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DESCRIPTION

FIELD OF THE INVENTION

[0001] The invention provides fusion proteins comprising antibodies that specifically bind to PD-L1, an IL 15 receptor binding domain and an IL15 receptor alpha sushi domain, nucleic acid molecules encoding the same, and medical uses thereof. The agents enhance T cell and NK cell function to increase cell and cytokine mediated immunity for the treatment of various immune dysfunction related disorders including cancers and infectious diseases.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to U.S. Provisional Application No. 61/927,907, filed January 15, 2014.

BACKGROUND OF THE INVENTION

[0003] Programmed death 1 (PD-1) is a member of the CD28 family of receptors comprising CD28, CTLA-4, PD-1, ICOS, and BTLA (Freeman et al. (2000) J Exp Med 192:1027-34; Latchman et al. (2001) Nat Immunol 2:261-8). PD-1 is an inducible immunosuppressive receptor mainly upregulated on activated T cells and B cells during the progression of immunopathological conditions. PD-1 interaction with its ligand PD-L1 results in the inhibition of TCR and BCR mediated proliferation and cytokine production and induction of apoptosis of antigen specific T cells through the intrinsic PD-1 mediated negative signaling of an immunoreceptor tyrosine-based inhibitory motif (ITIM) (Agata et al. (1996) Int. Immunol. 8:765, Unkeless and Jin. (1997) Curr. Opin. Immunol. 9:338-343, Okzaki et al. (2001) PNAS 98:13866-71, Dong et al. (2002) Nat. Med. 8:793-800). PD-L1 is a cell surface glycoprotein and a major ligand for PD-1. PD-L1 is also inducible on lymphoid tissues and non-lymphoid peripheral tissues following cellular activation. PD-L1 is upregulated in a variety of affected cell types including cancer and stromal cells in addition to immune cells, and plays an active role in immunosuppression during the course of the deterioration of diseases (Iwai et al (2002) PNAS 99:12293-7, Ohigashi et al. (2005) Clin Cancer Res 11:2947-53). PD-L1 upregulation has been linked to poor clinical outcomes in a variety of cancers and viral infection (Hofmeyer et al. (2011) J. BioMed. Biotech. 2011:1-9, McDermott and Atkins. (2013) Cancer Med. 2:662-73). The blockade of PD-1 or PD-L1 by antibody promoted CD8 T cell infiltration, CTL activity and increased presence of Th1 cytokine IFN-gamma in preclinical and clinical settings (Zhou et al. (2010) J. Immunol. 185:5082-92, Nomi et al. (2007) Clin Cancer Res. 13:2152-7, Flies et al. (2011) Yale J. Bio. Med. 48:409-21, Zitvogel and Kroemer. (2012) OncoImmunol. 1:1223-25). PD-L1 antibody as an immunomodulating agent has been shown to be efficacious when used as monotherapy or combined with antibodies to other immunosuppressive molecules.

[0004] However, the immunomodulating intervention to immunosuppressive factors only partially resolves the problems associated with impaired immunity in cancer, infection, and other diseases. It is still highly desirable to utilize biotherapeutic agents to directly stimulate and expand effector immune cells for lifting weakened innate and adaptive immune response to a more effective level to control tumor and infection. Immunotherapy using cytokines including interleukins, i.e. IL-2, IL-12, IL15, IL-21, and TNF α , GM-CSF, etc., has been shown to be efficacious to some extent in the treatment of cancer and infection, but clinical outcome is often limited by systemic toxicity associated with the high blood concentrations of cytokine that need to obtain efficacy and lack of specificity of target in affected cells and tissues.

[0005] Among assessed cytokines, IL15 has been recognized to be dedicated to stimulate effector and central memory CD8 T cells composing of a subset of antigen specific CD8 cells to exert antitumor immunity without modulating effects on other T cell populations. Moreover, unlike IL-2 that activates Treg, IL15 has been shown to have capacity to rescue T cells from apoptosis induced by Treg and other immunosuppressive cells in addition to its ability to activate natural killer (NK) cells and effector and memory CD8 T cells (Van Belle et al. (2012) PLoS One 7:e45299, Obar and Lefrancois. (2010) J. Immunol. 185:263-72, Pelletier and Girard. (2006) J Immunol 177:100-108, Elpek et al. (2010) PNAS 107:21647-21652).

[0006] IL15 was identified as a γ c cytokine in 1994 based on its ability to stimulate the proliferation of the murine T cell line CTLL-2 (Grabstein et al. (1994) Science 264:965-8, Bamford et al. (1996) PNAS 93:2897-902). Human IL15 shares approximately 97% and 96% amino acid sequence identity with simian and cynomolgus IL15, respectively. Human and mouse IL15 have 73% homology and are comparably active on mouse cells. IL15 is a 12.5 KD protein (114 amino acids), secreted by DC, macrophage and granular cells as a 14-15 kDa glycoprotein, and also a member of the four α -helix bundle-containing cytokines (Anderson et al. (1995) J Biol Chem. 270:29862-9, Steel et al. (2012) Trends Pharmacol. Sci. 33:35-41). IL15 is typically formed a complex with IL15 receptor alpha expressed on APCs prior to binding to functional IL15 receptor beta and gamma units on T cells and NK cells. IL15 may be presented in trans to responsive cells expressing CD122 and CD132 by cells expressing the cytokine itself bound to a membrane form of the receptor alpha chain (Dubois et al. (2002) Immunity 17:537-47). IL15 receptor alpha sushi domain (29.5KD in size) is a critical component to form a complex with IL15 prior to properly engagement with receptor β and γ (Wei et al. (2001) J. Immunol.167:277-82). IL15 and IL15R α complex and IL15/IL15R α sushi domain fusion protein were reported to be highly potent to stimulate CD8 T cells and NK cells *in vitro* and *in vivo* compared to IL15 alone (Mortier et al. (2005) J Biol Chem. 281:1612-19, Stoklasek et al. (2006) J. Immunol. 177:6072-80). IL15 also induces the proliferation and differentiation of stimulated human B cells (Armitage et al. (1995) J Immunol. 154:483-90). It was suggested that IL15 mostly opposed activation-induced cell death (AICD) by acting to prolong the survival of T lymphocytes (Marks-Konczalik et al. (2000) PNAS 97:11445-50). IL15 has an exceptional ability to support the maintenance of NK cells and memory phenotype and antigen specific memory CD8 T cells (Ma et al. (2006) Annu Rev Immunol. 24:657-79). Thus, among most active cytokines in immunomodulation, IL15 has an unique capacity to mediate

many important aspects of immunity against a variety of tumor types and viral infection including HIV, HBV, HCV, LCMV, etc (Steel et al. (2012) Trends Pharmacol. Sci. 33:35-41, Verbist and Klonowski, (2012) Cytokine. 59:467-478).

SUMMARY OF THE INVENTION

[0007] The present invention provides fusion proteins comprising antibodies that bind to PD-L1. In the fusion proteins of the invention, the antibodies bind to PD-L1 and block interaction with PD-1. By blocking the interaction of PD-L1 with PD-1, such antibodies are useful to reduce or inhibit immunosuppression.

[0008] Also disclosed are antibodies and binding proteins that bind specifically to PD-L1 and at least one other molecule. Examples include PD-L1 binding proteins that also bind to one or more other ligands and/or receptors, which may be membrane bound or soluble.

[0009] Also disclosed are molecules, such as fusion proteins that bind PD-L1 that, apart from reducing or inhibiting immunosuppression by binding to PD-L1, also promote one or more immune responses by interaction with other ligands or

[0010] In one aspect, the present invention provides a fusion protein comprising:

1. (i) a first domain that comprises an antibody to PD-L1, wherein the antibody comprises
 1. (a) a heavy chain CDR-1H comprising SEQ ID NO:121; a heavy chain CDR-2H comprising SEQ ID NO:123; a heavy chain CDR-3H comprising SEQ ID NO:125; a light chain CDR-1L comprising SEQ ID NO:127; a light chain CDR-2L comprising SEQ ID NO:128; and a light chain CDR-3L comprising SEQ ID NO:129;
 2. (b) a heavy chain CDR-1H comprising SEQ ID NO: 241, a CDR-2H comprising SEQ ID NO: 243, and a CDR-3H comprising SEQ ID NO: 245; and a light chain CDR-1L comprising SEQ ID NO:247, a CDR-2L comprising SEQ ID NO:248, and a CDR-3L comprising SEQ ID NO:249; or
 3. (c) a heavy chain CDR-1H comprising SEQ ID NO: 266, a CDR-2H comprising SEQ ID NO: 243, and a CDR-3H comprising SEQ ID NO: 245; and a light chain CDR-1L comprising SEQ ID NO:247, a CDR-2L comprising SEQ ID NO:248, and a CDR-3L comprising SEQ ID NO:249;
 and wherein the antibody binds to PD-L1 and blocks its interaction with PD-1,
2. (ii) a second domain that binds to IL-15 receptor ("IL-15R"), wherein the second domain comprises IL-15 or an IL-15R-binding fragment thereof, and
3. (iii) an IL-15 receptor alpha sushi domain.

[0011] In some embodiments, the fusion protein further comprises a flexible linker joining the sushi domain of the IL-15R alpha to the IL-15 or IL-15R-binding fragment, optionally wherein

the flexible linker comprises 15-20 amino acids which are predominantly serine and glycine. In further embodiments, the fusion protein comprises SEQ ID NO:315, SEQ ID NO:317, SEQ ID NO:319, SEQ ID NO:321, SEQ ID NO:323, or SEQ ID NO: 261.

[0012] In one embodiment, the antibody to PD-L1 comprises a heavy chain CDR-1H comprising SEQ ID NO:121; a heavy chain CDR-2H comprising SEQ ID NO:123; a heavy chain CDR-3H comprising SEQ ID NO:125; a light chain CDR-1L comprising SEQ ID NO:127; a light chain CDR-2L comprising SEQ ID NO:128; and a light chain CDR-3L comprising SEQ ID NO:129. In another embodiment, the antibody to PD-L1 comprises a heavy chain variable domain that is at least 85% identical to SEQ ID NO:126 and/or a light chain variable domain that is at least 85% identical to SEQ ID NO:130. In some embodiments, the antibody to PD-L1 comprises a heavy chain variable domain that has the sequence of SEQ ID NO:126 and a light chain variable domain that has the sequence of SEQ ID NO:130. In a further embodiment, the antibody to PD-L1 comprises a light chain CDR-1L comprising SEQ ID NO:247, a CDR-2L comprising SEQ ID NO:248, and a CDR-3L comprising SEQ ID NO:249; and a heavy chain CDR-1H comprising SEQ ID NO: 241, a CDR-2H comprising SEQ ID NO: 243, and a CDR-3H comprising SEQ ID NO: 245. In another embodiment, the antibody to PD-L1 comprises a light chain CDR-1L comprising SEQ ID NO:247, a CDR-2L comprising SEQ ID NO:248, and a CDR-3L comprising SEQ ID NO:249; and a heavy chain CDR-1H comprising SEQ ID NO: 266, a CDR-2H comprising SEQ ID NO: 243, and a CDR-3H comprising SEQ ID NO: 245. In another embodiment, the antibody to PD-L1 comprises a heavy chain variable domain that is at least 85% identical to SEQ ID NO:246 and/or a light chain variable domain that is at least 85% identical to SEQ ID NO:250. In some embodiments, the antibody to PD-L1 comprises a heavy chain variable domain that has the sequence of SEQ ID NO:246 or SEQ ID NO:267 and a light chain variable domain that has the sequence of SEQ ID NO:250. In some embodiments, the fusion protein comprises SEQ ID NO: 261.

