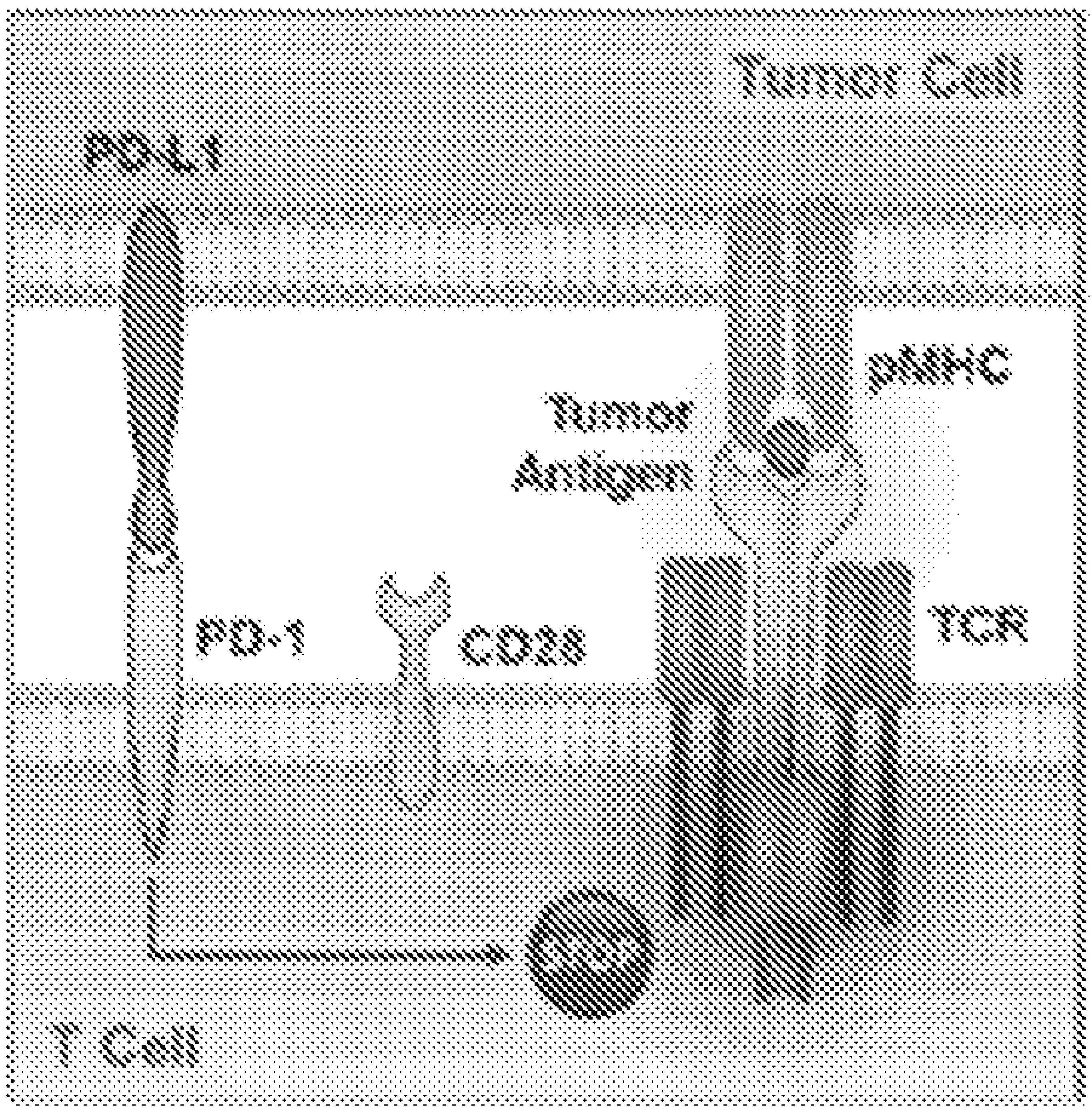


Fig. 15B

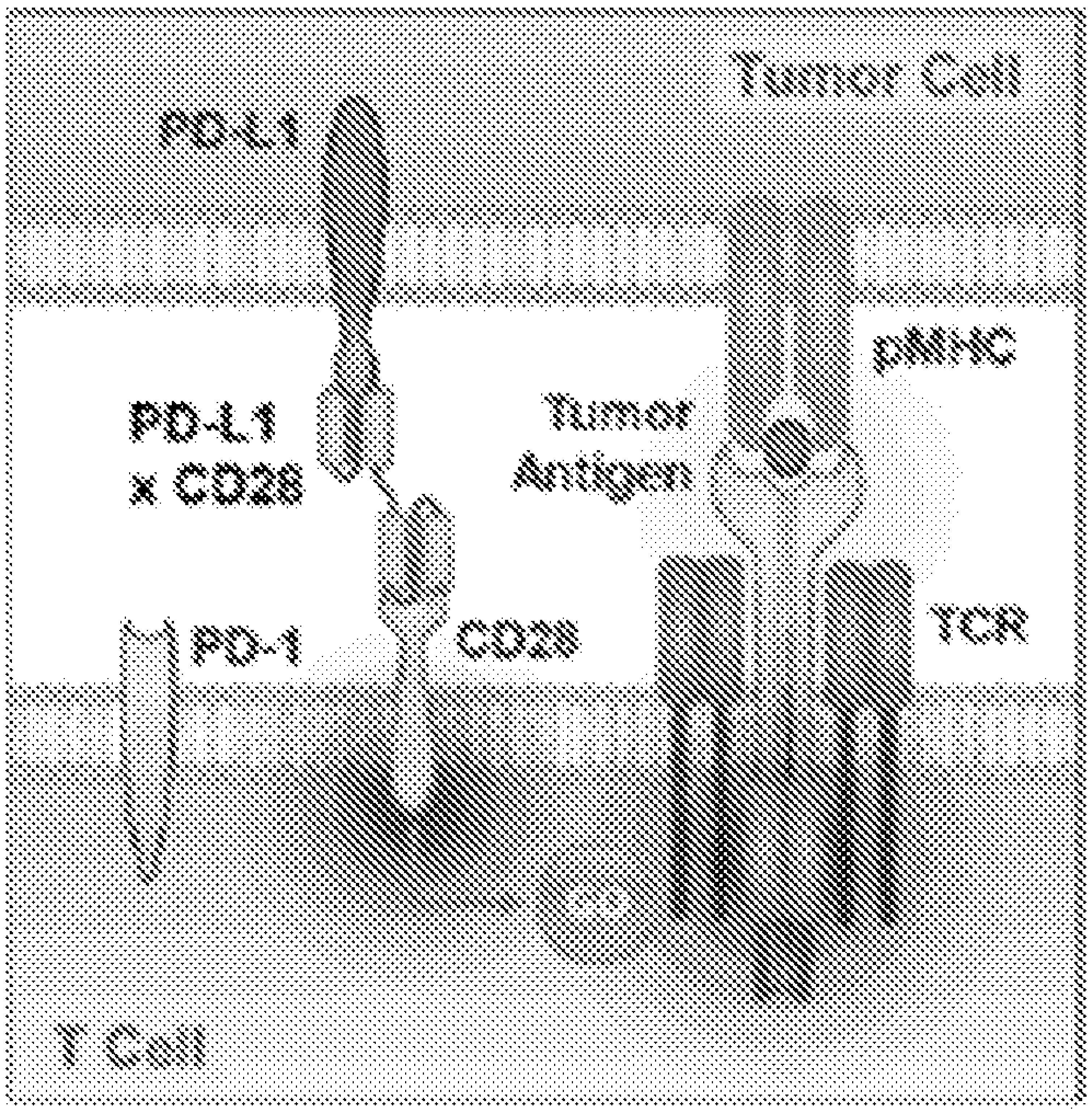


Fig. 15C

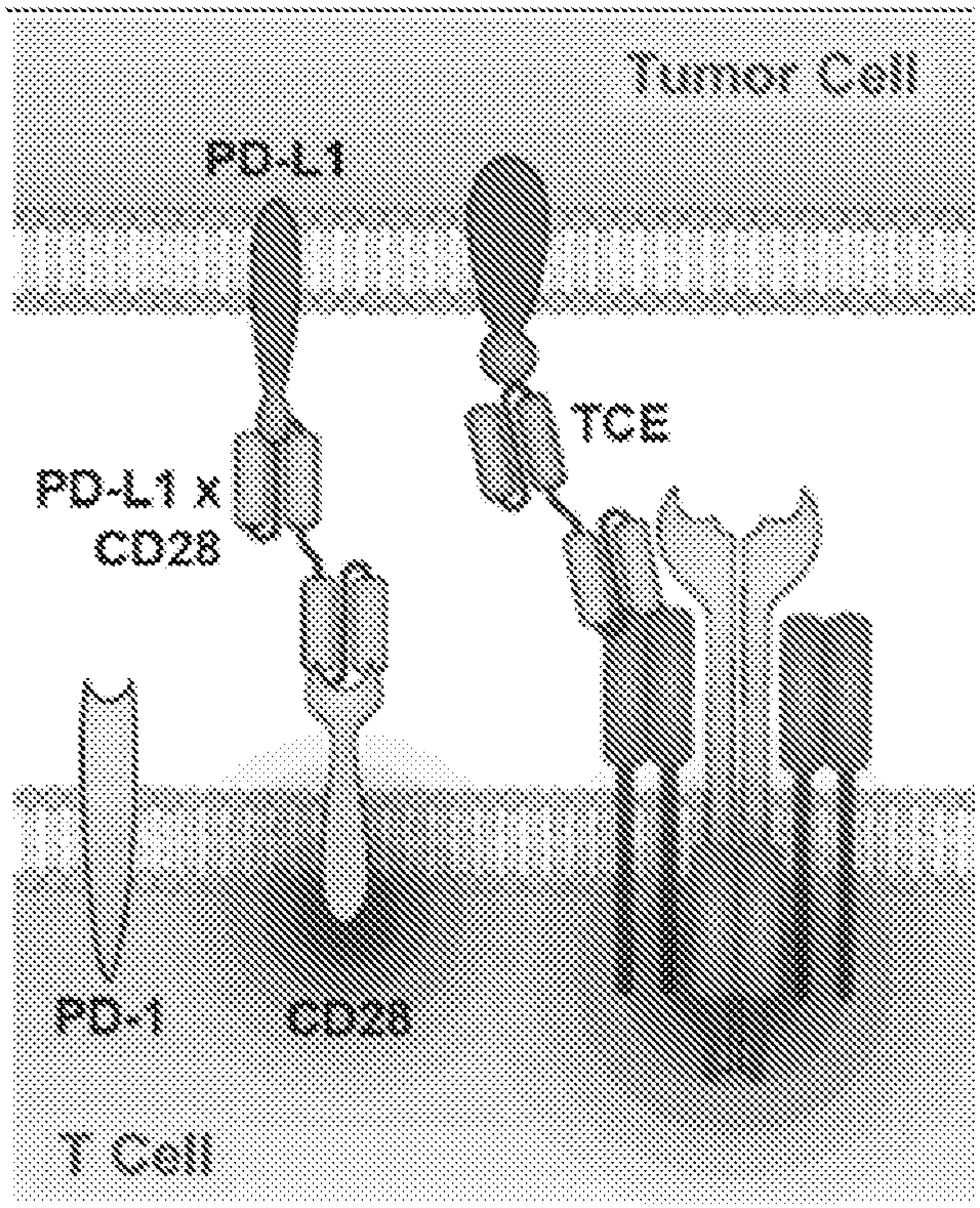


Fig. 16

SEQUENCE LISTING

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<120> MULTISPECIFIC ANTIBODIES FOR TARGETING CD28 AND PD-L1 AND METHODS
OF USE THEREOF

<130> 52426-726.601

<140>
<141>

<150> 63/189,843
<151> 2021-05-18

<150> 63/187,719
<151> 2021-05-12

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<170> PatentIn version 3.5

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<212> PRT
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<220>
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peptide