[0013] In another aspect, the present invention provides a medical use of the fusion protein of the invention in treating cancer. In a further aspect, the present invention provides a nucleic acid molecule comprising a nucleotide sequence encoding the fusion protein of the invention.

[0014] receptors. As disclosed herein, the molecule binds to PD-L1 on target cells, and also stimulates a cell-mediated immune response, for example, by promoting proliferation of T cells and/or NK cells. The molecule disclosed herein stimulates cells that respond to an interleukin or an interferon, such as, without limitation, IL2, IL7, IL15, and IL21. The molecule disclosed herein may include a sequence or domain that promotes IL15 stimulation of the IL15 receptor (IL15R). As disclosed herein, the molecule that promotes IL15R stimulation may be a portion of the IL15R alpha chain comprising a sushi domain. The molecule disclosed herein may provide the sushi domain of the IL15R alpha chain. The molecule disclosed herein may provide a complex of IL15 and the sushi domain of the IL15R alpha chain, which may be covalent or non-covalent. The experiments disclosed herein demonstrate that single molecules containing both a PD-L1 binding domain that blocks binding of PD-L1 to PD-1, and an IL15R stimulating domain, promote a better immune response than separate molecules used together. More particularly, providing a molecule that provides an anti-PD-L1 antibody domain as well as a

hybrid domain comprising IL15 and the IL15 alpha chain sushi domain, promoted increased proliferation, Th1 cytokine release, and killing activity-related molecules of NK and T cells, compared to providing the domains in separate molecules.

[0015] Also disclosed is an antibody or fragment that binds to PD-L1, which comprises a heavy chain CDR-1H which has the sequence $X_1YX_2MX_3$ (SEQ ID NO:328) wherein X_1 is A, G, M, Q, S, Y, or W, X_2 is A, L, M, Q, R, S, V, W, or Y, and X_3 is A, F, L, M, S, T, V, or Y, a heavy chain CDR-2H which has SEQ ID NO:243, and a heavy chain CDR-3H which has the sequence of SEQ ID NO:245. As disclosed herein, the heavy chain CDR-1H may have a sequence selected from SEQ ID NO:241, SEQ ID NO:264, SEQ ID NO:266, SEQ ID NO:268, SEQ ID NO:270, SEQ ID NO:272, SEQ ID NO:274, SEQ ID NO:276, SEQ ID NO:278, SEQ ID NO:280, SEQ ID NO:282, SEQ ID NO:284, SEQ ID NO:286, SEQ ID NO:288, SEQ ID NO:290, SEQ ID NO:292, SEQ ID NO:294, SEQ ID NO:296, SEQ ID NO:298, SEQ ID NO:300, SEQ ID NO:302, SEQ ID NO:304, SEQ ID NO:306, SEQ ID NO:308, SEQ ID NO:310, and SEQ ID NO:312. As disclosed herein, the heavy chain variable domain may be at least 80%, or at least 85%, or at least 90%, or at least 95% identical to SEQ ID NO:246. The antibodies may further comprise a light chain variable domain which comprises a CDR-1L which has SEQ ID NO:247, a CDR-2L which has SEQ ID NO:248, and a CDR-3L which has SEQ ID NO:249.

[0016] As disclosed herein, the light chain variable domain may be at least 80%, or at least 85%, or at least 90%, or at least 95% identical to SEQ ID NO:250. Also disclosed is an antibody or fragment thereof that binds to PD-L1, wherein the light chain comprises a CDR-1L which has SEQ ID NO:247, a CDR-2L which has SEQ ID NO:248, and a CDR-3L which has SEQ ID NO:249.

[0017] Also disclosed are conjugates of the antibodies, for example, and without limitation, to imaging agents, therapeutic agents, or cytotoxic agents.

[0018] Also disclosed are compositions comprising the antibodies and conjugates and a pharmaceutically acceptable carrier.

[0019] The invention provides a fusion protein capable of binding to PDL1, which also stimulates an immune response mediated by, for example, a T cell or an NK cell. In the invention the fusion protein includes a portion that binds to IL15 receptor. Also disclosed are fusion proteins that include a portion that binds to, e.g., an interleukin receptor or an interferon receptor. As disclosed herein, the portion of the fusion protein that binds to PD-L1 is an antibody or PD-L1 binding fragment thereof. As disclosed herein, the IL15 receptor-binding portion is IL15, whose binding may be enhanced by the presence in the fusion protein of an IL15R alpha sushi domain.

[0020] Also disclosed is a method of inhibiting the interaction of PD1 with PD-L1 in a subject, which comprises administering an effective amount of an antibody or fragment disclosed herein. Also disclosed is a method of inhibiting immunosuppression mediated by PD-L1 which comprises administering an effective amount of the antibody or fragment, or a fusion protein

disclosed herein.

[0021] Also disclosed is a method of stimulating an immune response against a cell or tissue that expresses PD-L1, which comprises administering to a subject an effective amount of the antibody or fragment, or a fusion protein as disclosed herein.

[0022] For example, the cell or tissue that expresses PD-L1 is a neoplastic cell or an infected cell.

BRIEF DESCRIPTION OF THE FIGURES

[0023]

Figure 1 depicts binding to human hPDL1-Fc (top left panel), blocking of hPDL1 to hPD1 (bottom left panel), binding to mouse mPDL1-Fc (top right panel), and blocking of mPDL1 to hPD1 (bottom right panel) of antibodies tccR3λF8, tccR3κA11, tccR3λH4, tctR3κA8, sR3λD7, and R2κA6.

Figure 2 depicts binding to human hPDL1-Fc (top left panel), blocking of hPDL1 to hPD1 (bottom left panel), binding to mouse mPDL1-Fc (top right panel), and blocking of mPDL1 to hPD1 (bottom right panel) of antibodies sR3λD7, tccR3κB7, tccR3κA4, tccR3λF8, tccR3λD7, tccR3λH4, and tccR3κD9.

Figure 3 depicts binding to human hPDL1-Fc (top left panel), blocking of hPDL1 to hPD1 (bottom left panel), binding to mouse mPDL1-Fc (top right panel), and blocking of mPDL1 to hPD1 (bottom right panel) of antibodies tccR3κF8, tccR3κD9, tccR3λD7, tccR3λD7 sR3κF10, sR3λD7, and tccR3λF8.

Figure 4 depicts binding to human hPDL1-Fc (top left panel), blocking of hPDL1 to hPD1 (bottom left panel), binding to mouse mPDL1-Fc (top right panel), and blocking of mPDL1 to hPD1 (bottom right panel) of antibodies P2κA6, sR3λD7, tccR3λD7, tccR3κB7, and tccR3κH4.

Figure 5 depicts binding to PDL1-293 cells (top) and MDS-MB-231 (bottom) cells of antibodies sR3λD7, tctR3κA8, tccR3κA11, tccR3λD7, tccR3κD9, tccR3λF8, tccR3κF8, tccR3κF10, tccR3λH4, tccR3κB7, and tccR3κA4.

Figure 6 depicts anti-PD-L1 antibodies binding to (A) human monocyte-derived dendritic cells, (B) human cancer cell line expressing PD-L1 MDA-MB-231 cells, and (C) mouse cell line expressing PD-L1 B16-F10.

Figure 7 shows functional blocking activity of anti-PD-L1 antibodies measured by (A) increase in CD4 proliferation when activated by aCD3 and PD-L1Fc coated beads, (B) increase in cytokine secretion in SEB-activated human PBMC, and (C) increase in CD4 proliferation in Mixed-Lymphocyte Reaction with mo-DC.

Figure 8 shows CD4 and CD8 activation when both anti-PDL1 antibody and IL15 were present in (A) mixed-lymphocyte reaction with mo-DC, and (B) CD8 stimulation by α CD3 and PD-L1Fc coated beads.

Figure 9 shows anti-PD-L1-sushi domain-IL15 (termed anti-PDL1-SD15) fusion proteins retain binding to PD-L1 as measured by (A) solid-phase ELISA, and (B) binding to CD4 activated by α CD3 coated beads.

Figure 10 shows PBMC cultured in vitro with anti-PD-L1-SD15 fusion proteins resulted in increased NK cell number (A), increased CD8 cell number (B) and activation status as measured by % granzymeB (C). No effect was observed on CD4 cells (D).

Figure 11 shows anti-PD-L1-SD15 fusion proteins function to activate CD8 similarly to IL15 when added to in vitro CD8 stimulation in the presence of α CD3 coated beads (A). However, in the presence of α CD3 and PD-L1Fc coated beads, anti-PD-L1-SD15 fusion proteins can increase CD8 proliferation by more than five-fold when compared to IL15 (B). cD7-SD15neg is anti-PD-L1 cD7 with non-functional IL15 serving as negative controls.

Figure 12 shows CD8 activation in the presence of PD-L1Fc on the antigen presenting cells. Anti-PD-L1-SD15 fusion protein cD7-SD15 stimulated CD8 at significantly lower concentrations as measured by (A) percent increase in granzymeB positive CD8, and (B) increased in total cytokine secretions. The maximum levels of CD8 activation were also increased in CD8 activated by α CD3 and PD-L1Fc with addition of cD7-SD15 as compared to IL15. (C) Data on CD8 proliferation in the presence of both anti-PD-L1 antibody and free IL15 (dotted lines) is superimposed on data of CD8 proliferation in presence of anti-PD-L1-SD15 fusion protein (straight lines).

Figure 13 provides amino acid sequences of V_H (Fig. 13A1-3) and V_L (Fig. 13B1-3) chains of anti-PD-L1 antibodies. For V_H sequences, boxed regions indicate CDRs. For CDR-1H, Chothia CDRs are in italics, and Kabat CDRs are underlined. For CDR-2H, Kabat CDRs are coextensive with the boxed sequences, with Chothia CDRs in italics. For V_L sequences, boxed regions indicate Kabat/Chothia CDRs.

Figure 14 shows the amino acid sequences of SD15 (SEQ ID NO:261), which includes the IL15R alpha sushi domain and IL15, tccAD7HC-SD15 (SEQ ID NO:262) and the LALA mutant of tccAD7HC-SD15 (SEQ ID NO:263), which contains alanine substitutions for two adjacent leucines at positions (Leu²³⁴ and Leu²³⁵) in the heavy chain constant region important for Fc γ RI.

Figure 15 shows cytotoxicity of anti-PD-L1-SD15 fusion protein (CD7SD15) compared to the PD-L1 binding portion of the molecule alone (cD7) and a fusion protein containing a binding domain specific for KLH and the IL15 domain (KLHSD15). Human CD8 T cells and MAD-MB-231 tumor cells were co-cultured in IMDM supplemented with 10% FBS for 7 days. Tumor cell killing activity was assessed by the measurement of the number of dead tumor cells stained by Viability Dye eFluor 780 in FACS.

Figure 16 shows anti-PD-L1-SD15 fusion protein prolonged the survival rate of mice bearing PD-L1 expressing tumors. Balb/c mice were intravenously injected with 2×10^5 murine CT26 colon tumor cells. 24 hrs later, mice received i.p. administration of the anti-PD-L1 antibody cD7 (purple line: 75 ug per dose), anti-PD-L1-SD15 fusion protein cD7-SD15 (green line: 75 ug per dose, blue line: 25 ug per dose) or sD7-SD15 (Grey line: 75 ug per dose, Red line: 25 ug per dose) twice a week in the first week then once weekly in the rest of treatment course. Mice in control groups received an equal volume of saline or normal IgG solution. Survival rate was measured by using Kaplan-Meier Plot.

Figure 17 shows binding of two affinity matured anti-PDL1 antibodies to soluble human PDL1, soluble mouse PDL1, and soluble rat PDL1, and no binding to human PDL2.

Figure 18 shows blocking of human PD1 to human PDL1 (left panel) and blocking of mouse PD1 to mouse PDL1 (right panel) by two affinity matured anti-PDL1 antibodies, compared to their parent tccAD7 antibody.

Figure 19 shows two affinity matured variants of anti-PD-L1 antibodies tccAD7 have higher binding activity to PD-L1 expressing human MDA-MB-231 tumor cells as measured by flow cytometry.

Figure 20 shows affinity matured variants of anti-PD-L1 antibodies tccAD7 having increased potency to promote production of Th1 cytokines IL2 (top panel) and IFN γ (bottom panel).

Figure 21 shows binding of fusion proteins disclosed herein to PD-L1-expressing MDA-MB-231 tumor cells.

Figure 22 shows stimulatory activity of proteins disclosed herein on IL15-responsive human megakaryoblastic leukemia cells.

Figure 23 shows hPD-L1 binding (left panel) and ligand blocking (right panel) activity for fusion proteins disclosed herein.

Figure 24 shows the results of size exclusion chromatography for fusion proteins disclosed herein.

Figure 25 shows serum stability for fusion proteins disclosed herein.

DETAILED DESCRIPTION

[0024] The interaction of PD-1 on immune cells with PD-L1 inhibits proliferation and cytokine production by immune cells. PD-L1 is also inducible and upregulated in various tissues, including cancer. Together, PD-1 and PD-L1 play a role in immunosuppression. The invention provides novel fusion proteins comprising antibodies that bind to PD-L1 and block the interaction with PD-1. In the fusion proteins of the invention, the antibodies reduce or inhibit

immunosuppression.

[0025] Novel antibodies disclosed herein are set forth in Table 1 and the accompanying sequence listing, which set forth amino acid sequences of heavy and light chain CDRs (identified according to the identification systems of Kabat and Chothia), as well as complete heavy and light chain variable region. The first two heavy chain CDRs are identified according to the common systems of Kabat and Chothia, which provide distinct, but overlapping locations for the CDRs. A comparison of the numerous heavy and light chains shows a significant similarity among many of the CDR sequences. Accordingly, it would be expected that many of the CDRs can be mixed and matched among the sequences.

[0026] The antibodies can have one or more amino acid substitutions, deletions, insertions, and/or additions. The antibodies disclosed herein may comprise one of the above-mentioned heavy chain variable domains and one of the above-mentioned light chain variable domains. The PD-L1 antibodies or binding fragments thereof as disclosed herein may comprise one or more CDRs or one or more variable domains with an amino acid sequence at least 85% at least 90%, at least 95%, at least 97%, at least 98%, or at least 99%, identical to the CDR and variable domain sequences set forth in Table 1.

[0027] "Identity" refers to the number or percentage of identical positions shared by two amino acid or nucleic acid sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. "Substantially identical" means an amino acid sequence which differs only by conservative amino acid substitutions, for example, substitution of one amino acid for another of the same class (e.g., valine for glycine, arginine for lysine, etc.) or by one or more non-conservative substitutions, deletions, or insertions located at positions of the amino acid sequence which do not destroy the function of the protein. Amino acid substitutions can be made, in some cases, by selecting substitutions that do not differ significantly in their effect on maintaining (a) the structure of the peptide backbone in the area of the substitution, (b) the charge or hydrophobicity of the molecule at the target site; or (c) the bulk of the side chain. For example, naturally occurring residues can be divided into groups based on side-chain properties; (1) hydrophobic amino acids (norleucine, methionine, alanine, valine, leucine, and isoleucine); (2) neutral hydrophilic amino acids (cysteine, serine, and threonine); (3) acidic amino acids (aspartic acid and glutamic acid); (4) basic amino acids (asparagine, glutamine, histidine, lysine, and arginine); (5) amino acids that influence chain orientation (glycine and proline); and (6) aromatic amino acids (tryptophan, tyrosine, and phenylalanine). Substitutions made within these groups can be considered conservative substitutions. Examples of substitutions include, without limitation, substitution of valine for alanine, lysine for arginine, glutamine for asparagine, glutamic acid for aspartic acid, serine for cysteine, asparagine for glutamine, aspartic acid for glutamic acid, proline for glycine, arginine for histidine, leucine for isoleucine, isoleucine for leucine, arginine for lysine, leucine for methionine, leucine for phenylalanine, glycine for proline, threonine for serine, serine for threonine, tyrosine for tryptophan, phenylalanine for tyrosine, and/or leucine for valine.

[0028] Preferably, the amino acid sequence is at least 80%, or at least 85%, or at least 90%, or at least 95% identical to an amino acid sequence disclosed herein. Methods and computer programs for determining sequence similarity are publically available, including, but not limited to, the GCG program package (Devereux et al., *Nucleic Acids Research* 12: 387, 1984), BLASTP, BLASTN, FASTA (Altschul et al., *J. Mol. Biol.* 215:403 (1990), and the ALIGN program (version 2.0). The well-known Smith Waterman algorithm may also be used to determine similarity. The BLAST program is publicly available from NCBI and other sources (BLAST Manual, Altschul, et al., NCBI NLM NIH, Bethesda, Md. 20894; BLAST 2.0 at <http://www.ncbi.nlm.nih.gov/blast/>). In comparing sequences, these methods account for various substitutions, deletions, and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine.

[0029] Antibodies disclosed herein also include those for which binding characteristics have been improved by direct mutation, methods of affinity maturation, phage display, or chain shuffling. Affinity and specificity may be modified or improved by mutating CDRs and screening for antigen binding sites having the desired characteristics. CDRs are mutated in a variety of ways. One way is to randomize individual residues or combinations of residues so that in a population of otherwise identical antigen binding sites, all twenty amino acids are found at particular positions. Alternatively, mutations are induced over a range of CDR residues by error prone PCR methods (see, e.g., Hawkins et al., *J. Mol. Biol.*, 226: 889-896 (1992)). For example, phage display vectors containing heavy and light chain variable region genes may be propagated in mutator strains of *E. coli* (see, e.g., Low et al., *J. Mol. Biol.*, 250: 359-368 (1996)). These methods of mutagenesis are illustrative of the many methods known to one of skill in the art.

[0030] To minimize the immunogenicity, antibodies which comprise human constant domain sequences are preferred. The antibodies may be or may combine members of any immunoglobulin class, such as IgG, IgM, IgA, IgD, or IgE, and the subclasses thereof. The antibody class may be selected to optimize effector functions (e.g., complement dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC)) of natural antibodies.

[0031] Also disclosed is the use of PD-L1-binding antibody fragments. An Fv is the smallest fragment that contains a complete heavy and light chain variable domain, including all six hypervariable loops (CDRs). Lacking constant domains, the variable domains are noncovalently associated. The heavy and light chains may be connected into a single polypeptide chain (a "single-chain Fv" or "scFv") using a linker that allows the V_H and V_L domains to associate to form an antigen binding site.

[0032] As disclosed herein, the linker may be (Gly-Gly-Gly-Gly-Ser)₃. Since scFv fragments lack the constant domains of whole antibodies, they are considerably smaller than whole antibodies. scFv fragments are also free of normal heavy-chain constant domain interactions with other biological molecules which may be undesired.

[0033] Fragments of an antibody containing V_H , V_L , and optionally C_L , C_H1 , or other constant domains can also be used. Monovalent fragments of antibodies generated by papain digestion are referred to as Fab and lack the heavy chain hinge region. Fragments generated by pepsin digestion, referred to as $F(ab')_2$, retain the heavy chain hinge and are divalent. Such fragments may also be recombinantly produced. Many other useful antigen-binding antibody fragments are known in the art, and include, without limitation, diabodies, triabodies, single domain antibodies, and other monovalent and multivalent forms.

[0034] Also disclosed are multivalent antigen-binding proteins, which can be in the form, without limitation, of antibodies, antigen-binding fragments thereof, and proteins comprising all or part of antigen-binding portions of antibodies. Multivalent antigen-binding proteins may be monospecific, bispecific, or multispecific. The term specificity refers to the number of different types of antigenic determinants to which a particular molecule can bind. If an immunoglobulin molecule binds to only one type of antigenic determinant, the immunoglobulin molecule is monospecific. If the immunoglobulin molecule binds to different types of antigenic determinants then the immunoglobulin molecule is multispecific.

[0035] The PD-L1 binding protein disclosed herein may have an on rate constant (K_{on}) of at least about $10^2 M^{-1}s^{-1}$; at least about $10^3 M^{-1}s^{-1}$; at least about $10^4 M^{-1}s^{-1}$; at least about $10^5 M^{-1}s^{-1}$; or at least about $10^6 M^{-1}s^{-1}$, as measured by surface plasmon resonance.

[0036] The PD-L1 binding protein disclosed herein may have an on rate constant (K_{on}) between $10^2 M^{-1}s^{-1}$ and $10^3 M^{-1}s^{-1}$; between $10^3 M^{-1}s^{-1}$ and $10^4 M^{-1}s^{-1}$; between $10^4 M^{-1}s^{-1}$ and $10^5 M^{-1}s^{-1}$; or between $10^5 M^{-1}s^{-1}$ and $10^6 M^{-1}s^{-1}$, as measured by surface plasmon resonance.

[0037] The PD-L1 binding protein disclosed herein may have an off rate constant (K_{off}) of at most about $10^{-3} s^{-1}$; at most about $10^{-4} s^{-1}$; at most about $10^{-5} s^{-1}$; or at most about $10^{-6} s^{-1}$ as measured by surface plasmon resonance. The PD-L1 binding protein disclosed herein may have an off rate constant (K_{off}) of $10^{-3} s^{-1}$ to $10^{-4} s^{-1}$; of $10^{-4} s^{-1}$ to $10^{-5} s^{-1}$; or of $10^{-5} s^{-1}$ to $10^{-6} s^{-1}$, as measured by surface plasmon resonance.