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1   5

```
<210> 2
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 2
Ile Tyr Pro Gly Asn Val Asn Thr
1               5


<210> 3
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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      peptide

<400> 3
Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val
1               5                   10


<210> 4
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 4
Gln Asn Ile Tyr Val Trp
1               5


<210> 5
<211> 2
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 5
Lys Ala
1
```

```
<210> 6
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 6
Gln Gln Gly Gln Thr Tyr Pro Tyr Thr
1               5


<210> 7
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

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


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


Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


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


Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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


Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100                 105                 110
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Gly Thr Thr Val Thr Val Ser Ser
115 120

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

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

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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 His Ala Ser Gln Asn Ile Tyr Val Trp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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

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

<210> 9
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

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

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

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

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

Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys His Ala
145                 150                 155                 160

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

Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Asn Leu His Thr Gly
            180                 185                 190

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

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
    210                 215                 220
```

```
Gln Gly Gln Thr Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
225                 230                 235                 240


Ile Lys



<210> 10
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 10
Gly Asp Thr Phe Ser Thr Tyr Ala
1               5


<210> 11
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 11
Ile Ile Pro Ile Phe Gly Lys Ala
1               5


<210> 12
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 12
Ala Arg Lys Phe His Phe Val Ser Gly Ser Pro Phe Gly Met Asp Val
1               5                   10                  15


<210> 13
<211> 6
<212> PRT
<213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 13
Gln Ser Val Ser Ser Tyr
1               5


<210> 14
<211> 2
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 14
Asp Ala
1


<210> 15
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 15
Gln Gln Arg Ser Asn Trp Pro Thr
1               5


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

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 16
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


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

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

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

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

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

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

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

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

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

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

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

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

Asn Arg Gly Glu Cys
    210
```

<210> 17
<211> 226
<212> PRT
<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 17
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 Thr Ser Gly Asp Thr Phe Ser Thr Tyr
            20                  25                  30


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


Gly Gly Ile Ile Pro Ile Phe Gly Lys Ala His Tyr Ala Gln Lys Phe
    50                  55                  60


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


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


Ala Arg Lys Phe His Phe Val Ser Gly Ser Pro Phe Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125


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


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


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


Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190
```

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


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


Ser Cys
225


<210> 18
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 18
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1               5                   10                  15


<210> 19
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 19
Gly Gly Gly Gly Ser
1               5


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

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 20
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15
```

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

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

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

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

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

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
            100   105   110

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

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

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

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

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

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

Asn Arg Gly Glu Cys
    210

<210> 21
<211> 473

```
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

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


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


Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


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


Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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


Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100                 105                 110


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


Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140


Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys His Ala
145                 150                 155                 160


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


Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Asn Leu His Thr Gly
            180                 185                 190
```

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

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

Gln Gly Gln Thr Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala
                245                 250                 255

Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Thr Ser
            260                 265                 270

Gly Asp Thr Phe Ser Thr Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro
        275                 280                 285

Gly Gln Gly Leu Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Lys
    290                 295                 300

Ala His Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp
305                 310                 315                 320

Glu Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu
                325                 330                 335

Asp Thr Ala Val Tyr Phe Cys Ala Arg Lys Phe His Phe Val Ser Gly
            340                 345                 350

Ser Pro Phe Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
        355                 360                 365

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
    370                 375                 380

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
385                 390                 395                 400
```

```
Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
                405                 410                 415


Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
            420                 425                 430


Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
        435                 440                 445


Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
    450                 455                 460


Asp Lys Lys Val Glu Pro Lys Ser Cys
465                 470


<210> 22
<211> 460
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

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


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


Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


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


Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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

```
Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys His Ala
145                 150                 155                 160

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

Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Asn Leu His Thr Gly
            180                 185                 190

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

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

Gln Gly Gln Thr Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
225                 230                 235                 240

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

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
            260                 265                 270

Ser Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
        275                 280                 285

Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly
    290                 295                 300

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
305                 310                 315                 320
```

```
Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln
                325                 330                 335


Gln Arg Ser Asn Trp Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            340                 345                 350


Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
        355                 360                 365


Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
    370                 375                 380


Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
385                 390                 395                 400


Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
                405                 410                 415


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
            420                 425                 430


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
        435                 440                 445


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    450                 455                 460


<210> 23
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 23
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 Thr Ser Gly Asp Thr Phe Ser Thr Tyr
            20                  25                  30
```

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

Gly Gly Ile Ile Pro Ile Phe Gly Lys Ala His Tyr Ala Gln Lys Phe
    50                  55                  60

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

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

Ala Arg Lys Phe His Phe Val Ser Gly Ser Pro Phe Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

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

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

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

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

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

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

Ser Cys
225
```

<210> 24
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 24
Gly Phe Thr Phe Ser Asp Ser Trp
1   5

<210> 25
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 25
Ile Ser Pro Tyr Gly Gly Ser Thr
1   5

<210> 26
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 26
Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr
1   5   10

<210> 27
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 27
Gly Phe Thr Phe Ser Ser Tyr Ile
1   5

<210> 28
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 28
Ile Tyr Pro Ser Gly Gly Ile Thr
1   5

<210> 29
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 29
Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr
1   5   10

<210> 30
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 30
Gly Phe Thr Phe Ser Arg Tyr Trp
1   5

<210> 31
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 31

```
Ile Lys Gln Asp Gly Ser Glu Lys
1               5


<210> 32
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 32
Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr
1               5                   10


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

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 33
Gln Asp Val Ser Thr Ala
1               5


<210> 34
<211> 2
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 34
Ser Ala
1


<210> 35
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide
```

```
<400> 35
Gln Gln Tyr Leu Tyr His Pro Ala Thr
1               5


<210> 36
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 36
Ser Ser Asp Val Gly Gly Tyr Asn Tyr
1               5


<210> 37
<211> 2
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 37
Asp Val
1


<210> 38
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 38
Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln Pro
1               5                   10


<210> 39
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
```

<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 39
Gln Arg Val Ser Ser Ser Tyr
1   5

<210> 40
<211> 2
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 40
Asp Ala
1

<210> 41
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 41
Gln Gln Tyr Gly Ser Leu Pro Trp Thr
1   5

<210> 42
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 42
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
            20   25   30

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
    210

<210> 43
<211> 221
<212> PRT
<213> Artificial Sequence

<220>

```
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 43
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


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


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


Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160


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


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


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

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


<210> 44
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 44
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30


Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


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


Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln
            100                 105                 110


Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125


Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140


Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145                 150                 155                 160
```

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


Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190


Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205


Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> 45
<211> 223
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 45
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


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


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


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


Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
            100                 105                 110
```

```
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125


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


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


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


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


Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220


<210> 46
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 46
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


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


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


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

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

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

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

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

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

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

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> 47
<211> 224
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 47
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

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

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

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60

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

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

Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
            100                 105                 110

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

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

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

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

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

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

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

```
<210> 48
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 48
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


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


Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


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


Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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


Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100                 105                 110


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


Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140


Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys His Ala
145                 150                 155                 160


Ser Gln Asn Ile Tyr Val Trp Leu Asn Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175
```

```
Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Asn Leu His Thr Gly
            180                 185                 190

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

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

Gln Gly Gln Thr Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly
                245                 250                 255

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
            260                 265                 270

Gly Phe Thr Phe Ser Asp Ser Trp Ile His Trp Val Arg Gln Ala Pro
        275                 280                 285

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

Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp
305                 310                 315                 320

Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Arg His Trp Pro Gly Gly Phe
            340                 345                 350

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        355                 360                 365

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    370                 375                 380

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
385                 390                 395                 400
```

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
405 410 415

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
420 425 430

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
435 440 445

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
450 455 460

Pro Lys Ser Cys
465

<210> 49
<211> 461
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 49
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

```
Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys His Ala
145                 150                 155                 160

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

Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Asn Leu His Thr Gly
            180                 185                 190

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

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

Gln Gly Gln Thr Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
                245                 250                 255

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
            260                 265                 270

Ser Gln Asp Val Ser Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly
        275                 280                 285

Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Gly
    290                 295                 300
```

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
305   310   315   320

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
                325   330   335

Gln Tyr Leu Tyr His Pro Ala Thr Phe Gly Gln Gly Thr Lys Val Glu
            340   345   350

Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
        355   360   365

Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn
    370   375   380

Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala
385   390   395   400

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

Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp
            420   425   430

Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu
        435   440   445

Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    450   455   460

<210> 50
<211> 470
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 50
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

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

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

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

Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys His Ala
145                 150                 155                 160

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

Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Asn Leu His Thr Gly
            180                 185                 190

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

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

Gln Gly Gln Thr Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
225                 230                 235                 240
```

```
Ile Lys Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly
                245                 250                 255

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
            260                 265                 270

Gly Phe Thr Phe Ser Ser Tyr Ile Met Met Trp Val Arg Gln Ala Pro
        275                 280                 285

Gly Lys Gly Leu Glu Trp Val Ser Ser Ile Tyr Pro Ser Gly Gly Ile
    290                 295                 300

Thr Phe Tyr Ala Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ile Lys Leu Gly Thr Val Thr
            340                 345                 350

Thr Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
        355                 360                 365

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
    370                 375                 380

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

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
                405                 410                 415

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
            420                 425                 430

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
        435                 440                 445
```

```
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
    450                 455                 460


Val Glu Pro Lys Ser Cys
465                 470


<210> 51
<211> 463
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 51
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


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


Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


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


Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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


Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100                 105                 110


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


Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140
```

```
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys His Ala
145                 150                 155                 160

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

Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Asn Leu His Thr Gly
            180                 185                 190

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

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

Gln Gly Gln Thr Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser
                245                 250                 255

Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr
            260                 265                 270

Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His
        275                 280                 285

Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg Pro
    290                 295                 300

Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala
305                 310                 315                 320

Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr
                325                 330                 335

Cys Ser Ser Tyr Thr Ser Ser Ser Thr Arg Val Phe Gly Thr Gly Thr
            340                 345                 350

Lys Val Thr Val Leu Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu
        355                 360                 365
```

Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val
    370   375   380

Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys
385   390   395   400

Ala Asp Gly Ser Pro Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser
                405   410   415

Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr
            420   425   430

Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His
        435   440   445

Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
    450   455   460

<210> 52
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 52
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

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

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45

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

Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65   70   75   80

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

Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys His Ala
145                 150                 155                 160

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

Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Asn Leu His Thr Gly
            180                 185                 190

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

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

Gln Gly Gln Thr Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly
                245                 250                 255

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
            260                 265                 270

Gly Phe Thr Phe Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro
        275                 280                 285
```

```
Gly Lys Gly Leu Glu Trp Val Ala Asn Ile Lys Gln Asp Gly Ser Glu
    290                 295                 300


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


Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
                325                 330                 335


Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Gly Gly Trp Phe Gly Glu
            340                 345                 350


Leu Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        355                 360                 365


Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
    370                 375                 380


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
385                 390                 395                 400


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
                405                 410                 415


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
            420                 425                 430


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
        435                 440                 445


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
    450                 455                 460


Arg Val Glu Pro Lys Ser Cys
465                 470


<210> 53
<211> 462
<212> PRT
<213> Artificial Sequence

<220>
```

<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 53
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

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

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45

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

Lys Asp Arg Ala Thr Leu Thr Val Asp Thr Ser Ile Ser Thr Ala Tyr
65   70   75   80

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

Thr Arg Ser His Tyr Gly Leu Asp Trp Asn Phe Asp Val Trp Gly Gln
            100   105   110

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

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130   135   140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys His Ala
145   150   155   160

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

Lys Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Asn Leu His Thr Gly
            180   185   190

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

```
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
    210                 215                 220

Gln Gly Gln Thr Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
                245                 250                 255

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
            260                 265                 270

Ser Gln Arg Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
        275                 280                 285

Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg Ala Thr
    290                 295                 300

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
305                 310                 315                 320

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
                325                 330                 335

Gln Gln Tyr Gly Ser Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val
            340                 345                 350

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
        355                 360                 365

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
    370                 375                 380

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
385                 390                 395                 400

Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
                405                 410                 415
```

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
            420   425   430

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
        435   440   445

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    450   455   460

<210> 54
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 54
Gly Ser Thr Phe Tyr Thr Ala Val
1   5

<210> 55
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 55
Ile Arg Trp Thr Ala Leu Thr Thr
1   5

<210> 56
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 56
Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
1   5   10   15

Tyr

<210> 57
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 57
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50   55   60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100   105   110

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

<210> 58
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

```
<220>
<223> See specification as filed for detailed description of
      substitutions and preferred embodiments

<400> 58
Gly Ser Gly Gly Ser
1               5


<210> 59
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<220>
<223> See specification as filed for detailed description of
      substitutions and preferred embodiments

<400> 59
Gly Gly Gly Ser
1


<210> 60
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<220>
<223> See specification as filed for detailed description of
      substitutions and preferred embodiments

<400> 60
Gly Gly Gly Gly Ser
1               5


<210> 61
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide
```

```
<220>
<223> See specification as filed for detailed description of
      substitutions and preferred embodiments

<400> 61
Gly Ser Ser Gly Gly Ser
1               5


<210> 62
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 62
Gly Gly Gly Gly Ser Gly Gly Gly Ser
1               5


<210> 63
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 63
Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly
1               5                   10                  15


Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly Ser
            20                  25


<210> 64
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 64
Gly Gly Gly Gly Ser Leu Ser Gly Arg Ser Asp Asn His Gly Ser Ser
1               5                   10                  15
```

```
Gly Thr



<210> 65
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 65
Gly Gly Gly Gly Ser Ser Gly Gly Ser Gly Gly Ser Gly Leu Ser Gly
1               5                   10                  15


Arg Ser Asp Asn His Gly Ser Ser Gly Thr
            20                  25


<210> 66
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 66
Ala Ser Gly Arg Ser Asp Asn His
1               5


<210> 67
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 67
Leu Ala Gly Arg Ser Asp Asn His
1               5


<210> 68
<211> 13
```

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 68
Ile Ser Ser Gly Leu Ala Ser Gly Arg Ser Asp Asn His
1   5   10

<210> 69
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 69
Ile Ser Ser Gly Leu Leu Ala Gly Arg Ser Asp Asn His
1   5   10

<210> 70
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 70
Leu Ser Gly Arg Ser Asp Asn His
1   5

<210> 71
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 71
Ile Ser Ser Gly Leu Leu Ser Gly Arg Ser Asp Asn Pro
1   5   10

<210> 72
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 72
Ile Ser Ser Gly Leu Leu Ser Gly Arg Ser Asp Asn His
1   5   10

<210> 73
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 73
Leu Ser Gly Arg Ser Asp Asn His Ser Pro Leu Gly Leu Ala Gly Ser
1   5   10   15

<210> 74
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 74
Ser Pro Leu Gly Leu Ala Gly Ser Leu Ser Gly Arg Ser Asp Asn His
1   5   10   15

<210> 75
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 75
Ser Pro Leu Gly Leu Ser Gly Arg Ser Asp Asn His
1   5   10

<210> 76
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 76
Leu Ala Gly Arg Ser Asp Asn His Ser Pro Leu Gly Leu Ala Gly Ser
1 5 10 15

<210> 77
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 77
Leu Ser Gly Arg Ser Asp Asn His Val Pro Leu Ser Leu Lys Met Gly
1 5 10 15

<210> 78
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 78
Leu Ser Gly Arg Ser Asp Asn His Val Pro Leu Ser Leu Ser Met Gly
1 5 10 15

<210> 79
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 79

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

Gly Leu Leu Ser Gly Arg Ser Asp Asn His Gly Ser Ser Gly Thr
            20   25   30

<210> 80
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 80
Gly Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ile Ser Ser Gly Leu
1   5   10   15

Leu Ser Gly Arg Ser Asp Asn His Gly Gly Gly Ser
            20   25

<210> 81
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 81
Ala Ser Gly Arg Ser Asp Asn His
1   5

<210> 82
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 82
Leu Ala Gly Arg Ser Asp Asn His
1   5

```
<210> 83
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 83
Ile Ser Ser Gly Leu Ala Ser Gly Arg Ser Asp Asn His
1               5                   10


<210> 84
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 84
Leu Ser Gly Arg Ser Asp Ala Gly
1               5


<210> 85
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 85
Ile Ser Ser Gly Leu Leu Ser Gly Arg Ser Asp Ala Gly
1               5                   10


<210> 86
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 86
Ala Ala Gly Leu Leu Ala Pro Pro Gly Gly Leu Ser Gly Arg Ser Asp
1               5                   10                  15
```

Ala Gly

<210> 87
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 87
Ser Pro Leu Gly Leu Ser Gly Arg Ser Asp Ala Gly
1   5   10

<210> 88
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 88
Leu Ser Gly Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly
1   5   10   15

<210> 89
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 89
Gly Phe Thr Phe Asn Lys Tyr Ala
1   5

<210> 90
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 90
Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr
1   5   10

<210> 91
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 91
Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr
1   5   10   15

<210> 92
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 92
Thr Gly Ala Val Thr Ser Gly Asn Tyr
1   5

<210> 93
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 93
Gly Thr Lys
1

<210> 94
<211> 9
<212> PRT
<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 94
Val Leu Trp Tyr Ser Asn Arg Trp Val
1               5


<210> 95
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 95
Gly Phe Thr Phe Asn Thr Tyr Ala
1               5


<210> 96
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 96
Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr
1               5                   10                  15


<210> 97
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 97
Thr Gly Ala Val Thr Thr Ser Asn Tyr
1               5


<210> 98
<211> 2
```

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 98
Gly Thr
1

<210> 99
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 99
Ala Leu Trp Tyr Ser Asn Leu Trp Val
1   5

<210> 100
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 100
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20   25   30

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

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50   55   60

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

```
Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

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

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

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 101
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

```
<400> 101
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15


Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30


Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45


Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80


Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


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


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


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


Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
145                 150                 155                 160


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


Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
            180                 185                 190


Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
        195                 200                 205
```

```
Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
    210                 215                 220


His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
225                 230                 235                 240


Gln Gly Thr Leu Val Thr Val Ser Ser
                245


<210> 102
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 102
Gln Ser Ile Gly Thr Asn
1               5


<210> 103
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 103
Tyr Ala Ser
1


<210> 104
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 104
Gln Gln Asn Asn Asn Trp Pro Thr Thr
1               5
```

<210> 105
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 105
Gly Phe Ser Leu Thr Asn Tyr Gly
1   5

<210> 106
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 106
Ile Trp Ser Gly Gly Asn Thr
1   5

<210> 107
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 107
Ala Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr
1   5   10

<210> 108
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 108
Gln Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
1   5   10   15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
            20   25   30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35   40   45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50   55   60

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

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
                85   90   95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
            100   105   110

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
    210

<210> 109
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 109
Asp Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
1   5   10   15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
            20   25   30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35   40   45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50   55   60

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

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
                85   90   95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
            100   105   110

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 110
<211> 222
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 110
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1 5 10 15

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

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

Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
50 55 60

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

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

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210   215   220

<210> 111
<211> 222
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 111
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1   5   10   15

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

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

Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
    50   55   60

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65   70   75   80

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

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> 112
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 112
Gly Tyr Thr Phe Thr Asn Tyr Gly
1 5

<210> 113
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 113
Ile Asn Thr Tyr Thr Gly Glu Pro
1   5

<210> 114
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 114
Ala Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val
1   5   10

<210> 115
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 115
Gln Asp Val Ser Ile Ala
1   5

<210> 116
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 116
Ser Ala Ser
1

<210> 117
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 117
Gln Gln His Tyr Ile Thr Pro Leu Thr
1   5

<210> 118
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 118
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala
            20   25   30

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu
                85   90   95

Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110

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

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


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


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


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


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


Phe Asn Arg Gly Glu Cys
    210


<210> 119
<211> 224
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 119
Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


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


Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35                  40                  45


Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe
    50                  55                  60


Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80
```

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

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

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

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

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

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

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

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

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210   215   220

<210> 120
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 120
Gly Phe Ala Phe Ser Arg Tyr Gly
1   5

<210> 121
<211> 8
<212> PRT
<213> Artificial Sequence

```
<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 121
Ile Trp Tyr Asp Gly Ser Asn Lys
1               5


<210> 122
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 122
Ala Arg Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
1               5                   10                  15


<210> 123
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 123
Gln Gly Ile Ser Asn Tyr
1               5


<210> 124
<211> 2
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 124
Glu Ala
1


<210> 125
<211> 9
```

```
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 125
Gln Asn Tyr Asn Ser Ala Pro Phe Thr
1               5


<210> 126
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 126
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 Gly Ile Ser Asn Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile
        35                  40                  45


Tyr Glu Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


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


Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


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

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


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


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


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


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


Phe Asn Arg Gly Glu Cys
    210


<210> 127
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 127
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


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


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln 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 Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125


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


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


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


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


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


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


Ser Cys
225


<210> 128
<211> 478
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 128
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15
```

```
Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

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

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

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

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
145                 150                 155                 160

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

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
            180                 185                 190

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
        195                 200                 205

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
    210                 215                 220

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
225                 230                 235                 240
```

```
Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gln Val
                245                 250                 255

Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val
            260                 265                 270

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met
        275                 280                 285

Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp
    290                 295                 300

Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly
305                 310                 315                 320

Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln
                325                 330                 335

Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala Arg
            340                 345                 350

Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly
        355                 360                 365

Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
    370                 375                 380

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
385                 390                 395                 400

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

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            420                 425                 430

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        435                 440                 445
```

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
450 455 460

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
465 470 475

<210> 129
<211> 224
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 129
Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

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

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

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

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

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

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

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

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

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

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

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210   215   220

<210> 130
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 130
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1   5   10   15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20   25   30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35   40   45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
    50   55   60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65   70   75   80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85   90   95

```
Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

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

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

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
145                 150                 155                 160

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

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
            180                 185                 190

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
        195                 200                 205

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
    210                 215                 220

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Ile
                245                 250                 255

Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
            260                 265                 270

Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala
        275                 280                 285

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

Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
305                 310                 315                 320
```

```
Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
                325                 330                 335


Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe
            340                 345                 350


Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser
        355                 360                 365


Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
    370                 375                 380


Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
385                 390                 395                 400


Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
                405                 410                 415


Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
            420                 425                 430


Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
        435                 440                 445


Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
    450                 455                 460


Arg Gly Glu Cys
465


<210> 131
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 131
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15
```

```
Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala
            20                  25                  30

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
    210
```

<210> 132
<211> 478
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 132
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20   25   30

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

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50   55   60

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

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85   90   95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100   105   110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130   135   140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145   150   155   160

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

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

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln Val
                    245                 250                 255

Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val
            260                 265                 270

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met
        275                 280                 285

Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp
    290                 295                 300

Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly
305                 310                 315                 320

Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln
                    325                 330                 335

Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala Arg
            340                 345                 350

Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly
        355                 360                 365

Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
    370                 375                 380

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
385                 390                 395                 400
```

```
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
                405                 410                 415


Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            420                 425                 430


Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        435                 440                 445


Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
    450                 455                 460


Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
465                 470                 475


<210> 133
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 133
Gly Gly Val Asp Phe Cys Lys Ile Tyr Ser Trp Pro Val Cys His Gln
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Gln Leu Thr Gln
        35                  40                  45


Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr
    50                  55                  60


Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln
65                  70                  75                  80


Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg
                85                  90                  95
```

Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100   105   110

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr
        115   120   125

Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr
    130   135   140

Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145   150   155   160

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165   170   175

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180   185   190

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195   200   205

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210   215   220

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225   230   235   240

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

<210> 134
<211> 655
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 134
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110

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

Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140

Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220
```

```
Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
        435                 440                 445
```

```
Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
    450                 455                 460

Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
465                 470                 475                 480

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys
                485                 490                 495

Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu
            500                 505                 510

Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
        515                 520                 525

Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
    530                 535                 540

Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
545                 550                 555                 560

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                565                 570                 575

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
            580                 585                 590

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
        595                 600                 605

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
    610                 615                 620

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
625                 630                 635                 640

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
                645                 650                 655
```

```
<210> 135
<211> 224
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 135
Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


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


Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35                  40                  45


Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe
    50                  55                  60


Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80


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


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


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


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


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


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

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


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


Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220


<210> 136
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 136
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15


Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30


Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45


Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80


Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


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


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

```
Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu
    130                 135                 140

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
145                 150                 155                 160

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

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
            180                 185                 190

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
        195                 200                 205

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
    210                 215                 220

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Ile
                245                 250                 255

Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
            260                 265                 270

Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala
        275                 280                 285

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

Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
305                 310                 315                 320

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
                325                 330                 335

Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe
            340                 345                 350
```

Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser
355 360 365

Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
370 375 380

Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
385 390 395 400

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
405 410 415

Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
420 425 430

Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
435 440 445

Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
450 455 460

Arg Gly Glu Cys
465

<210> 137
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 137
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala
20 25 30

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

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


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu
                85                  90                  95


Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


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


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


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


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


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


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


Phe Asn Arg Gly Glu Cys
    210


<210> 138
<211> 478
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
```

```
<400> 138
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20                  25                  30


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


Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60


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


Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100                 105                 110


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


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140


Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160


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


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


Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205
```

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210   215   220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225   230   235   240

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln Val
                245   250   255

Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val
            260   265   270

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met
        275   280   285

Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp
    290   295   300

Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly
305   310   315   320

Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln
                325   330   335

Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala Arg
            340   345   350

Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly
        355   360   365

Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
    370   375   380

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
385   390   395   400

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

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            420   425   430

```
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        435                 440                 445


Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
    450                 455                 460


Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
465                 470                 475


<210> 139
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 139
Gln Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
1               5                   10                  15


Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
            20                  25                  30


Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35                  40                  45


Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


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


Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
                85                  90                  95


Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
            100                 105                 110


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

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


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


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


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


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


Phe Asn Arg Gly Glu Cys
    210


<210> 140
<211> 222
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 140
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1               5                   10                  15


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


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


Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
    50                  55                  60


Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65                  70                  75                  80
```

```
Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95


Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110


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


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


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


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


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


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


Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220


<210> 141
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 141
Asp Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
1               5                   10                  15


Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
            20                  25                  30
```

```
Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35                  40                  45


Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


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


Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
                85                  90                  95


Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
            100                 105                 110


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


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


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


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


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


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


Phe Asn Arg Gly Glu Cys
    210


<210> 142
<211> 222
<212> PRT
<213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 142
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1               5                   10                  15


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


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


Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
    50                  55                  60


Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65                  70                  75                  80


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


Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110


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


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


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


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


Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190
```

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

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210   215   220

<210> 143
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 143
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala
            20   25   30

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu
                85   90   95

Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110

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

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

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


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


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


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


Phe Asn Arg Gly Glu Cys
    210


<210> 144
<211> 478
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 144
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20                  25                  30


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


Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60


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


Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95
```

```
Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

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

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

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln Val
                245                 250                 255

Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val
            260                 265                 270

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met
        275                 280                 285

Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp
    290                 295                 300

Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly
305                 310                 315                 320
```

Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln
                325   330   335

Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala Arg
            340   345   350

Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly
        355   360   365

Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
    370   375   380

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
385   390   395   400

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

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            420   425   430

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        435   440   445

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
    450   455   460

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
465   470   475

<210> 145
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 145
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

```
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20                  25                  30

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

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

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

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

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

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

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220
```

```
Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp Ile
                245                 250                 255

Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
            260                 265                 270

Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala
        275                 280                 285

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

Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
305                 310                 315                 320

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
                325                 330                 335

Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe
            340                 345                 350

Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser
        355                 360                 365

Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
    370                 375                 380

Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
385                 390                 395                 400

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
                405                 410                 415

Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
            420                 425                 430

Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
        435                 440                 445
```

```
Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
    450                 455                 460


Arg Gly Glu Cys
465


<210> 146
<211> 224
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 146
Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


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


Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35                  40                  45


Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe
    50                  55                  60


Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80


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


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


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


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

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

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

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

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

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210   215   220

<210> 147
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 147
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala
            20   25   30

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu
                85   90   95

Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
    210

<210> 148
<211> 478
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 148
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1   5   10   15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20   25   30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35   40   45

```
Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

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

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

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

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
145                 150                 155                 160

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

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
            180                 185                 190

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
        195                 200                 205

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
    210                 215                 220

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gln Val
                245                 250                 255
```

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

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met
        275                 280                 285

Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp
    290                 295                 300

Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly
305                 310                 315                 320

Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln
                325                 330                 335

Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala Arg
            340                 345                 350

Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly
        355                 360                 365

Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
    370                 375                 380

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
385                 390                 395                 400

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

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            420                 425                 430

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        435                 440                 445

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
    450                 455                 460

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
465                 470                 475
```

```
<210> 149
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 149
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15


Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30


Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45


Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80


Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


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


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


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


Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
145                 150                 155                 160


Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
                165                 170                 175
```

```
Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
            180                 185                 190

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
        195                 200                 205

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
    210                 215                 220

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Ile
                245                 250                 255

Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
            260                 265                 270

Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala
        275                 280                 285

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

Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
305                 310                 315                 320

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
                325                 330                 335

Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe
            340                 345                 350

Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser
        355                 360                 365

Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
    370                 375                 380
```

Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
385   390   395   400

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
                405   410   415

Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
            420   425   430

Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
        435   440   445

Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
    450   455   460

Arg Gly Glu Cys
465

<210> 150
<211> 224
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 150
Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1   5   10   15

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

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35   40   45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe
    50   55   60

Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65   70   75   80

```
Leu Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


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


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


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


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


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


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


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


Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220


<210> 151
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 151
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 Gly Ile Thr Asn Tyr
            20                  25                  30
```

```
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Ile
                85                  90                  95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
    210

<210> 152
<211> 481
<212> PRT
<213> Artificial Sequence

<220>
```

```
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 152
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15


Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30


Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45


Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80


Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


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


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


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


Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
145                 150                 155                 160


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


Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
            180                 185                 190


Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
        195                 200                 205
```

```
Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
    210                 215                 220

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gln Val
                245                 250                 255

Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu
            260                 265                 270

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Val Met
        275                 280                 285

His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Ile
    290                 295                 300

Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys Gly
305                 310                 315                 320

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
                325                 330                 335

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Gly
            340                 345                 350

Gly Tyr Asn Trp Asn Tyr Glu Tyr His Tyr Tyr Gly Met Asp Val Trp
        355                 360                 365

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
    370                 375                 380

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

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                405                 410                 415
```

```
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            420                 425                 430


Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        435                 440                 445


Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
    450                 455                 460


His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
465                 470                 475                 480


Cys



<210> 153
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 153
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 Gly Ile Ser Asn Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile
        35                  40                  45


Tyr Glu Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Val Ala Thr Tyr Tyr Cys Gln Asn Tyr Asn Ser Ala Pro Phe
                85                  90                  95
```

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
    210


<210> 154
<211> 480
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 154
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45
```

```
Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

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

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

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

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
145                 150                 155                 160

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

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
            180                 185                 190

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
        195                 200                 205

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
    210                 215                 220

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gln Val
                245                 250                 255

Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu
            260                 265                 270
```

Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Arg Tyr Gly Met
275 280 285

His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Val
290 295 300

Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys Gly
305 310 315 320

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln Tyr Leu Gln
325 330 335

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
340 345 350

Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly
355 360 365

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
370 375 380

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

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
405 410 415

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
420 425 430

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
435 440 445

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
450 455 460

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
465 470 475 480

```
<210> 155
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 155
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15


Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30


Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45


Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80


Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


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


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


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


Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
145                 150                 155                 160


Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
                165                 170                 175
```

```
Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
            180                 185                 190

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
        195                 200                 205

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
    210                 215                 220

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Asp Ile
                245                 250                 255

Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
            260                 265                 270

Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
        275                 280                 285

Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile Tyr Glu
    290                 295                 300

Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Gly Gly
305                 310                 315                 320

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
                325                 330                 335

Val Ala Thr Tyr Tyr Cys Gln Asn Tyr Asn Ser Ala Pro Phe Thr Phe
            340                 345                 350

Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala Pro Ser
        355                 360                 365

Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
    370                 375                 380

Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
385                 390                 395                 400
```

```
Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
                405                 410                 415


Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
            420                 425                 430


Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
        435                 440                 445


Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
    450                 455                 460


Arg Gly Glu Cys
465


<210> 156
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 156
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


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


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln 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 Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100   105   110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115   120   125

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

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

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

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

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

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

Ser Cys
225

<210> 157
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 157
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 Gly Ile Ser Asn Tyr
            20   25   30

```
Leu Ala Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile
        35                  40                  45

Tyr Glu Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

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

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
    210

<210> 158
<211> 480
<212> PRT
<213> Artificial Sequence
```

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 158
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
20 25 30

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

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

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

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
100 105 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
130 135 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145 150 155 160

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

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

```
Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln Val
                245                 250                 255

Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu
            260                 265                 270

Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Arg Tyr Gly Met
        275                 280                 285

His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Val
    290                 295                 300

Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys Gly
305                 310                 315                 320

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln Tyr Leu Gln
                325                 330                 335

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
            340                 345                 350

Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly
        355                 360                 365

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
    370                 375                 380

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

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                405                 410                 415
```

```
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            420                 425                 430


Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        435                 440                 445


Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    450                 455                 460


Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
465                 470                 475                 480


<210> 159
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 159
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20                  25                  30


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


Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60


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


Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100                 105                 110
```

```
Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

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

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

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp Ile
                245                 250                 255

Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
            260                 265                 270

Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
        275                 280                 285

Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile Tyr Glu
    290                 295                 300

Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Gly Gly
305                 310                 315                 320
```

```
Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
                325                 330                 335

Val Ala Thr Tyr Tyr Cys Gln Asn Tyr Asn Ser Ala Pro Phe Thr Phe
            340                 345                 350

Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala Pro Ser
        355                 360                 365

Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
    370                 375                 380

Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
385                 390                 395                 400

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
                405                 410                 415

Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
            420                 425                 430

Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
        435                 440                 445

Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
    450                 455                 460

Arg Gly Glu Cys
465


<210> 160
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 160
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
```

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

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln 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 Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

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

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

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

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

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

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

Ser Cys
225
```

```
<210> 161
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 161
Gly Ser Gln Cys Leu Gly Pro Glu Trp Glu Val Cys Pro Tyr
1               5                   10


<210> 162
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 162
Val Tyr Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met
1               5                   10


<210> 163
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 163
Pro Cys Arg Ser His Ile Asp Val Ala Lys Pro Ile Cys Val
1               5                   10


<210> 164
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 164
```

```
Gly Gly Pro Cys Arg Ser His Ile Asp Val Ala Lys Pro Ile Cys Val
1               5                   10                  15

Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
                20                  25                  30

Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Leu Leu Thr Gln
        35                  40                  45

Ser Pro Val Ile Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe Ser
    50                  55                  60

Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile His Trp Tyr Gln Gln
65                  70                  75                  80

Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser
                85                  90                  95

Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110

Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr
        115                 120                 125

Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr Thr Phe Gly Ala Gly Thr
    130                 135                 140

Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220
```

```
Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240


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


<210> 165
<211> 653
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 165
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110


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


Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140
```

```
Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350
```

```
Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

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

Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr Gly
    450                 455                 460

Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu Gly
465                 470                 475                 480

Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr Ser
                485                 490                 495

Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe Lys
            500                 505                 510

Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala Arg
        515                 520                 525

Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr
    530                 535                 540

Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
545                 550                 555                 560

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
                565                 570                 575
```

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
            580   585   590

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
        595   600   605

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
    610   615   620

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
625   630   635   640

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
                645   650

<210> 166
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 166
Gly Gly Pro Cys Arg Ser His Ile Asp Val Ala Lys Pro Ile Cys Val
1   5   10   15

Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20   25   30

Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Leu Leu Thr Gln
        35   40   45

Ser Pro Val Ile Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe Ser
    50   55   60

Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile His Trp Tyr Gln Gln
65   70   75   80

Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser
                85   90   95

```
Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110

Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr
        115                 120                 125

Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr Thr Phe Gly Ala Gly Thr
    130                 135                 140

Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240

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


<210> 167
<211> 644
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 167
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe
            20                  25                  30

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

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125

Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser Pro Leu Gly
145                 150                 155                 160

Leu Ala Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220
```

```
Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Gln Val Gln Leu Lys Gln Ser Gly Pro Gly
            420                 425                 430

Leu Val Gln Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
        435                 440                 445
```

```
Phe Ser Leu Thr Asn Tyr Gly Val His Trp Val Arg Gln Ser Pro Gly
    450                 455                 460

Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ser Gly Gly Asn Thr Asp
465                 470                 475                 480

Tyr Asn Thr Pro Phe Thr Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser
                485                 490                 495

Lys Ser Gln Val Phe Phe Lys Met Asn Ser Leu Gln Ser Asn Asp Thr
            500                 505                 510

Ala Ile Tyr Tyr Cys Ala Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe
        515                 520                 525

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr
    530                 535                 540

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
545                 550                 555                 560

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                565                 570                 575

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            580                 585                 590

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        595                 600                 605

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    610                 615                 620

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
625                 630                 635                 640

Pro Lys Ser Cys
```

```
<210> 168
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 168
Gly Gly Pro Cys Arg Ser His Ile Asp Val Ala Lys Pro Ile Cys Val
1               5                   10                  15


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


Gly Gly Ala Ser Ser Gly Ala Gly Gly Ser Asp Ile Leu Leu Thr Gln
        35                  40                  45


Ser Pro Val Ile Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe Ser
    50                  55                  60


Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile His Trp Tyr Gln Gln
65                  70                  75                  80


Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser
                85                  90                  95


Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110


Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr
        115                 120                 125


Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr Thr Phe Gly Ala Gly Thr
    130                 135                 140


Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160


Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175
```

```
Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190


Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205


Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220


Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240


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


<210> 169
<211> 644
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 169
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15


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


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


Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60


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


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

```
Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125

Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Ala Ser Ser Gly
145                 150                 155                 160

Ala Gly Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320
```

```
Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Gln Val Gln Leu Lys Gln Ser Gly Pro Gly
            420                 425                 430

Leu Val Gln Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
        435                 440                 445

Phe Ser Leu Thr Asn Tyr Gly Val His Trp Val Arg Gln Ser Pro Gly
    450                 455                 460

Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ser Gly Gly Asn Thr Asp
465                 470                 475                 480

Tyr Asn Thr Pro Phe Thr Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser
                485                 490                 495

Lys Ser Gln Val Phe Phe Lys Met Asn Ser Leu Gln Ser Gln Asp Thr
            500                 505                 510

Ala Ile Tyr Tyr Cys Ala Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe
        515                 520                 525
```

```
Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr
    530                 535                 540


Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
545                 550                 555                 560


Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                565                 570                 575


Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            580                 585                 590


Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        595                 600                 605


Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    610                 615                 620


Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
625                 630                 635                 640


Pro Lys Ser Cys



<210> 170
<211> 261
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 170
Gly Gly Pro Cys Arg Ser His Ile Asp Val Ala Lys Pro Ile Cys Val
1               5                   10                  15


Gly Gly Gly Gly Ser Ser Gly Gly Ser Ala Ala Gly Leu Leu Ala Pro
            20                  25                  30


Pro Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Gly Gly Gly Ser Asp
        35                  40                  45
```

```
Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly Glu
    50                  55                  60

Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile
65                  70                  75                  80

His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Lys
                85                  90                  95

Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser
            100                 105                 110

Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu
        115                 120                 125

Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr Thr
    130                 135                 140

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

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
                165                 170                 175

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

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
        195                 200                 205

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
    210                 215                 220

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
225                 230                 235                 240

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
                245                 250                 255

Asn Arg Gly Glu Cys
            260
```

```
<210> 171
<211> 644
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 171
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15


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


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


Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125


Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Ser Ser Gly
    130                 135                 140


Gly Ser Ala Ala Gly Leu Leu Ala Pro Pro Gly Gly Leu Ser Gly Arg
145                 150                 155                 160


Ser Asp Ala Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175
```

```
Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380
```

```
Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Gln Val Gln Leu Lys Gln Ser Gly Pro Gly
            420                 425                 430

Leu Val Gln Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
        435                 440                 445

Phe Ser Leu Thr Asn Tyr Gly Val His Trp Val Arg Gln Ser Pro Gly
    450                 455                 460

Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ser Gly Gly Asn Thr Asp
465                 470                 475                 480

Tyr Asn Thr Pro Phe Thr Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser
                485                 490                 495

Lys Ser Gln Val Phe Phe Lys Met Asn Ser Leu Gln Ser Gln Asp Thr
            500                 505                 510

Ala Ile Tyr Tyr Cys Ala Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe
        515                 520                 525

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr
    530                 535                 540

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
545                 550                 555                 560

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                565                 570                 575

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            580                 585                 590

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        595                 600                 605
```

```
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    610                 615                 620

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
625                 630                 635                 640

Pro Lys Ser Cys



<210> 172
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 172
Gly Gly Pro Cys Arg Ser His Ile Asp Val Ala Lys Pro Ile Cys Val
1               5                   10                  15

Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30

Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Leu Leu Thr Gln
        35                  40                  45

Ser Pro Val Ile Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe Ser
    50                  55                  60

Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile His Trp Tyr Gln Gln
65                  70                  75                  80

Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser
                85                  90                  95

Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110

Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr
        115                 120                 125
```

```
Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr Thr Phe Gly Ala Gly Thr
    130                 135                 140


Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160


Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175


Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190


Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205


Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220


Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240


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


<210> 173
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 173
Gly Gly Pro Cys Arg Ser His Ile Asp Val Ala Lys Pro Ile Cys Val
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Leu Leu Thr Gln
        35                  40                  45
```

```
Ser Pro Val Ile Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe Ser
    50                  55                  60

Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile His Trp Tyr Gln Gln
65                  70                  75                  80

Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser
                85                  90                  95

Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110

Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr
        115                 120                 125

Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr Thr Phe Gly Ala Gly Thr
    130                 135                 140

Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
                245                 250                 255
```

```
<210> 174
<211> 644
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 174
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15


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


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


Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125


Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140


Ser Gly Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser Pro Leu Gly
145                 150                 155                 160


Leu Ala Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175
```

```
Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400
```

```
Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Gln Val Gln Leu Lys Gln Ser Gly Pro Gly
            420                 425                 430

Leu Val Gln Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
        435                 440                 445

Phe Ser Leu Thr Asn Tyr Gly Val His Trp Val Arg Gln Ser Pro Gly
    450                 455                 460

Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ser Gly Gly Asn Thr Asp
465                 470                 475                 480

Tyr Asn Thr Pro Phe Thr Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser
                485                 490                 495

Lys Ser Gln Val Phe Phe Lys Met Asn Ser Leu Gln Ser Gln Asp Thr
            500                 505                 510

Ala Ile Tyr Tyr Cys Ala Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe
        515                 520                 525

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr
    530                 535                 540

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
545                 550                 555                 560

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                565                 570                 575

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            580                 585                 590

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        595                 600                 605
```

```
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    610                 615                 620


Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
625                 630                 635                 640


Pro Lys Ser Cys




<210> 175
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 175
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20                  25                  30


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


Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60


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


Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
```

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

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

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

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln Ile
                245                 250                 255

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

Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile His
        275                 280                 285

Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Lys Tyr
    290                 295                 300

Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly
305                 310                 315                 320

Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu Asp
                325                 330                 335

Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr Thr Phe
            340                 345                 350
```

```
Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro Ser
        355                 360                 365


Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
    370                 375                 380


Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
385                 390                 395                 400


Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
                405                 410                 415


Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
            420                 425                 430


Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
        435                 440                 445


Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
    450                 455                 460


Arg Gly Glu Cys
465


<210> 176
<211> 222
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 176
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1               5                   10                  15


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


Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45
```

```
Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
    50                  55                  60

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65                  70                  75                  80

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

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110

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

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

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

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

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

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

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

<210> 177
<211> 645
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 177
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50   55   60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100   105   110

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

Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130   135   140

Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145   150   155   160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165   170   175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180   185   190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195   200   205

```
Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430
```

```
Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly Glu
        435                 440                 445

Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile
    450                 455                 460

His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Lys
465                 470                 475                 480

Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser
                485                 490                 495

Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu
            500                 505                 510

Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr Thr
        515                 520                 525

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
    530                 535                 540

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
545                 550                 555                 560

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
                565                 570                 575

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
            580                 585                 590

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
        595                 600                 605

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
    610                 615                 620

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
625                 630                 635                 640
```

```
Asn Arg Gly Glu Cys
                645


<210> 178
<211> 264
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 178
Gly Gly Pro Cys Arg Ser His Ile Asp Val Ala Lys Pro Ile Cys Val
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Gln Val Gln Leu Lys Gln
        35                  40                  45


Ser Gly Pro Gly Leu Val Gln Pro Ser Gln Ser Leu Ser Ile Thr Cys
    50                  55                  60


Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr Gly Val His Trp Val Arg
65                  70                  75                  80


Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ser Gly
                85                  90                  95


Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr Ser Arg Leu Ser Ile Asn
            100                 105                 110


Lys Asp Asn Ser Lys Ser Gln Val Phe Phe Lys Met Asn Ser Leu Gln
        115                 120                 125


Ser Gln Asp Thr Ala Ile Tyr Tyr Cys Ala Arg Ala Leu Thr Tyr Tyr
    130                 135                 140


Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
145                 150                 155                 160
```

```
Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
                165                 170                 175


Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
            180                 185                 190


Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
        195                 200                 205


Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
    210                 215                 220


Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
225                 230                 235                 240


Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
                245                 250                 255


Lys Lys Val Glu Pro Lys Ser Cys
            260


<210> 179
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 179
Ser Val Leu Phe Cys Val Lys Asn Leu Tyr Cys Trp Val Thr
1               5                   10


<210> 180
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 180
Val Asp Phe Cys Lys Ile Tyr Ser Trp Pro Val Cys His Gln
1               5                   10
```

<210> 181
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 181
Ile Asp Phe Cys Met Leu Tyr Asn Trp Pro Ile Cys Ala Gly
1 5 10

<210> 182
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 182
Gly Gly Val Asp Phe Cys Lys Ile Tyr Ser Trp Pro Val Cys His Gln
1 5 10 15

Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
20 25 30

Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Gln Leu Thr Gln
35 40 45

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr
50 55 60

Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln
65 70 75 80

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg
85 90 95

Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
100 105 110

```
Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr
        115                 120                 125


Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr
    130                 135                 140


Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160


Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175


Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190


Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205


Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220


Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240


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


<210> 183
<211> 655
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 183
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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

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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110


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


Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140


Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160


Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175


Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190


Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205


Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220


Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240


Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255
```

```
Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
        435                 440                 445

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
    450                 455                 460
```

```
Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
465                 470                 475                 480


Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys
                485                 490                 495


Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu
            500                 505                 510


Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
        515                 520                 525


Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
    530                 535                 540


Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
545                 550                 555                 560


Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                565                 570                 575


Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
            580                 585                 590


Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
        595                 600                 605


Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
    610                 615                 620


Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
625                 630                 635                 640


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
                645                 650                 655


<210> 184
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
```

```
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 184
Gly Gly Ser Val Leu Phe Cys Val Lys Asn Leu Tyr Cys Trp Val Thr
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Gln Leu Thr Gln
        35                  40                  45


Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr
    50                  55                  60


Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln
65                  70                  75                  80


Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg
                85                  90                  95


Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110


Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr
        115                 120                 125


Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr
    130                 135                 140


Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160


Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175


Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190


Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205
```

```
Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220


Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240


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


<210> 185
<211> 655
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 185
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110


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

```
Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140

Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335
```

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
340 345 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
355 360 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
370 375 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
405 410 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
420 425 430

Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
435 440 445

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
450 455 460

Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
465 470 475 480

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys
485 490 495

Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu
500 505 510

Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
515 520 525

Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
530 535 540

Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
545 550 555 560

```
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                565                 570                 575


Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
            580                 585                 590


Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
        595                 600                 605


Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
    610                 615                 620


Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
625                 630                 635                 640


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
                645                 650                 655


<210> 186
<211> 645
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 186
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110

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

Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140

Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285
```

```
Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp
            420                 425                 430

Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
        435                 440                 445

Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val
    450                 455                 460

Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
465                 470                 475                 480

Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser
                485                 490                 495

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
            500                 505                 510
```

```
Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr
        515                 520                 525


Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
    530                 535                 540


Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
545                 550                 555                 560


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
                565                 570                 575


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
            580                 585                 590


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
        595                 600                 605


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
    610                 615                 620


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
625                 630                 635                 640


Asn Arg Gly Glu Cys
                645


<210> 187
<211> 266
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 187
Gly Gly Val Asp Phe Cys Lys Ile Tyr Ser Trp Pro Val Cys His Gln
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30
```

Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Gln
        35   40   45

Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
    50   55   60

Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys
65   70   75   80

Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr
                85   90   95

Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe
            100   105   110

Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu
        115   120   125

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

Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr
145   150   155   160

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
                165   170   175

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
            180   185   190

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

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
    210   215   220

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
225   230   235   240

```
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
                245                 250                 255


Val Asp Lys Lys Val Glu Pro Lys Ser Cys
            260                 265


<210> 188
<211> 645
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 188
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110


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


Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140
```

```
Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365
```

```
Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp
            420                 425                 430

Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
        435                 440                 445

Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val
    450                 455                 460

Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
465                 470                 475                 480

Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser
                485                 490                 495

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
            500                 505                 510

Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr
        515                 520                 525

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
    530                 535                 540

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
545                 550                 555                 560

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
                565                 570                 575
```

```
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
            580                 585                 590


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
        595                 600                 605


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
    610                 615                 620


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
625                 630                 635                 640


Asn Arg Gly Glu Cys
                645


<210> 189
<211> 266
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 189
Gly Gly Ser Val Leu Phe Cys Val Lys Asn Leu Tyr Cys Trp Val Thr
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Gln
        35                  40                  45


Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
    50                  55                  60


Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys
65                  70                  75                  80


Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr
                85                  90                  95
```

```
Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe
            100                 105                 110

Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu
        115                 120                 125

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

Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr
145                 150                 155                 160

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
                165                 170                 175

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
            180                 185                 190

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

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
    210                 215                 220

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
225                 230                 235                 240

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
                245                 250                 255

Val Asp Lys Lys Val Glu Pro Lys Ser Cys
            260                 265
```

<210> 190
<211> 655
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 190

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

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110

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

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Cys Leu Gly Pro Glu Trp
    130                 135                 140

Glu Val Cys Pro Tyr Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220
```

```
Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430
```

```
Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
        435                 440                 445

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
    450                 455                 460

Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
465                 470                 475                 480

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys
                485                 490                 495

Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu
            500                 505                 510

Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
        515                 520                 525

Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
    530                 535                 540

Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
545                 550                 555                 560

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                565                 570                 575

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
            580                 585                 590

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
        595                 600                 605

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
    610                 615                 620

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
625                 630                 635                 640

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
                645                 650                 655
```

<210> 191
<211> 645
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 191
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
100 105 110

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

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Cys Leu Gly Pro Glu Trp
130 135 140

Glu Val Cys Pro Tyr Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145 150 155 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
165 170 175

```
Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380
```

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405   410   415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp
            420   425   430

Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
        435   440   445

Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val
    450   455   460

Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
465   470   475   480

Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser
                485   490   495

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
            500   505   510

Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr
        515   520   525

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
    530   535   540

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
545   550   555   560

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
                565   570   575

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
            580   585   590

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
        595   600   605

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
    610   615   620

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
625   630   635   640

Asn Arg Gly Glu Cys
                645

<210> 192
<211> 266
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 192
Gly Gly Val Asp Phe Cys Lys Ile Tyr Ser Trp Pro Val Cys His Gln
1   5   10   15

Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20   25   30

Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Gln
        35   40   45

Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
    50   55   60

Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys
65   70   75   80

Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr
                85   90   95

Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe
            100   105   110

Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu
        115   120   125

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

Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr
145                 150                 155                 160

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
                165                 170                 175

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
            180                 185                 190

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

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
    210                 215                 220

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
225                 230                 235                 240

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
                245                 250                 255

Val Asp Lys Lys Val Glu Pro Lys Ser Cys
            260                 265


<210> 193
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 193
Gly Gly Ser Val Leu Phe Cys Val Lys Asn Leu Tyr Cys Trp Val Thr
1               5                   10                  15

Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30
```

```
Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Gln Leu Thr Gln
        35                  40                  45

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr
    50                  55                  60

Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln
65                  70                  75                  80

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg
                85                  90                  95

Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr
        115                 120                 125

Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr
    130                 135                 140

Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240
```

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

<210> 194
<211> 655
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 194
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50   55   60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100   105   110

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

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Cys Leu Gly Pro Glu Trp
    130   135   140

Glu Val Cys Pro Tyr Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145   150   155   160

```
Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380
```

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
        435                 440                 445

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
    450                 455                 460

Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
465                 470                 475                 480

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys
                485                 490                 495

Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu
            500                 505                 510

Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
        515                 520                 525

Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
    530                 535                 540

Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
545                 550                 555                 560

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                565                 570                 575

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
            580                 585                 590
```

```
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
        595                 600                 605


Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
    610                 615                 620


Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
625                 630                 635                 640


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
                645                 650                 655


<210> 195
<211> 645
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 195
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110
```

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

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Cys Leu Gly Pro Glu Trp
130 135 140

Glu Val Cys Pro Tyr Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145 150 155 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
165 170 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
180 185 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
195 200 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
210 215 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225 230 235 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
245 250 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
260 265 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
275 280 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
290 295 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305 310 315 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
325 330 335

```
Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp
            420                 425                 430

Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
        435                 440                 445

Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val
    450                 455                 460

Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
465                 470                 475                 480

Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser
                485                 490                 495

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
            500                 505                 510

Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr
        515                 520                 525

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
    530                 535                 540
```

```
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
545                 550                 555                 560


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
                565                 570                 575


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
            580                 585                 590


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
        595                 600                 605


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
    610                 615                 620


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
625                 630                 635                 640


Asn Arg Gly Glu Cys
                645


<210> 196
<211> 266
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 196
Gly Gly Ser Val Leu Phe Cys Val Lys Asn Leu Tyr Cys Trp Val Thr
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Gln
        35                  40                  45


Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
    50                  55                  60
```

Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys
65   70   75   80

Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr
                85   90   95

Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe
            100   105   110

Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu
        115   120   125

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

Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr
145   150   155   160

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
                165   170   175

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
            180   185   190

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

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
    210   215   220

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
225   230   235   240

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
                245   250   255

Val Asp Lys Lys Val Glu Pro Lys Ser Cys
            260   265

<210> 197
<211> 256

```
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 197
Gly Gly Val Asp Phe Cys Lys Ile Tyr Ser Trp Pro Val Cys His Gln
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Gln Leu Thr Gln
        35                  40                  45


Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr
    50                  55                  60


Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln
65                  70                  75                  80


Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg
                85                  90                  95


Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110


Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr
        115                 120                 125


Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr
    130                 135                 140


Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160


Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175


Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190
```

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
    195   200   205

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
  210   215   220

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225   230   235   240

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

<210> 198
<211> 646
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 198
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1   5   10   15

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

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

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50   55   60

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

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

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100   105   110

```
Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125

Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser Pro Leu Gly
145                 150                 155                 160

Leu Ala Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320
```

```
Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ser Glu
            420                 425                 430

Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        435                 440                 445

Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly
    450                 455                 460

Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro
465                 470                 475                 480

Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr
                485                 490                 495

Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Asp Asp
            500                 505                 510

Thr Ala Val Tyr Phe Cys Ala Arg Gly Gly Phe Gly Ser Ser Tyr Trp
        515                 520                 525

Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser Ala
    530                 535                 540
```

```
Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
545                 550                 555                 560


Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                565                 570                 575


Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            580                 585                 590


Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        595                 600                 605


Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
    610                 615                 620


Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
625                 630                 635                 640


Val Glu Pro Lys Ser Cys
                645


<210> 199
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 199
Gly Gly Ser Val Leu Phe Cys Val Lys Asn Leu Tyr Cys Trp Val Thr
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Gln Leu Thr Gln
        35                  40                  45


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

```
Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln
65                  70                  75                  80


Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg
                85                  90                  95


Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110


Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr
        115                 120                 125


Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr
    130                 135                 140


Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160


Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175


Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190


Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205


Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220


Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240


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


<210> 200
<211> 646
<212> PRT
<213> Artificial Sequence
```

```
<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 200
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15


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


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


Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125


Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140


Ser Gly Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser Pro Leu Gly
145                 150                 155                 160


Leu Ala Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175


Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190
```

```
Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415
```

```
Leu Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ser Glu
            420                 425                 430

Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        435                 440                 445

Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly
    450                 455                 460

Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro
465                 470                 475                 480

Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr
                485                 490                 495

Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Asp Asp
            500                 505                 510

Thr Ala Val Tyr Phe Cys Ala Arg Gly Gly Phe Gly Ser Ser Tyr Trp
        515                 520                 525

Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser Ala
    530                 535                 540

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
545                 550                 555                 560

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                565                 570                 575

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            580                 585                 590

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        595                 600                 605

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
    610                 615                 620
```

```
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
625                 630                 635                 640


Val Glu Pro Lys Ser Cys
                645


<210> 201
<211> 636
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 201
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15


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


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


Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125


Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140
```

```
Ser Gly Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser Pro Leu Gly
145                 150                 155                 160

Leu Ala Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365
```

```
Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser
            420                 425                 430

Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser
        435                 440                 445

Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    450                 455                 460

Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val
465                 470                 475                 480

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                485                 490                 495

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
            500                 505                 510

His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Val Glu Ile
        515                 520                 525

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    530                 535                 540

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
545                 550                 555                 560

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                565                 570                 575
```

```
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            580                 585                 590


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        595                 600                 605


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    610                 615                 620


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
625                 630                 635


<210> 202
<211> 266
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 202
Gly Gly Val Asp Phe Cys Lys Ile Tyr Ser Trp Pro Val Cys His Gln
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Gln
        35                  40                  45


Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
    50                  55                  60


Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys
65                  70                  75                  80


Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr
                85                  90                  95


Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe
            100                 105                 110
```

```
Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu
        115                 120                 125


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


Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr
145                 150                 155                 160


Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
                165                 170                 175


Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
            180                 185                 190


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


Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
    210                 215                 220


Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
225                 230                 235                 240


Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
                245                 250                 255


Val Asp Lys Lys Val Glu Pro Lys Ser Cys
            260                 265


<210> 203
<211> 636
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 203
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe
            20                  25                  30

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

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125

Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser Pro Leu Gly
145                 150                 155                 160

Leu Ala Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240
```

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245   250   255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260   265   270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275   280   285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290   295   300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305   310   315   320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325   330   335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340   345   350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355   360   365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370   375   380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385   390   395   400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405   410   415

Leu Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser
            420   425   430

Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser
        435   440   445

Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
450 455 460

Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val
465 470 475 480

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
485 490 495

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
500 505 510

His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Val Glu Ile
515 520 525

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
530 535 540

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
545 550 555 560

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
565 570 575

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
580 585 590

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
595 600 605

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
610 615 620

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
625 630 635

<210> 204
<211> 266
<212> PRT
<213> Artificial Sequence

<220>

```
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 204
Gly Gly Ser Val Leu Phe Cys Val Lys Asn Leu Tyr Cys Trp Val Thr
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Gln Val Gln Leu Gln Gln
        35                  40                  45


Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
    50                  55                  60


Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys
65                  70                  75                  80


Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr
                85                  90                  95


Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe
            100                 105                 110


Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu
        115                 120                 125


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


Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr
145                 150                 155                 160


Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
                165                 170                 175


Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
            180                 185                 190


Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
        195                 200                 205
```

```
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
    210                 215                 220


Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
225                 230                 235                 240


Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
                245                 250                 255


Val Asp Lys Lys Val Glu Pro Lys Ser Cys
            260                 265


<210> 205
<211> 261
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 205
Gly Gly Ile Asp Phe Cys Met Leu Tyr Asn Trp Pro Ile Cys Ala Gly
1               5                   10                  15


Gly Gly Gly Gly Ser Ser Gly Gly Ser Ala Ala Gly Leu Leu Ala Pro
            20                  25                  30


Pro Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Gly Gly Gly Ser Asp
        35                  40                  45


Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    50                  55                  60


Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val
65                  70                  75                  80


Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
                85                  90                  95


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

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

Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr
    130   135   140

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
145   150   155   160

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
                165   170   175

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

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
        195   200   205

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
    210   215   220

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
225   230   235   240

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
                245   250   255

Asn Arg Gly Glu Cys
            260

<210> 206
<211> 646
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 206
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1   5   10   15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe
            20                  25                  30

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

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125

Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Ser Ser Gly
    130                 135                 140

Gly Ser Ala Ala Gly Leu Leu Ala Pro Pro Gly Gly Leu Ser Gly Arg
145                 150                 155                 160

Ser Asp Ala Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220
```

```
Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ser Glu
            420                 425                 430

Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        435                 440                 445
```

Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly
450 455 460

Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro
465 470 475 480

Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr
485 490 495

Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Asp Asp
500 505 510

Thr Ala Val Tyr Phe Cys Ala Arg Gly Gly Phe Gly Ser Ser Tyr Trp
515 520 525

Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser Ala
530 535 540

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
545 550 555 560

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
565 570 575

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
580 585 590

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
595 600 605

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
610 615 620

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
625 630 635 640

Val Glu Pro Lys Ser Cys
645

<210> 207
<211> 261
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 207
Gly Gly Ile Asp Phe Cys Met Leu Tyr Asn Trp Pro Ile Cys Ala Gly
1   5   10   15

Gly Gly Gly Gly Ser Ser Gly Gly Ser Ala Ala Gly Leu Leu Ala Pro
            20   25   30

Pro Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Gly Gly Gly Ser Asp
        35   40   45

Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    50   55   60

Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val
65   70   75   80

Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
                85   90   95

Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser
            100   105   110

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

Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr
    130   135   140

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
145   150   155   160

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
                165   170   175

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

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
        195   200   205

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
    210   215   220

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
225   230   235   240

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
                245   250   255

Asn Arg Gly Glu Cys
            260

<210> 208
<211> 655
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 208
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50   55   60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110

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

Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140

Ser Val Gly Cys Met Gly Ser Ser Gly Gly Ser Ala Ala Gly Leu Leu
145                 150                 155                 160

Ala Pro Pro Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300
```

```
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
        435                 440                 445

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
    450                 455                 460

Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
465                 470                 475                 480

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys
                485                 490                 495

Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu
            500                 505                 510
```

Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
515 520 525

Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
530 535 540

Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
545 550 555 560

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
565 570 575

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
580 585 590

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
595 600 605

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
610 615 620

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
625 630 635 640

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
645 650 655

<210> 209
<211> 645
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 209
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110

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

Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140

Ser Val Gly Cys Met Gly Ser Ser Gly Gly Ser Ala Ala Gly Leu Leu
145                 150                 155                 160

Ala Pro Pro Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255
```

```
Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp
            420                 425                 430

Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
        435                 440                 445

Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val
    450                 455                 460
```

```
Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
465                 470                 475                 480


Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser
                485                 490                 495


Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
            500                 505                 510


Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr
        515                 520                 525


Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
    530                 535                 540


Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
545                 550                 555                 560


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
                565                 570                 575


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
            580                 585                 590


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
        595                 600                 605


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
    610                 615                 620


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
625                 630                 635                 640


Asn Arg Gly Glu Cys
                645


<210> 210
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
```

```
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 210
Gly Gly Ile Asp Phe Cys Met Leu Tyr Asn Trp Pro Ile Cys Ala Gly
1               5                   10                  15


Gly Gly Gly Gly Ser Ser Gly Gly Ser Ala Ala Gly Leu Leu Ala Pro
            20                  25                  30


Pro Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Gly Gly Gly Ser Gln
        35                  40                  45


Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
    50                  55                  60


Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
65                  70                  75                  80


Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
                85                  90                  95


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


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


Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
    130                 135                 140


Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
145                 150                 155                 160


Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
                165                 170                 175


Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
            180                 185                 190


Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
        195                 200                 205
```

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
210 215 220

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
225 230 235 240

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
245 250 255

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
260 265 270

<210> 211
<211> 636
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 211
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1 5 10 15

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

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

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

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

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

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
100 105 110

```
Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125

Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Ser Ser Gly
    130                 135                 140

Gly Ser Ala Ala Gly Leu Leu Ala Pro Pro Gly Gly Leu Ser Gly Arg
145                 150                 155                 160

Ser Asp Ala Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320
```

```
Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser
            420                 425                 430

Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser
        435                 440                 445

Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    450                 455                 460

Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val
465                 470                 475                 480

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                485                 490                 495

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
            500                 505                 510

His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Val Glu Ile
        515                 520                 525

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    530                 535                 540
```

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
545 550 555 560

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
565 570 575

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
580 585 590

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
595 600 605

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
610 615 620

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
625 630 635

<210> 212
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 212
Gly Gly Ile Asp Phe Cys Met Leu Tyr Asn Trp Pro Ile Cys Ala Gly
1 5 10 15

Gly Gly Gly Gly Ser Ser Gly Gly Ser Ala Ala Gly Leu Leu Ala Pro
20 25 30

Pro Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Gly Gly Gly Ser Gln
35 40 45

Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
50 55 60

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
65 70 75 80

```
Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
                85                  90                  95

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

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

Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
    130                 135                 140

Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
145                 150                 155                 160

Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
                165                 170                 175

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
            180                 185                 190

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
        195                 200                 205

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
    210                 215                 220

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
225                 230                 235                 240

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
                245                 250                 255

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
            260                 265                 270
```

<210> 213
<211> 655
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 213
```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110


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


Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140


Ser Val Gly Cys Met Gly Ser Ser Gly Gly Ser Ala Ala Gly Leu Leu
145                 150                 155                 160


Ala Pro Pro Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Gly Gly Gly
                165                 170                 175


Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190
```

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
195 200 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
210 215 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225 230 235 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
245 250 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
260 265 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
275 280 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
290 295 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305 310 315 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
325 330 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
340 345 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
355 360 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
370 375 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
405 410 415

```
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
        435                 440                 445

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
    450                 455                 460

Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
465                 470                 475                 480

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys
                485                 490                 495

Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu
            500                 505                 510

Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
        515                 520                 525

Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
    530                 535                 540

Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
545                 550                 555                 560

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                565                 570                 575

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
            580                 585                 590

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
        595                 600                 605

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
    610                 615                 620
```

```
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
625                 630                 635                 640


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
                645                 650                 655


<210> 214
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 214
Gly Gly Ile Asp Phe Cys Met Leu Tyr Asn Trp Pro Ile Cys Ala Gly
1               5                   10                  15


Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30


Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Gln Leu Thr Gln
        35                  40                  45


Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr
    50                  55                  60


Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln
65                  70                  75                  80


Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg
                85                  90                  95


Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110


Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr
        115                 120                 125


Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr
    130                 135                 140
```

Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145 150 155 160

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
165 170 175

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
180 185 190

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
195 200 205

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
210 215 220

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225 230 235 240

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

<210> 215
<211> 655
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 215
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110

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

Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140

Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285
```

```
Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser
        435                 440                 445

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Gly
    450                 455                 460

Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met Gly
465                 470                 475                 480

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Thr Asp Asp Phe Lys
                485                 490                 495
```

Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu
            500   505   510

Gln Ile Ser Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Phe Cys Ala
        515   520   525

Arg Gly Gly Phe Gly Ser Ser Tyr Trp Tyr Phe Asp Val Trp Gly Gln
    530   535   540

Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
545   550   555   560

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
                565   570   575

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
            580   585   590

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
        595   600   605

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
    610   615   620

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
625   630   635   640

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
                645   650   655

<210> 216
<211> 256
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 216
Gly Gly Ile Asp Phe Cys Met Leu Tyr Asn Trp Pro Ile Cys Ala Gly
1   5   10   15

```
Gly Gly Gly Gly Ser Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser
            20                  25                  30

Pro Leu Gly Leu Ala Gly Ser Gly Gly Ser Asp Ile Gln Leu Thr Gln
        35                  40                  45

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr
    50                  55                  60

Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala Trp Tyr Gln Gln
65                  70                  75                  80

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Tyr Arg
                85                  90                  95

Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            100                 105                 110

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr
        115                 120                 125

Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe Gly Ala Gly Thr
    130                 135                 140

Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
145                 150                 155                 160

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
                165                 170                 175

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            180                 185                 190

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
        195                 200                 205

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
    210                 215                 220

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
225                 230                 235                 240
```

```
Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
                245                 250                 255


<210> 217
<211> 646
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 217
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15


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


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


Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125


Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140


Ser Gly Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser Pro Leu Gly
145                 150                 155                 160
```

```
Leu Ala Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365
```

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370   375   380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385   390   395   400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405   410   415

Leu Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ser Glu
            420   425   430

Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        435   440   445

Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly
    450   455   460

Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro
465   470   475   480

Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr
                485   490   495

Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Asp Asp
            500   505   510

Thr Ala Val Tyr Phe Cys Ala Arg Gly Gly Phe Gly Ser Ser Tyr Trp
        515   520   525

Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser Ala
    530   535   540

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
545   550   555   560

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                565   570   575

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            580   585   590

```
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        595                 600                 605


Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
    610                 615                 620


Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
625                 630                 635                 640


Val Glu Pro Lys Ser Cys
                645


<210> 218
<211> 259
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 218
Gly Gly Ile Asp Phe Cys Met Leu Tyr Asn Trp Pro Ile Cys Ala Gly
1               5                   10                  15


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


Gly Gly Ala Ser Ser Gly Ala Gly Gly Ser Gly Gly Ser Asp Ile Gln
        35                  40                  45


Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
    50                  55                  60


Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val Ala Trp
65                  70                  75                  80


Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala
                85                  90                  95


Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
            100                 105                 110
```

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

Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr Phe Gly
    130   135   140

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

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
                165   170   175

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
            180   185   190

Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
        195   200   205

Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
    210   215   220

Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
225   230   235   240

Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg
                245   250   255

Gly Glu Cys

<210> 219
<211> 646
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 219
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1   5   10   15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Phe
            20                  25                  30

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

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125

Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Ala Ser Ser Gly
145                 150                 155                 160

Ala Gly Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220
```

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225   230   235   240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245   250   255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260   265   270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275   280   285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290   295   300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305   310   315   320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325   330   335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340   345   350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355   360   365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370   375   380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385   390   395   400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405   410   415

Leu Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ser Glu
            420   425   430

Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        435   440   445

```
Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly
    450                 455                 460

Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro
465                 470                 475                 480

Thr Tyr Thr Asp Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr
                485                 490                 495

Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Asp Asp
            500                 505                 510

Thr Ala Val Tyr Phe Cys Ala Arg Gly Gly Phe Gly Ser Ser Tyr Trp
        515                 520                 525

Tyr Phe Asp Val Trp Gly Gln Gly Ser Leu Val Thr Val Ser Ser Ala
    530                 535                 540

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
545                 550                 555                 560

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                565                 570                 575

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            580                 585                 590

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        595                 600                 605

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
    610                 615                 620

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
625                 630                 635                 640

Val Glu Pro Lys Ser Cys
                645
```

```
<210> 220
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 220
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 Gly Ile Ser Asn Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile
        35                  40                  45


Tyr Glu Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


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


Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


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


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


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


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

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


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


Phe Asn Arg Gly Glu Cys
    210


<210> 221
<211> 657
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 221
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110


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

```
Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Cys Leu Gly Pro Glu Trp
    130                 135                 140


Glu Val Cys Pro Tyr Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160


Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175


Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190


Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205


Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220


Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240


Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255


Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270


Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285


Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320


Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335


Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350
```

```
Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser
        435                 440                 445

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Arg Tyr Gly
    450                 455                 460

Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
465                 470                 475                 480

Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
                485                 490                 495

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln Tyr Leu
            500                 505                 510

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
        515                 520                 525

Arg Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp
    530                 535                 540