[0038] The PD-L1 binding protein disclosed herein may have a dissociation constant (K_D) of at most about $10^{-7} M$; at most about $10^{-8} M$; at most about $10^{-9} M$; at most about $10^{-10} M$; at most about $10^{-11} M$; at most about $10^{-12} M$; or at most $10^{-13} M$. The binding protein disclosed herein may have a dissociation constant (K_D) to its targets of $10^{-7} M$ to $10^{-8} M$; of $10^{-8} M$ to $10^{-9} M$; of $10^{-9} M$ to $10^{-10} M$; of $10^{-10} M$ to $10^{-11} M$; of $10^{-11} M$ to $10^{-12} M$; or of $10^{-12} M$ to $10^{-13} M$.

[0039] The binding protein described herein may be a conjugate further comprising an imaging agent, a therapeutic agent, or a cytotoxic agent. The imaging agent may be a radiolabel, an enzyme, a fluorescent label, a luminescent label, bioluminescent label, a magnetic label, or

biotin. Theradiolabel may be: ^3H , ^{14}C , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I , ^{177}Lu , or ^{153}Sm . The therapeutic or cytotoxic agent may be an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, or an apoptotic agent. As discussed below, immunostimulatory cytokines are of particular importance.

[0040] The invention also provides fusion proteins that bind PD-L1 to inhibit immunosuppression, which also promote immune responses by interaction with other ligands or receptors. As exemplified herein, such a fusion proteins combines the PD-L1-binding domain of an antibody with a domain that stimulates NK or T cell function. Such a stimulatory domain binds to and stimulates a receptor that is responsive to interleukin IL15. The stimulatory domain exemplified herein is a hybrid domain comprising the sushi domain of the IL15R alpha chain attached to IL15 by a linker (e.g., SEQ ID NO:261). An example of a complete molecule is set forth by SEQ ID NO:262. A nearly identical molecule, modified with two amino acid substitutions in the region between the antibody domain and the IL15R-stimulating domain, to inhibit proteolysis in the region, is set forth by SEQ ID NO:263. As demonstrated herein, a molecule which comprises a PD-L1 binding domain that inhibits immunosuppression, and a second domain which promotes an immune response, provides for increased immune cell activity, compared to two distinct molecules that providing the functions separately.

[0041] PD-L1-binding portion of the fusion protein is an antigen-binding domain of an antibody. Several novel antibody heavy and light chain variable domains and antibodies that include them are provided. According to the invention, the PD-L1-binding portion is an antibody that binds to PD-L1 and blocks immunosuppression. Also disclosed are anti-PD-L1 antibodies and fragments, not limited to those novel antibodies disclosed herein, as well as peptides and proteins derived from PD1, the natural ligand of PD-L1.

[0042] As disclosed herein, the PD-L1-binding domain is linked to a domain that stimulates NK and T cell activity. The domain comprises IL15, and joined to it by a flexible linker, the "sushi" domain from the alpha chain of the IL15 receptor. The sushi domain binds to IL15 with high affinity and the complex of IL15 with the sushi domain is particularly active for stimulating NK and T cell proliferation. What is especially notable is that, as shown in the Examples, treatment with an agent combining the PD-L1-binding domain in the same molecule as the IL15 stimulatory domain is more effective than combined treatment using the PD-L1-binding domain and IL15 stimulatory domain as separate molecules.

[0043] Thus, the invention contemplates fusion proteins comprising a domain that bind to PD-L1 and blocks binding to PD1, and a domain that stimulates IL15R, thus proliferation of immune cells. As exemplified, the IL15R stimulatory domain comprises the sushi domain of the IL15R alpha chain joined to IL15 by a flexible linker similar to those employed for, e.g., single chain Fv molecules (i.e., containing 15-20 amino acids which are predominantly serine and glycine. In practice, there are other methods that can be used, which may be preferred for example for manufacturing procedures. Further, one recognizes the domain structures, thus

the modular aspects and other features of the disclosed hybrid proteins. For example, the linker joining the sushi domain to IL15 is useful for expressing the hybrid as one polypeptide, but could just as well be replaced by other agents, linkers, or cross linkers. Alternatively, the high affinity of IL15 for the sushi-containing portion of the IL15R alpha chain indicates that the sushi domain and IL15 would form a stable complex that need not be covalent. Similarly, while the exemplified protein comprises an entire antibody constant region, other antigen binding fragments of a PD-L1-binding antibody would suffice.

[0044] Also disclosed is a PD-L1-binding domain linked to an IL15R stimulatory domain, which IL15R stimulatory domain comprises the sushi domain of the IL15R alpha chain or a variant thereof and IL15 or a variant thereof. As disclosed herein, the variants would be 80%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, or 95% identical to the sequences disclosed herein. As disclosed herein, the sushi domain of the IL15R alpha chain, and IL15 may form a covalent complex. As disclosed herein, the sushi domain of the IL15R alpha chain and IL15 may form a non-covalent complex. The PD-L1 binding domain can comprise one, two, three, four, five, or six CDRs, or the heavy and or light chain variable domain of an antibody thereof disclosed herein, or be an antigen-binding fragment thereof, or a variant thereof, such as a variant that is 80%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, or 95% identical, or a PD-L1 antibody known in the art that blocks binding to PD-1 or an antigen binding fragment thereof.

[0045] It is understood that the fusion proteins comprising anti-PD-L1 antibodies of the invention, when used in a mammal for the purpose of prophylaxis or treatment, will be administered in the form of a composition additionally comprising a pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers include, for example, one or more of water, saline, phosphate buffered saline, dextrose, glycerol, sucrose, polysorbate, ethanol and the like, as well as combinations thereof. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibodies.

[0046] In the medical uses of the present invention, a therapeutically effective amount of the fusion protein of the invention is administered to a mammal in need thereof. The term "administering" as used herein means delivering the fusion proteins of the present invention to a mammal by any method that may achieve the result sought. They may be administered, for example, intravenously or intramuscularly. Although the exemplified fusion proteins of the invention are particularly useful for administration to humans, they may be administered to other mammals as well. The term "mammal" as used herein is intended to include, but is not limited to, humans, laboratory animals, domestic pets and farm animals. "Therapeutically effective amount" means an amount of fusion protein of the present invention that, when administered to a mammal, is effective in producing the desired therapeutic effect, such as inhibiting kinase activity.

[0047] Fusion proteins of the invention are useful for inhibiting tumors and other neoplastic diseases, as well as treating other pathologic conditions associated with immunosuppression. Tumors that can be treated include primary tumors, metastatic tumors, and refractory tumors.

Refractory tumors include tumors that fail to respond or are resistant to treatment with chemotherapeutic agents alone, antibodies alone, radiation alone or combinations thereof. Refractory tumors also encompass tumors that appear to be inhibited by treatment with such agents, but recur up to five years, sometimes up to ten years or longer after treatment is discontinued. The antibodies are effective for treating vascularized tumors and tumors that are not vascularized, or not yet substantially vascularized.

[0048] Examples of solid tumors which may be accordingly treated include breast carcinoma, lung carcinoma, colorectal carcinoma, pancreatic carcinoma, glioma and lymphoma. Some examples of such tumors include epidermoid tumors, squamous tumors, such as head and neck tumors, colorectal tumors, prostate tumors, breast tumors, lung tumors, including small cell and non-small cell lung tumors, pancreatic tumors, thyroid tumors, ovarian tumors, and liver tumors. Other examples include Kaposi's sarcoma, CNS neoplasms, neuroblastomas, capillary hemangioblastomas, meningiomas and cerebral metastases, melanoma, gastrointestinal and renal carcinomas and sarcomas, rhabdomyosarcoma, glioblastoma, preferably glioblastoma multiforme, and leiomyosarcoma. Examples of vascularized skin cancers for which the antagonists disclosed herein are effective include squamous cell carcinoma, basal cell carcinoma and skin cancers that can be treated by suppressing the growth of malignant keratinocytes, such as human malignant keratinocytes.

[0049] Examples of non-solid tumors include leukemia, multiple myeloma and lymphoma that are unresponsive to cytokines, such as IL15. Some examples of leukemias include acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), erythrocytic leukemia or monocytic leukemia. Some examples of lymphomas include Hodgkin's and non-Hodgkin's lymphoma.

[0050] The PD-L1 antibodies and immune cell stimulating hybrid proteins disclosed herein are also used in the treatment of viral infections. PD-1 expression on T cells correlates with viral load in HIV and HCV infected patients and PD-1 expression has been identified as a marker for exhausted virus-specific CD8⁺ T cells. For example, PD-1⁺CD8⁺ T cells show impaired effector functions and PD-1 associated T cell exhaustion which can be restored by blocking the PD-1/PD-L1 interaction. This results in recovery of virus-specific CD8⁺ T cell mediated immunity, indicating that interrupting PD-1 signaling using an antagonistic antibody restores T-cell effector functions. Immunotherapy based on the blockade of PD-1/PD-L1 results in breakdown of T-cell tolerance not only to tumor antigens, but also provides a strategy to reactivate virus-specific effector T cells and eradicate pathogens in chronic viral infections. Accordingly, the antibodies and hybrid proteins disclosed herein are useful to treat chronic viral infections, including, without limitation, HCV and HIV, and lymphocytic choriomeningitis virus (LCMV).

[0051] The fusion proteins of the invention can be advantageously administered with second agents to patients in need thereof. For example, fusion protein of the invention may be administered to a subject with an anti-neoplastic agent, with a second angiogenesis inhibitor or with an antiinflammatory agent or an immunosuppressant.

[0052] Antineoplastic agents include cytotoxic chemotherapeutic agents, targeted small molecules and biological molecules, and radiation. Non-limiting examples of chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, irinotecan, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin, paclitaxel (taxol), docetaxel (taxotrec), aldesleukin, asparaginase, busulfan, carboplatin, cladribine, dacarbazine, floxuridine, fludarabine, hydroxyurea, ifosfamide, interferon alpha, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, streptozocin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil, taxol and combinations thereof.

[0053] Targeted small molecules and biological molecules include, without limitation, inhibitors of components of signal transduction pathways, such as modulators of tyrosine kinases and inhibitors of receptor tyrosine kinases, and agents that bind to tumorspecific antigens. Non-limiting examples of growth factor receptors involved in tumorigenesis are the receptors for platelet-derived growth factor (PDGFR), insulin-like growth factor (IGFR), nerve growth factor (NGFR), and fibroblast growth factor (FGFR), and receptors of the epidermal growth factor receptor family, including EGFR (erbB1), HER2 (erbB2), erbB3, and erbB4.

[0054] EGFR antagonists include antibodies that bind to EGFR or to an EGFR ligand, and inhibits ligand binding and/or receptor activation. For example, the agent can block formation of receptor dimers or heterodimer with other EGFR family members. Ligands for EGFR include, for example, EGF, TGF- α amphiregulin, heparin-binding EGF (HB-EGF) and betaregullin. An EGFR antagonist can bind externally to the extracellular portion of EGFR, which may or may not inhibit binding of the ligand, or internally to the tyrosine kinase domain. EGFR antagonists further include agents that inhibit EGFR-dependent signal transduction, for example, by inhibiting the function of a component of the EGFR signal transduction pathway. Examples of EGFR antagonists that bind EGFR include, without limitation, biological molecules, such as antibodies (and functional equivalents thereof) specific for EGFR, and small molecules, such as synthetic kinase inhibitors that act directly on the cytoplasmic domain of EGFR.

[0055] Small molecule and biological inhibitors include inhibitors of epidermal growth factor receptor (EGFR), including gefitinib, erlotinib, and cetuximab, inhibitors of HER2 (e.g., trastuzumab, trastuzumab emtansine (trastuzumab-DM1; T-DM1) and pertuzumab), anti-VEGF antibodies and fragments (e.g., bevacizumab), antibodies that inhibit CD20 (e.g., rituximab, ibritumomab), anti-VEGFR antibodies (e.g., ramucirumab (IMC-1121B), IMC-1C11, and CDP791), anti-PDGFR antibodies, and imatinib. Small molecule kinase inhibitors can be specific for a particular tyrosine kinase or be inhibitors of two or more kinases. For example, the compound N-(3,4-dichloro-2-fluorophenyl)-7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine (also known as XL647, EXEL-7647 and KD-019) is an *in vitro* inhibitor of several receptor tyrosine kinases (RTKs), including EGFR, EphB4, KDR (VEGFR), Flt4 (VEGFR3) and ErbB2, and is also an inhibitor of the SRC

kinase, which is involved in pathways that result in nonresponsiveness of tumors to certain TKIs. As disclosed herein, treatment of a subject in need may comprise administration of a rho-kinase inhibitor of Formula I and administration of KD-019.

[0056] Dasatinib (BMS-354825; Bristol-Myers Squibb, New York) is another orally bioavailable, ATP-site competitive Src inhibitor. Dasatinib also targets Bcr-Abl (FDA-approved for use in patients with chronic myelogenous leukemia (CML) or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL)) as well as c-Kit, PDGFR, c-FMS, EphA2, and SFKs. Two other oral tyrosine kinase inhibitor of Src and Bcr-Abl are bosutinib (SKI-606) and saracatinib (AZD0530).

[0057] A PD-L1 antibody or conjugate disclosed herein may be used in combination with an anti-viral agent to treat a chronic virus infection. For example, for HCV, the following agents can be used. HCV protease inhibitors include, without limitation, boceprevir, telaprevir (VX-950), ITMN-191, SCH-900518, TMC-435, BI-201335, MK-7009, VX-500, VX-813, BMS790052, BMS650032, and VBY376. HCV nonstructural protein 4B (NS4B) inhibitors include, but are not limited to, clemizole, and other NS4B-RNA binding inhibitors, including but not limited to benzimidazole RBIs (B-RBIs) and indazole RBIs (I-RBIs). HCV nonstructural protein 5A (NS5A) inhibitors include, but are not limited to, BMS-790052, A-689, A-831, EDP239, GS5885, and PP1461. HCV polymerase (NS5B) inhibitors include, but are not limited to nucleoside analogs (e.g., valopicitabine, R1479, R1626, R7128), nucleotide analogs (e.g., IDX184, PSI-7851, PSI-7977, and non-nucleoside analogs (e.g., filibuvir, HCV-796, VCH-759, VCH-916, ANA598, VCH-222 (VX-222), BI-207127, MK-3281, ABT-072, ABT-333, GS9190, BMS791325). Also, ribavirin or a ribavirin analog such as Taribavirin (viramidine; ICN 3142), Mizoribine, Merimepodib (VX-497), Mycophenolate mofetil, and Mycophenolate can be used.

[0058] A fusion protein of the invention may be administered to a subject every day, every other day, every couple of days, every third day, once a week, twice a week, three times a week, or once every two weeks. Two, three or four doses of a fusion protein of the invention may be administered to a subject every day, every couple of days, every third day, once a week or once every two weeks. A dose(s) of a fusion protein of the invention may be administered for 2 days, 3 days, 5 days, 7 days, 14 days, or 21 days. A dose of a fusion protein of the invention may also be administered for 1 month, 1.5 months, 2 months, 2.5 months, 3 months, 4 months, 5 months, 6 months or more.

[0059] Methods of administration include but are not limited to parenteral, intradermal, intravitreal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intravaginal, transdermal, transmucosal, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the practitioner. In most instances, administration will result in the release of a compound into the bloodstream. For treatment of ocular disease, intravitreal administration of biological agents is preferred.

[0060] It may be desirable to administer a compound locally. This may be achieved, for

example, and not by way of limitation, by local infusion, topical application, by injection, by means of a catheter, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In such instances, administration may selectively target a local tissue without substantial release of a compound into the bloodstream.

[0061] Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. A compound disclosed herein may be formulated as a suppository, with traditional binders and vehicles such as triglycerides.

[0062] A compound disclosed herein may be delivered in a vesicle, in particular a liposome (See Langer, 1990, *Science* 249:1527 - 1533; Treat et al., in *Liposomes in the Therapy of Infectious Disease and Bacterial infection*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353 - 365 (1989); Lopez Berestein, *ibid.*, pp. 317 - 327; see generally *ibid.*).

[0063] A compound disclosed herein may be delivered in a controlled release system (See, e.g., Goodson, in *Medical Applications of Controlled Release*, supra, vol. 2, pp. 115 - 138 (1984)). Examples of controlled-release systems are discussed in the review by Langer, 1990, *Science* 249:1527 - 1533 may be used. As disclosed herein, a pump may be used (See Langer, supra; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201; Buchwald et al., 1980, *Surgery* 88:507; Saudek et al., 1989, *N. Engl. J. Med.* 321:574).

[0064] As disclosed herein, polymeric materials can be used (See *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61; See also Levy et al., 1985, *Science* 228:190; During et al., 1989, *Ann. Neurol.* 25:351; Howard et al., 1989, *J. Neurosurg.* 71:105).

[0065] Throughout this application, various publications are referenced. The following examples further illustrate the invention, but should not be construed to limit the scope of the invention in any way.

EXAMPLES

Mixed-Lymphocyte Reactions:

[0066] CD14 positive monocytes were isolated by negative selection from whole blood using RosetteSep human monocyte enrichment kit (StemCell technologies). Immature monocyte-derived dendritic cells (mo-DC) were generated by culturing CD14 positive cells in IMDM

supplemented with 10% FBS with 150ng/mL GM-CSF and 50ng/mL IL-4 for 6 to 7 days. CD4 positive cells were negatively isolated from whole blood using RosetteSep human CD4 enrichment kit (StemCell technologies). Mo-DC and CD4 positive cells from a different donor were then co-cultured at a ratio 1 to 10 of mo-DC to CD4 cells respectively. To assess blocking function of anti-PDL1 antibodies, increasing amount of anti-PDL1 antibodies was added in the beginning of co-culture. In some cases, increasing amount of IL15 was also added at the beginning of co-culture. At day 6 or 7, the supernatants were collected for measurements of secreted IL-2 and IFN γ by ELISA. The number of CD4 cells and expression of the proliferation marker, Ki67, were evaluated by flow cytometry.

Activation of PBMC:

[0067] PBMC was isolated from whole blood using Histopaque-1077 (Sigma), cultured in IMDM supplemented with 10% FBS and activated by either SEB (0.1 μ g/mL), PHA (1 μ g/mL) or anti-CD3 clone HiT3a (1 μ g/mL, eBioscience) for 3 to 7 days. Binding of either anti-PDL1 antibodies or anti-PDL1-SD15 fusion proteins were evaluated in activated PBMC after 3 days by flow cytometry. Functional assessment of anti-PDL1 antibodies were done by addition of increasing amount of anti-PDL1 antibodies during PBMC activation with SEB. At day 2 or 3 supernatants were collected for measurements of IL-2 and IFN γ . In the case of anti-PDL1-SD15 fusion proteins, PBMC were cultured in the presence of either anti-PDL1-SD15 or anti-PDL1 antibodies, with no other activations. At day 6, cells were collected, and the numbers of CD8 and granzymeB, CD8 and perforin, and CD4 cells were evaluated by flow cytometry.

Activation of CD4 and CD8 cells:

[0068] CD4 and CD8 positive cells were negatively isolated from whole blood using RosetteSep enrichment kits (StemCell technologies). CD4 cells were activated by either anti-CD3 or anti-CD3 and PDL1Fc coated beads in IMDM, 10%FBS in the presence of anti-PDL1 antibodies. At day 5, supernatants were collected for IFN γ measurements by ELISA, and cells were evaluated for expression of the proliferation marker Ki67 using flow cytometry. CD8 cells were activated by anti-CD3 coated beads and either IL15 or anti-PDL1-SD15 fusion proteins. In some cases anti-CD3 and PDL1Fc was used in place of anti-CD3 coated beads. At day 6 or 7 the supernatants were collected for measurements of IFN γ and TNF α secretions by ELISA. The cells were collected for measurements of CD8 activation by granzymeB and perforin markers using flow cytometry.

Nomenclature of antibody-fusion proteins:

[0069] In experiments with anti-PD-L1 IL15 fusion proteins, shorter names for the fusion proteins are identified in the legends. The fusion protein tcc1D7HC-SD15 is identified in figure

legends as cD7-SD15. The fusion protein tcclF8HC-SD15 is identified in figure legends as F8-SD15.

Specific high affinity antibodies to PD-L1 from phage-display library

[0070] Anti-PD-L1 antibodies with high affinity were obtained using a phage display library. In one procedure, phage Fabs amplified from Dyax libraries were panned on either recombinant human PDL1-Fc (PDL1 ECD and human Fc fusion protein, Q9NZQ7) or murine PDL1-Fc (Q9EP73) which were immobilized on immune-tubes for three rounds. The ELISA positive clones from round (R2) and round 3 (R3) were sequenced.

[0071] In a second procedure, phage Fabs amplified from the Dyax libraries were panned on recombinant human PDL1-Fc (PDL1 ECD and human Fc fusion protein, Q9NZQ7) for the first round, and then panned on activated T cells for second round. For third round, either the activated T cells or recombinant human PDL1-Fc were used for the panning. Clones which can bind to both soluble PDL1-Fc and cell expressed PDL1-Fc were sequenced. V_H and V_L variable domain sequences of these antibodies are set forth in Fig. 13 and the rows 1-26 of Table 1.

[0072] Unique clones were converted to IgG for the further characterization. The variable domains were inserted to Dyax expression vector pBh1. Both wild type CH1-CH2 - CH3 domains and mutated CH1-CH2-CH3 (L234A and L235A, also referred to herein as LALA mutants) were prepared in the IgG format.

Table 1 - Antibody Amino Acid Sequences by SEQ ID NO.