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
545                 550                 555                 560
```

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
565 570 575

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
580 585 590

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
595 600 605

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
610 615 620

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
625 630 635 640

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
645 650 655

Cys

<210> 222
<211> 645
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 222
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110

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

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Cys Leu Gly Pro Glu Trp
    130                 135                 140

Glu Val Cys Pro Tyr Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285
```

```
Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp
            420                 425                 430

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
        435                 440                 445

Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu
    450                 455                 460

Ala Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile Tyr
465                 470                 475                 480

Glu Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Gly
                485                 490                 495
```

```
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
            500                 505                 510


Asp Val Ala Thr Tyr Tyr Cys Gln Asn Tyr Asn Ser Ala Pro Phe Thr
        515                 520                 525


Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala Pro
    530                 535                 540


Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
545                 550                 555                 560


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
                565                 570                 575


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
            580                 585                 590


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
        595                 600                 605


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
    610                 615                 620


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
625                 630                 635                 640


Asn Arg Gly Glu Cys
                645


<210> 223
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 223
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
```

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

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln 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 Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

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

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

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

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

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

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

Ser Cys
225
```

```
<210> 224
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 224
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 Gly Ile Ser Asn Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile
        35                  40                  45


Tyr Glu Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


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


Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


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


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


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


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

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

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

Phe Asn Arg Gly Glu Cys
    210

<210> 225
<211> 657
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 225
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

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

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

Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50   55   60

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100   105   110

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

```
Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140

Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335
```

```
Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser
        435                 440                 445

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Arg Tyr Gly
    450                 455                 460

Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
465                 470                 475                 480

Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
                485                 490                 495

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln Tyr Leu
            500                 505                 510

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
        515                 520                 525

Arg Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp
    530                 535                 540

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
545                 550                 555                 560
```

```
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
                565                 570                 575


Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
            580                 585                 590


Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
        595                 600                 605


Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
    610                 615                 620


Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
625                 630                 635                 640


His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
                645                 650                 655


Cys




<210> 226
<211> 645
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 226
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60
```

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110

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

Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140

Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270
```

```
Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp
            420                 425                 430

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
        435                 440                 445

Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu
    450                 455                 460

Ala Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile Tyr
465                 470                 475                 480

Glu Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Gly
                485                 490                 495
```

```
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
            500                 505                 510


Asp Val Ala Thr Tyr Tyr Cys Gln Asn Tyr Asn Ser Ala Pro Phe Thr
        515                 520                 525


Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala Pro
    530                 535                 540


Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
545                 550                 555                 560


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
                565                 570                 575


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
            580                 585                 590


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
        595                 600                 605


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
    610                 615                 620


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
625                 630                 635                 640


Asn Arg Gly Glu Cys
                645


<210> 227
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 227
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
```

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

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln 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 Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

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

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

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

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

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

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

```
Ser Cys
225


<210> 228
<211> 636
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 228
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15


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


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


Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125


Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140


Ser Gly Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Ser Pro Leu Gly
145                 150                 155                 160
```

```
Leu Ala Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380
```

```
Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            420                 425                 430

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        435                 440                 445

Gln Gly Ile Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Thr Gly Lys
    450                 455                 460

Val Pro Lys Phe Leu Ile Tyr Glu Ala Ser Thr Leu Gln Ser Gly Val
465                 470                 475                 480

Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr
                485                 490                 495

Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Asn
            500                 505                 510

Tyr Asn Ser Ala Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        515                 520                 525

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    530                 535                 540

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
545                 550                 555                 560

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                565                 570                 575

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            580                 585                 590
```

```
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        595                 600                 605


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    610                 615                 620


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
625                 630                 635


<210> 229
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 229
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


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


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln 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 Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125
```

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

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

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

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

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

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

Ser Cys
225

<210> 230
<211> 636
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 230
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1   5   10   15

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

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

Ser Ser Ile Ser Gly Ser Gly Arg Asp Thr Leu Tyr Ala Asp Ser Val
    50   55   60

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

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

Thr Ile Gly Gly Ser Leu Ser Val Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Val Tyr
        115                 120                 125

Cys Gly Pro Glu Phe Asp Glu Ser Val Gly Cys Met Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Ala Ser Ser Gly
145                 150                 155                 160

Ala Gly Gly Ser Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
                165                 170                 175

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala
            180                 185                 190

Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala
        195                 200                 205

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
    210                 215                 220

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
225                 230                 235                 240

Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu
                245                 250                 255

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
            260                 265                 270

Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu
        275                 280                 285
```

```
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    290                 295                 300

Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val
305                 310                 315                 320

Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala
                325                 330                 335

Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln
            340                 345                 350

Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr
        355                 360                 365

Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr
    370                 375                 380

Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu
385                 390                 395                 400

Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                405                 410                 415

Leu Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            420                 425                 430

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        435                 440                 445

Gln Gly Ile Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Thr Gly Lys
    450                 455                 460

Val Pro Lys Phe Leu Ile Tyr Glu Ala Ser Thr Leu Gln Ser Gly Val
465                 470                 475                 480

Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr
                485                 490                 495
```

```
Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Asn
            500                 505                 510


Tyr Asn Ser Ala Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        515                 520                 525


Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    530                 535                 540


Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
545                 550                 555                 560


Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                565                 570                 575


Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            580                 585                 590


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        595                 600                 605


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    610                 615                 620


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
625                 630                 635


<210> 231
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 231
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


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

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Gln 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 Gly Gly Asp Phe Leu Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

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

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

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

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

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

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

Ser Cys
225

<210> 232
<211> 468

```
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 232
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20                  25                  30


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


Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60


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


Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100                 105                 110


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


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140


Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160


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


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

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195   200   205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210   215   220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225   230   235   240

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Asp Ile
                245   250   255

Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
            260   265   270

Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
        275   280   285

Trp Tyr Gln Gln Lys Thr Gly Lys Val Pro Lys Phe Leu Ile Tyr Glu
    290   295   300

Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Gly Gly
305   310   315   320

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp
                325   330   335

Val Ala Thr Tyr Tyr Cys Gln Asn Tyr Asn Ser Ala Pro Phe Thr Phe
            340   345   350

Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala Pro Ser
        355   360   365

Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
    370   375   380

Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
385   390   395   400

```
Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser
                405                 410                 415


Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr
            420                 425                 430


Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys
        435                 440                 445


Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn
    450                 455                 460


Arg Gly Glu Cys
465


<210> 233
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide


<220>
<221> SITE
<222> (1)..(9)
<223> This sequence may encompass 1-3 "Gly Gly Ser"
      repeating units

<400> 233
Gly Gly Ser Gly Gly Ser Gly Gly Ser
1               5


<210> 234
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 234
Gly Ser Gly Gly Ser
1               5
```

<210> 235
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 235
Gly Gly Gly Ser
1

<210> 236
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 236
Gly Gly Gly Gly Ser
1   5

<210> 237
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 237
Gly Ser Ser Gly Gly Ser
1   5

<210> 238
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<220>

```
<221> SITE
<222> (1)..(6)
<223> This sequence may encompass 1-3 "Gly Ser"
      repeating units

<400> 238
Gly Ser Gly Ser Gly Ser
1               5


<210> 239
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide


<220>
<221> SITE
<222> (1)..(15)
<223> This sequence may encompass 1-3 "Gly Ser Gly Gly Ser"
      repeating units

<400> 239
Gly Ser Gly Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly Gly Ser
1               5                   10                  15


<210> 240
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide


<220>
<221> SITE
<222> (1)..(12)
<223> This sequence may encompass 1-3 "Gly Gly Gly Ser"
      repeating units

<400> 240
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1               5                   10


<210> 241
<211> 15
```

```
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide


<220>
<221> SITE
<222> (1)..(15)
<223> This sequence may encompass 1-3 "Gly Gly Gly Gly Ser"
      repeating units

<400> 241
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1               5                   10                  15


<210> 242
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide


<220>
<221> SITE
<222> (1)..(18)
<223> This sequence may encompass 1-3 "Gly Ser Ser Gly Gly Ser"
      repeating units

<400> 242
Gly Ser Ser Gly Gly Ser Gly Ser Ser Gly Gly Ser Gly Ser Ser Gly
1               5                   10                  15


Gly Ser



<210> 243
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
```

```
<220>
<221> SITE
<222> (1)..(30)
<223> This sequence may encompass 1-10 "Gly Gly Ser"
      repeating units

<400> 243
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1               5                   10                  15


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


<210> 244
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide


<220>
<221> SITE
<222> (1)..(20)
<223> This sequence may encompass 1-10 "Gly Ser"
      repeating units

<400> 244
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1               5                   10                  15


Gly Ser Gly Ser
            20


<210> 245
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> SITE
<222> (1)..(50)
<223> This sequence may encompass 1-10 "Gly Ser Gly Gly Ser"
```

```
      repeating units

<400> 245
Gly Ser Gly Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly Gly Ser Gly
1               5                   10                  15


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


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


Gly Ser
    50


<210> 246
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> SITE
<222> (1)..(40)
<223> This sequence may encompass 1-10 "Gly Gly Gly Ser"
      repeating units

<400> 246
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1               5                   10                  15


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


Gly Gly Gly Ser Gly Gly Gly Ser
        35                  40


<210> 247
<211> 50
<212> PRT
<213> Artificial Sequence

<220>
```

```
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> SITE
<222> (1)..(50)
<223> This sequence may encompass 1-10 "Gly Gly Gly Gly Ser"
      repeating units

<400> 247
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15


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


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


Gly Ser
    50


<210> 248
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide


<220>
<221> SITE
<222> (1)..(60)
<223> This sequence may encompass 1-10 "Gly Ser Ser Gly Gly Ser"
      repeating units

<400> 248
Gly Ser Ser Gly Gly Ser Gly Ser Ser Gly Gly Ser Gly Ser Ser Gly
1               5                   10                  15


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


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

```
Gly Ser Ser Gly Gly Ser Gly Ser Ser Gly Gly Ser
    50                  55                  60


<210> 249
<211> 261
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 249
Gly Gly Val Asp Phe Cys Lys Ile Tyr Ser Trp Pro Val Cys His Gln
1               5                   10                  15


Gly Gly Gly Gly Ser Ser Gly Gly Ser Ala Ala Gly Leu Leu Ala Pro
            20                  25                  30


Pro Gly Gly Leu Ser Gly Arg Ser Asp Ala Gly Gly Gly Gly Ser Asp
        35                  40                  45


Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    50                  55                  60


Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Ala Val
65                  70                  75                  80


Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
                85                  90                  95


Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly Ser
            100                 105                 110


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


Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Leu Thr
    130                 135                 140


Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
145                 150                 155                 160
```

```
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
                165                 170                 175


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


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
        195                 200                 205


Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
    210                 215                 220


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
225                 230                 235                 240


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
                245                 250                 255


Asn Arg Gly Glu Cys
            260


<210> 250
<211> 653
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 250
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


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


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


Ala Ala Ile Arg Trp Thr Ala Leu Thr Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60
```

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

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

Ala Ala Arg Gly Thr Leu Gly Leu Phe Thr Thr Ala Asp Ser Tyr Asp
            100                 105                 110

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

Ser Gly Gly Gly Ser Gly Gly Val Tyr Cys Gly Pro Glu Phe Asp Glu
    130                 135                 140

Ser Val Gly Cys Met Gly Gly Gly Gly Ser Gly Gly Gly Leu Ser Gly
145                 150                 155                 160

Arg Ser Asp Ala Gly Ser Pro Leu Gly Leu Ala Gly Ser Gly Gly Gly
                165                 170                 175

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
            180                 185                 190

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys
        195                 200                 205

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
    210                 215                 220

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
225                 230                 235                 240

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
                245                 250                 255

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val
            260                 265                 270
```

```
Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr
        275                 280                 285

Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    290                 295                 300

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val
305                 310                 315                 320

Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr
                325                 330                 335

Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro
            340                 345                 350

Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly
        355                 360                 365

Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser
    370                 375                 380

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

Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val
                405                 410                 415

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gln
            420                 425                 430

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

Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr Gly
    450                 455                 460

Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu Gly
465                 470                 475                 480

Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr Ser
                485                 490                 495
```

```
Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe Lys
            500                 505                 510

Met Asn Ser Leu Gln Ser Gln Asp Thr Ala Ile Tyr Tyr Cys Ala Arg
        515                 520                 525

Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly Thr
    530                 535                 540

Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
545                 550                 555                 560

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
                565                 570                 575

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
            580                 585                 590

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
        595                 600                 605

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
    610                 615                 620

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
625                 630                 635                 640

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
                645                 650
```