Mab	V_H CDRs					V_H	V_L CDRs			V_L
	H1 (K)	H1 (C)	H2 (K)	H2 (C)	H3		L1	L1	L3	
K2kA3	1	2	3	4	5	6	7	8	9	10
K2kA4	11	12	13	14	15	16	17	18	19	20
K2kA6	21	22	23	24	25	26	27	28	29	30
R2kF4	31	32	33	34	35	36	37	38	39	40
K2kH5	41	42	43	44	45	46	47	48	49	50
K2kH6	51	52	54	54	55	56	57	58	59	60
K2kH3	61	62	63	64	65	66	67	68	69	70
sR3kA8	71	72	73	74	75	76	77	78	79	80
sR3kA9	81	82	83	84	85	86	87	88	89	90
sR3kB2	91	92	93	94	95	96	97	98	99	100
sR3kB5	101	102	103	104	105	106	107	108	109	110
tccR3kA8	111	112	113	114	115	116	117	118	119	120
tccR3kA11	121	122	123	124	125	126	127	128	129	130

Table 1 - Antibody Amino Acid Sequences by SEQ ID NO.

Mab	V _H CDRs					V _H	V _L CDRs			V _L
	H1 (K)	H1 (C)	H2 (K)	H2 (C)	H3		L1	L1	L3	
tccR3κB7	131	132	133	134	135	136	137	138	139	140
tccR3κD9	141	142	143	144	145	146	147	148	149	150
tccκF10	161	162	163	164	165	166	157	158	159	160
tctR3κA4	161	162	163	164	165	166	167	168	169	170
tctR3κF8	171	172	173	174	175	176	177	178	179	180
K2λA7	181	182	183	184	185	186	187	188	189	190
K2λB12	191	192	193	194	195	196	197	198	199	200
K2λD12	201	202	203	204	205	206	207	208	209	210
sR3λD7	211	212	213	214	215	216	217	218	219	220
sR3λE1	221	222	223	224	225	226	227	228	229	230
tccλF8	231	232	233	234	235	236	237	238	239	240
tccλD7	241	242	243	244	245	246	247	248	249	250
tctR3λH4	251	252	253	254	255	256	257	258	259	260
#101	264	-	243	244	245	265	247	248	249	250
#102	266	-	243	244	245	267	247	248	249	250
#103	268	-	243	244	245	269	247	248	249	250
#104	270	-	243	244	245	271	247	248	249	250
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#108	278	-	243	244	245	279	247	248	249	250
#109	280	-	243	244	245	281	247	248	249	250
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#112	286	-	243	244	245	287	247	248	249	250
#113	288	-	243	244	245	289	247	248	249	250
#114	290	-	243	244	245	291	247	248	249	250
#115	292	-	243	244	245	293	247	248	249	250
#116	294	-	243	244	245	295	247	248	249	250
#117	296	-	243	244	245	297	247	248	249	250
#118	298	-	243	244	245	299	247	248	249	250
#119	300	-	243	244	245	301	247	248	249	250

Table 1 - Antibody Amino Acid Sequences by SEQ ID NO.

Mab	V _H CDRs					V _H	V _L CDRs			V _L
	H1 (K)	H1 (C)	H2 (K)	H2 (C)	H3		L1	L1	L3	
#120	302	-	243	244	245	303	247	248	249	250
#121	304	-	243	244	245	305	247	248	249	250
#122	306	-	243	244	245	307	247	248	249	250
#123	308	-	243	244	245	309	247	248	249	250
#124	310	-	243	244	245	311	247	248	249	250
#125	312	-	243	244	245	313	247	248	249	250

[0073] These antibodies were verified to have specific binding to PD-L1 by solid-phase ELISA (Figs. 1-4) and HEK-293 cells (Fig. 5). Blocking of PD-1:PD-L1 interactions in the presence of these antibodies was determined by solid phase ELISA and by 293-HEK cells expressing PD-L1. Biacore was used to calculate the affinity constant for each antibody.

Table 2 - EC₅₀ and IC₅₀ for antibodies of Figs. 1-4

Fig.1	tccR3λF8	tccR3κA11	tccR3λH4	tctR3κA8	sR3λD7	K2κA6	
h_EC ₅₀	0.167	0.172	0.056	0.106	0.388	0.117	
h_IC ₅₀	1.19	1.58	1.17	2.94	2.89	3.17	
m_EC ₅₀	0.0714	ND	0.144	ND	ND	ND	
m_IC ₅₀	0.925	ND	9.14	ND	ND	ND	
Fig.2	sR3λD7	tccR3κB7	tccR3κA4	tccR3λF8	tccR3λD7	tccR3λH4	tccR3κD9
h_EC ₅₀	0.255	0.3	0.443	0.265	0.155	0.0947	0.132
h_IC ₅₀	1.47	1.26	ND	1.36	1.24	1.12	2.75
m_EC ₅₀	ND	ND	ND	0.205	0.185	0.282	ND
m_IC ₅₀	ND	ND	ND	1.08	1.13	2.88	ND
Fig.3	tccR3κF8	tccR3κD9	tccR3λD7	tccR3κF10	sR3λD7	tccR3F8	
h_EC ₅₀	0.13	0.0259	0.14	0.137	0.244	0.174	
h_IC ₅₀	2.78	3.23	1.09	6.22	2.52	2.89	
m_EC ₅₀	ND	1.31	0.13	ND	ND	0.13	
m_IC ₅₀	ND	52.3	0.349	ND	ND	0.184	

Fig.4	control	K2κA6	sR3λD7	tccR3λD7	tccR3κB7	tccR3λH4	
h_EC ₅₀	0.146	0.0909	0.129	0.0682	0.126	0.117	
h_IC ₅₀	1.49	2	2.55	1.97	2.05	1.68	
m_EC ₅₀	ND	ND	ND	0.0622	ND	ND	
m_IC ₅₀	ND	ND	ND	1.58	ND	ND	

Table 3 - EC₅₀ on PDLI-293, MDA-MB-231, and mPDLI cells

	PDLI-293	MDA-MB-231	mPDL1
sR3λD7	1.377×10^{-9}	2.138×10^{-10}	ND
tctR3κA8	1.179×10^{-9}	1.886×10^{-10}	ND
tccR3κA11	8.731×10^{-10}	1.437×10^{-10}	ND
tccR3λD7	1.153×10^{-9}	6.943×10^{-10}	3.413×10^{-10}
tccR3κD9	7.886×10^{-10}	1.241×10^{-8}	4.004×10^{-9}
tccR3λF8	1.335×10^{-9}	2.610×10^{-10}	3.695×10^{-10}
tccR3κF8	7.430×10^{-10}	7.777×10^{-11}	ND
tccR3κF10	9.143×10^{-10}	1.922×10^{-8}	ND
tccR3λH4	1.410×10^{-9}	1.049×10^{-9}	ND
tccR3κB7	9.732×10^{-10}	9.833×10^{-11}	2.688×10^{-9}
tccR3κA4	9.062×10^{-8}	0.0001903	2.025×10^{-10}

[0074] These antibodies were also verified for binding on native cells expressing PD-L1 by binding to immature monocyte-derived dendritic cells (Figure 6A), the human PD-L1-expressing breast cancer line MDA-MB-231 cells (Figure 6B), the mouse PD-L1-expressing tumor line B16-F10 cells (Figure 6C) as well as human activated CD4 and CD8 T cells.

Functionally active anti-PD-LI antibodies block PD-1 PD-L1 interaction and increase T cell proliferation and activation

[0075] High affinity binding anti-PD-LI antibodies were evaluated for their function to block PD-1 PD-L1 interactions and increase T cell proliferation. Negatively purified CD4 T cells were activated in vitro with either αCD3 or αCD3 and PD-L1Fc coated beads in the presence of anti-PD-LI antibodies. CD4 cells stimulated with αCD3 and PD-L1Fc coated beads showed lower proliferation and IFNγ as well as IL-2 secretions as compared to CD4 cells stimulated with αCD3 only coated beads. Addition of functionally active anti-PD-LI antibodies to CD4 cultures stimulated with αCD3 and PD-L1Fc coated beads increases CD4 proliferation (measured by

either total CD4 number or percentage of the proliferation marker Ki67) (Figure 7A) as compared to cultures with no antibody added. Addition of functionally active blocking anti-PD-L1 antibodies to CD4 cultures with α CD3 and PD-L1Fc coated beads also increases cytokine secretions by CD4 (measured by ELISA of accumulated IFN γ and IL-2 in the supernatant).

[0076] When PBMC isolated from whole blood are stimulated with the super antigen Staphylococcus Enterotoxin B (SEB) in the presence of anti-PD-L1 blocking antibodies, increase in cytokine secretions is observed. Supernatants of PBMC (previously frozen) cultured with SEB for 48 hours were collected, and IFN γ and IL-2 were measured by ELISA. No increase in T cells numbers were observed, but significant increases in the levels of IFN γ and IL-2 were observed in cultures of several anti-PD-L1 antibodies when compared to controls where no antibodies were added (Figure 7B).

[0077] In addition, an increase in CD4 proliferation and activation is also observed in mixed-lymphocyte reaction (MLR) of CD4 T cells and mo-DC cultured in the presence of anti-PD-L1 blocking antibodies. Several of anti-PD-L1 antibodies increased CD4 proliferation in MLR when compared to cultures where no antibody was added (Figure 7C). These antibodies also increased IFN γ and IL-2 secretion as evaluated by ELISA.

IL15 increases anti-PD-L1 antibodies effects on T cell proliferation and activation in vitro

[0078] MLR of CD4 T cells and mo-DC in the presence of both anti-PD-L1 blocking antibodies and the cytokine IL15 resulted in significant increases in CD4 proliferation (Figure 8A), IFN γ and IL-2 secretions when compared to cultures of CD4 and mo-DC with anti-PD-L1 antibodies alone. IL15 was added at equimolar concentrations as anti-PD-L1 antibodies in these assays. At lower anti-PD-L1 antibody and IL15 concentrations (0.5 nM, Figure 8A), some synergistic effect on CD4 proliferation was observed.

[0079] Negatively purified CD8 from whole blood stimulated in vitro with α CD3 and PD-L1Fc coated beads also responds to IL15 in a dose-dependent fashion. Addition of IL15 to cultures of CD8 with α CD3 and PD-L1Fc coated beads and anti-PD-L1 antibodies resulted in large increases in CD8 proliferation (Figure 8B).

Anti-PD-L1-IL5 fusion protein targets IL15 to PD-L1-expressing antigen presenting cells and increases proliferation and activation of responding CD8 cells

[0080] Anti-PD-L1 antibody and IL15 fusion protein was constructed by linking the Fc domain of the antibody to the sushi-domain of IL15R and to IL15 molecule itself. The fusion of the IL15R α sushi domain, IRD-11 exone3, linker and IL15 (designated "SD15") is provided as SEQ ID NO:261. SD15 was appended to the heavy chain c-terminal of conventional IgG. The fusion

protein with IL15R α sushi domain, IRD-11 exone3, linker and IL15 was appended to the heavy chain c-terminal of tcc λ D7 variable domain and IgG1 C_H1-C_H2-C_H3 variable domain (SEQ ID NO:262). The construct also included a K to S replacement at the end of the IgG1 heavy chain (1) to diminish the possibility of "G-K" cleavage; (2) to add the cloning site (BamHI) to the vector.

[0081] The light chain is that of a conventional antibody. Both the light chain and fusion heavy chain with or without LALA mutant were inserted to Dyax pBh1 vector for expression.

[0082] This fusion molecule is designate anti-PD-L1-sushi domain-IL15 or anti-PD-L1-SD15. A different version of the fusion protein where IL15 was linked to the Fc instead of the sushi domain was also constructed, and as this fusion protein did not have IL15 functional activity we used this protein as negative control in some assays (termed anti-PD-L1-SD15neg).

[0083] No significant change was observed when binding of anti-PD-L1-SD15 fusion proteins were compared to anti-PD-L1 antibodies in solid-phase PD-L1Fc binding ELISA assay (Figure 9A). Some changes in binding affinity to activated CD4 cells expressing PD-L1 was observed when binding of anti-PD-L1-SD15 proteins were compared to their respective original anti-PD-L1 antibodies (Figure 9B). Anti-PD-L1-SD15 proteins have lower affinity to cells expressing PD-L1 when compared to their respective anti-PD-L1 antibodies; although, there might be differences in binding of the secondary antibody to the bound anti-PD-L1-SD15 versus bound anti-PD-L1 on the surface of cells.

[0084] To evaluate the function of IL15 of anti-PD-L1-SD15 fusion proteins, PBMC isolated from whole blood was cultured in the presence of either anti-PD-L1-SD15 fusion proteins or IL15. No other stimulations were added to the cultures. Anti-PD-L1-SD15 fusion proteins increased NK cell number (Fig. 10A), increased CD8 proliferation (Fig. 10B) and activation (measured by % of granzymeB positive CD8, Fig. 10C) similarly as IL15. No significant increase in CD4 numbers were observed for all cultures (Fig. 10D).

[0085] To assess anti-PD-L1-SD15 activity on CD8, these fusion proteins were added to CD8 cultures in the presence of either α CD3 or α CD3 and PDL1Fc coated beads. Anti-PD-L1-SD15 increased CD8 proliferation significantly when PDL1Fc was present on the antigen presenting cells, α CD3 and PDL1Fc coated beads in this case (Figure 11A, no PD-L1Fc versus Figure 11B, with PD-L1Fc on the beads). Moreover, significant increase of CD8 activation was also observed. cD7-SD15 lowers the effective dose needed to activate CD8 as measured by increase in % of granzymeB positive CD8 cells (Figure 12A) and IFN γ secretion (Figure 12B) by about ten-fold. cD7-SD15 also increases maximum level of CD8 activation when compared to IL15 (Figure 12A and B). When compared to addition of anti-PD-L1 antibody plus free IL15, the anti-PD-L1-SD15 fusion protein increased CD8 proliferation to a level higher than the combination added separately (Figure 12C). These properties of anti-PD-L1-SD15 fusion protein will be beneficial in the setting of immunotherapy as lower doses of anti-PD-L1-SD15 fusion protein can be used to achieve a higher level of CD8 activation and proliferation. The high amplified response of CD8 to anti-PD-L1-SD15 fusion protein in cases where the antigen

presenting cells express PD-L1 will be advantageous in achieving selective CD8 activation.

Cytotoxicity of anti-PD-L1-IL15 fusion protein

[0086] To determine whether anti-PD-L1-SD15 fusion protein will increase IL15 induced cytotoxicity of CD8 T cells to PD-L1 expressing tumor cells, CD8 T cells were co-cultured with human PD-L1 expressing MAD-MB-231 tumor cells in the presence of anti-PD-L1-SD15 fusion protein or anti-KLH-SD15, which has no binding activity to PD-L1 expressing tumor cells, for 7 days prior to the measurement of tumor cell death. Human CD8 T cells and the tumor cells were co-cultured in IMDM supplemented with 10% FBS for 7 days. Tumor cell killing activity was assessed by the measurement of the number of dead tumor cells stained by Viability Dye eFluor 780 in FACS. The CD8 T cell mediated cytotoxicity of MDA-MB-231 was significantly enhanced by anti-PD-L1-SD15 fusion protein in comparison to the treatment with anti-KLH-SD15 in the co-culture (Figure 15). Moreover, PD-L1-SD15 fusion protein cD7-SD15 significantly increased the survival rate of mice bearing PD-L1 expressing tumor cells in the tumor model of mice intravenously injected with murine CT26 colon tumor cells in comparison to the mice treated with vehicle or PD-L1-SD15 fusion protein sD7-SD15, which does not have binding activity to murine PD-L1 (Figure 16). These results indicate that the targeting IL15 stimulated immunological effector cells to PD-L1 overexpressed tumor sites by the bifunctional anti-PD-L1-SD15 fusion protein has advantage to enhance antitumor immunity while minimize side effects. This type of bifunctional antibody cytokine fusion proteins has potential as novel immunomodulatory therapeutics to achieve greater antitumor efficacy in the control of tumor progression.

Affinity Maturation

[0087] Variants of the tccλD7 heavy chain were produced by introducing amino acid substitutions at three of the methionine positions in CDR-1H and screening for improved affinity. More particularly, a library containing about 1×10^8 variants of CDRH1 of tccλD7 was generated in which the first, second and fourth methionine positions were simultaneously varied. The library was panned on recombinant human PDL1-Fc (PDL1 ECD and human Fc fusion protein, Q9NZQ7) or murine PDL1-Fc (Q9EP73) which were immobilized on immune-tubes for four rounds. The ELISA positive clones from rounds 3 and 4 were sequenced. The unique clones were compared by competition ELISA. Table 4 shows the amino acid substitutions observed in 25 variants obtained from the screen, with SEQ ID NOs: for the affinity matured CDR-1H sequences and heavy chain variable domains containing the CDRs. The amino acid sequences of these variants are also set forth the sequence listing as indicated in Table 1.

Table 4 - CDR-H1 sequences of affinity matured variants of tccλD7.												
											SEQ ID NO	
											CDR-1H	VH
tccλD7	G	F	T	F	S	M	Y	M	M	M		
#101	-	-	-	-	-	A	-	A	-	A	264	265
#102	-	-	-	-	-	A	-	R	-	F	266	267
#103	-	-	-	-	-	A	-	L	-	V	268	269
#104	-	-	-	-	-	A	-	V	-	F	270	271
#105	-	-	-	-	-	A	-	V	-	s	272	273
#106	-	-	-	-	-	G	-	L	-	V	274	275
#107	-	-	-	-	-	G	-	Q	-	L	276	277
#108	-	-	-	-	-	G	-	S	-	F	278	279
#109	-	-	-	-	-	G	-	W	-	A	280	281
#110	-	-	-	-	-	Q	-	L	-	Y	282	283
#111	-	-	-	-	-	Q	-	V	-	F	284	285
#112	-	-	-	-	-	Q	-	Y	-	Y	286	287
#113	-	-	-	-	-	S	-	L	-	S	288	289
#114	-	-	-	-	-	S	-	L	-	V	290	291
#115	-	-	-	-	-	S	-	L	-	T	292	293
#116	-	-	-	-	-	S	-	Q	-	V	294	295
#117	-	-	-	-	-	S	-	S	-	A	296	297
#118	-	-	-	-	-	S	-	V	-	F	298	299
#119	-	-	-	-	-	S	-	V	-	s	300	301
#120	-	-	-	-	-	S	-	V	-	Y	302	301
#121	-	-	-	-	-	S	-	Y	-	F	304	305
#122	-	-	-	-	-	S	-	Y	-	V	306	307
#123	-	-	-	-	-	Y	-	S	-	V	308	309
#124	-	-	-	-	-	W	-	L	-	A	310	311
#125	-	-	-	-	-	W	-	Q	-	S	312	313

[0088] Two variants, tccD7_#114 and tccD7_#102 (also respectively referred to herein as tccD7_#1 and tccD7_#2) were converted to IgG and also to an IgG form containing two Leu-Ala substitutions in the hinge region for reduced ADCC, as described elsewhere herein. The antibodies were expressed and purified for the further characterization. Improved binding to soluble PDL1 is shown in Fig. 17 for the two affinity matured variants. Fig. 18 shows the two variants blocked binding of human PD1 to human PDL1 (left panel) and blocked binding of

mouse PD1 to mouse PDL1 (right panel). The variants also demonstrated higher binding activity to MDA-MB-231 cells compared to the parent (Fig. 19).

[0089] The affinity matured variants were tested for their ability to promote production of Th1 cytokines IL2 and IFN γ . PBMC isolated from whole blood were stimulated with the super antigen Staphylococcus Enterotoxin B (SEB, 0.1 ug/mL) in the presence of anti-PD-L1 antibodies. Supernatants of PBMC cultured with SEB for 7 days were collected, and IFN γ and IL-2 were measured by ELISA. Significant increases in the levels of IFN γ and IL-2 were observed in cultures with the variants of anti-PD-L1 antibodies cD7#1 and #2 when compared to cD7 (Fig. 20).

[0090] Several fusion protein variants comprising a PD-L1 binding domain, an IL15R α sushi domain and IL15 were constructed. Certain constructs include a linker between the IL15R α sushi domain and the IL15 portion. In one construct, 11 amino acids of exon 3 present in the C-terminal of the IL15 receptor α sushi domain were replaced with "GS" linkers of various lengths. GS linkers include SGGSGGGSGGGSGGGGS (SEQ ID NO:324; 18 amino acids), SGGSGGGSGGGSGGGGSLQ (SEQ ID NO:314; 20 amino acids), SGGGSGGGSGGGSGGGSGGGG (SEQ ID NO:316; 25 amino acids), SGGGSGGGSGGGSGGGSGGGSGGGG (SEQ ID NO:318; 30 amino acids), SGGGSGGGSGGGSGGGSGGGSGGGSGGGG (SEQ ID NO:320; 40 amino acids), and SGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGG (SEQ ID NO:322; 50 amino acids) in constructs having SEQ ID NOS:325, 315, 317, 319, 321, and 323, respectively.

[0091] Fusion proteins were expressed in HEK293 cells, transiently or stably, and purified by protein A column chromatography according to manufacturers instructions. In certain experiments, to stabilize the association between the Ig heavy and light chain constant domains of the anti-PD-L1 portion of the molecule, the C-terminal serine of the lambda light chain was deleted, referred to herein by the designation "ds."

[0092] Fusion proteins containing the tcc λ D7 affinity matured variant #102 with the sushi domain and IL15 (SEQ ID NO:325) were tested for binding to MDA-MB-231 by flow cytometry. All demonstrated improved binding compared to the fusion protein containing tcc λ D7 (Fig. 21). The fusion proteins containing the tcc λ D7 affinity matured variant #102 were also confirmed to have stimulatory activity on IL15-responsive human megakaryoblastic leukemia cells. Cells were cultured with anti-PD-L1-SD15 fusion proteins in RPMI 1640 supplemented with 10% FBS and 20% conditioned medium of human bladder carcinoma 5637 cells for 48 hours. Cell proliferation was measured as Relative Luminescence Units (RLU) by CellTiter-Glo[®] Luminescent Cell Viability Assay (Fig. 22).

[0093] Analysis by size exclusion chromatography showed less than 5% aggregation (Fig. 24) and improved serum stability of the expressed fusion protein (Fig. 25).

SEQUENCE LISTING

[0094]

<110> Kadmon Corporation LLC

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<140> EP15736953.9

<141> 2015-01-15

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			20					25					30		

Met	Met	His	Met	Val	Arg	Gln	Ala	Pro	Glu	Thr	Glu	Leu	Glu	Met	Val
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<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 7

Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
 1 5 10

<210> 8

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 8

Gly Ala Ser Ala Arg Ala Ile
 1 5

<210> 9

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 9

Gln Gln Ser Tyr Ser Ile Pro Ile Thr

1 5
 <210> 10
 <211> 108
 <212> PRT
 <213> Artificial Sequence
 <220>
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<400> 10
 Asp Ile Gln Met Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ala Arg Ala Ile Gly Val Pro Asp Arg Phe Arg
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
 65 70 75 80
 Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ile Pro
 85 90 95
 Ile Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 11
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 <400> 11
 Pro Tyr Pro Met Trp
 1 5

<210> 12
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 12

Gly Phe Thr Phe Ser Pro Tyr
 1 5

<210> 13

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 13

Ser Ile Ser Pro Ser Gly Gly Phe Thr Phe Tyr Ala Asp Ser Val Lys
 1 5 10 15

Gly

<210> 14

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 14

Ser Pro Ser Gly Gly Phe
 1 5

<210> 15

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 15

Asp Arg Val Ser Trp Asn Asp Tyr Thr Gly Met Asp Val
 1 5 10

<210> 16

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 16

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 Pro Tyr
 20 25 30

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

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

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

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

Ala Arg Asp Arg Val Ser Trp Asn Asp Tyr Thr Gly Met Asp Val Trp
 100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 17

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 17

Arg Ala Ser Glu Ser Ile Gly Lys Phe Leu Asn
 1 5 10

<210> 18

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 18

Ser Ala Ser Ser Leu Gln Ser
 1 5

<210> 19

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 19

Gln Gln Ser Phe Asp Met Pro Ile Thr
 1 5

<210> 20

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 20

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 Glu Ser Ile Gly Lys Phe
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Thr Leu Leu Ile
 35 40 45

His Ser Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

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

Glu Asp Phe Thr Thr Tyr Phe Cys Gln Gln Ser Phe Asp Met Pro Ile
 85 90 95

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

<210> 21

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 21

Ala Tyr Ile Met Gly
 1 5

<210> 22

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 22

Gly Phe Thr Phe Ser Ala Tyr
1 5

<210> 23

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 23

Tyr Ile Ser Ser Ser Gly Gly Trp Thr Ala Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 24

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 24

Ser Ser Ser Gly Gly Trp
1 5

<210> 25

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 25

Asp Gln Asp Gly Tyr Asn Asp Phe Asp Tyr
1 5 10

<210> 26

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 26

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 Ala Tyr
 20 25 30

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

Ser Tyr Ile Ser Ser Ser Gly Gly Trp Thr Ala Tyr Ala Asp Ser Val
 50 55 60

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

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

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 27

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 27

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
 1 5 10

<210> 28

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 28

Ala Ala Ser Ser Leu Gln Ser
 1 5

<210> 29

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 29

Gln	Gln	Ser	Tyr	Ser	Thr	Pro	Arg	Thr
1				5				

<210> 30

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 30

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10						15	

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr
			20					25					30		

Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Asn	Leu	Leu	Ile
	35					40						45			

Tyr	Ala	Ala	Ser	Ser	Leu	Gln	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	Ser	Tyr	Ser	Thr	Pro	Arg
				85					90					95	

Thr	Phe	Gly	His	Gly	Thr	Lys	Val	Glu	Ile	Lys
			100					105		

<210> 31

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 31

Met	Tyr	Trp	Met	Ala
1			5	

<210> 32

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 32

Gly Phe Thr Phe Ser Met Tyr
1 5

<210> 33

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 33

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

Gly

<210> 34

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 34

Val Pro Ser Gly Gly Ile
1 5

<210> 35

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 35

Gln Val Arg Gly Gly Ala Phe Asp Ile
1 5

<210> 36

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 36

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 Met Tyr
 20 25 30

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

Ser Tyr Ile Val Pro Ser Gly Gly Ile Thr Leu Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Gln Val Arg Gly Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr
 100 105 110

Met Val Thr Val Ser Ser
 115

<210> 37

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 37

Gln Ala Ser His Asp Ile Ser Asn Tyr Leu Asn
 1 5 10

<210> 38

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 38

Asp Ala Ser Asn Leu Glu Thr
 1 5

<210> 39

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 39

Gln His Tyr Asp Asn Leu Pro Pro Ser
 1 5

<210> 40

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 40

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 Gln Ala Ser His Asp Ile Ser Asn Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Tyr Asp Asn Leu Pro Pro
 85 90 95

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

<210> 41

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 41

His Tyr Pro Met Val
 1 5

<210> 42

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 42

Gly	Phe	Thr	Phe	Ser	His	Tyr
1				5		

<210> 43

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 43

Trp	Ile	Gly	Ser	Ser	Gly	Gly	Phe	Thr	Met	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 44

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 44

Gly	Ser	Ser	Gly	Gly	Phe
1				5	

<210> 45

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 45

Asp	Ser	Phe	Glu	Asp	His	Tyr	Tyr	Met	Asp	Val
1				5					10	

<210> 46

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 46

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

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

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

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

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

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

Thr Arg Asp Ser Phe Glu Asp His Tyr Tyr Met Asp Val Trp Gly Lys
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 47

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 47

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp
 1 5 10 15

<210> 48

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 48

Leu Gly Ser Asn Arg Ala Ser
1 5

<210> 49

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 49

Met Gln Ala Leu Gln Thr Pro Leu Thr
1 5

<210> 50

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 50

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

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

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 51

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 51

Glu Tyr Val Met Ile
 1 5

<210> 52

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 52

Gly Phe Thr Phe Ser Glu Tyr
 1 5

<210> 53

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 53

Ser Ile Ser Ser Ser Gly Gly Phe Thr Trp Tyr Ala Asp Ser Val Lys
 1 5 10 15

Gly

<210> 54

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 54

Ser Ser Ser Gly Gly Phe
 1 5

<210> 55

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 55

Ala Arg Ala Pro Val Gly Ala Asp Ala Phe Asp Ile

1 5 10

<210> 56

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 56

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 Glu Tyr
 20 25 30

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

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

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

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

Ala Arg Ala Arg Ala Pro Val Gly Ala Asp Ala Phe Asp Ile Trp Gly
 100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
 115 120

<210> 57

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 57

Arg Ala Ser Gln Arg Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 58

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 58

Asn Ala Ala Ser Leu Trp Asn
1 5

<210> 59

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 59

Gln Gln Ser His Ser Ser Pro Tyr Thr
1 5

<210> 60

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 60

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 Arg Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35 40 45

Asp Asn Ala Ala Ser Leu Trp Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Thr Leu Met Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ser His Ser Ser Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Arg
100 105

<210> 61

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 61

Ser	Tyr	Glu	Met	His
1				5

<210> 62

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 62

Gly	Phe	Thr	Phe	Ser	Ser	Tyr
1				5		

<210> 63

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 63

Gly	Ile	Trp	Pro	Ser	Gly	Gly	Val	Thr	Leu	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 64

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 64

Trp	Pro	Ser	Gly	Gly	Val
1				5	

<210> 65

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 65

Phe Arg Thr Gln Pro Phe Asp Ile
1 5

<210> 66

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 66

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

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

Ser Gly Ile Trp Pro Ser Gly Gly Val Thr Leu Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Phe Arg Thr Gln Pro Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser
115

<210> 67

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 67

Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> 68

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 68

Ala	Ala	Ser	Thr	Leu	Gln	Ser
1				5		

<210> 69

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 69

His	Asn	Tyr	Asn	Ser	Ala	Leu	Thr
1			5				

<210> 70

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 70

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Asp	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	Pro	Gly	Lys	Val	Pro	Lys	Leu	Leu	Ile
		35					40					45			

Tyr	Ala	Ala	Ser	Thr	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	

Glu	Asp	Val	Ala	Thr	Tyr	Phe	Cys	His	Asn	Tyr	Asn	Ser	Ala	Leu	Thr
					85					90				95	

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

<210> 71
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 71
 Arg Tyr Gly Met Gly
 1 5

<210> 72
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 72
 Gly Phe Thr Phe Ser Arg Tyr
 1 5

<210> 73
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 73
 Ser Ile Ser Ser Ser Gly Gly Gln Thr Ser Tyr Ala Asp Ser Val Lys
 1 5 10 15

Gly

<210> 74
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 74
 Ser Ser Ser Gly Gly Gln
 1 5

<210> 75

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 75

Gly Gly Leu Trp Phe Gly Leu Asp Pro
 1 5

<210> 76

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 76

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 Arg Tyr
 20 25 30

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

Ser Ser Ile Ser Ser Ser Gly Gly Gln Thr Ser Tyr Ala Asp Ser Val
 50 55 60

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

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

Thr Arg Gly Gly Leu Trp Phe Gly Leu Asp Pro Trp Gly Gln Gly Thr
 100 105 110

Leu Val Thr Val Ser Ser
 115

<210> 77

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 77

Arg Ala Ser Gln Gly Ile Ser Thr Trp Leu Ala
1 5 10

<210> 78

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 78

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 79

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 79

Gln Gln Ala Asn Ser Phe Pro Ser Thr
1 5

<210> 80

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 80

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ser
85 90 95

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

<210> 81

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 81

Lys Tyr Val Met His
 1 5

<210> 82

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 82

Gly Phe Thr Phe Ser Lys Tyr
 1 5

<210> 83

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 83

Tyr Ile Ser Ser Ser Gly Gly Phe Thr Val Tyr Ala Asp Ser Val Lys
 1 5 10 15

Gly

<210> 84

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 84

Ser Ser Ser Gly Gly Phe

1 5

<210> 85

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 85

Val Phe Asp Ser Gly Asp Ala Phe Asp Ile
1 5 10

<210> 86

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 86

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

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

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

Ser Tyr Ile Ser Ser Ser Gly Gly Phe Thr Val Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Val Phe Asp Ser Gly Asp Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ser
115

<210> 87

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 87

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Asn Asn Tyr Leu
1 5 10 15

Ala

<210> 88

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 88

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 89

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 89

Gln Gln Tyr Tyr Ser Thr Pro Pro Thr
1 5

<210> 90

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 90

Asp Ile Gln Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Asn Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

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

Lys

<210> 91

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 91

Trp Tyr Pro Met His
1 5

<210> 92

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 92

Gly Phe Thr Phe Ser Trp Tyr
1 5

<210> 93

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 93

Ser Ile Ser Ser Ser Gly Gly Phe Thr Met Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 94

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 94

Ser Ser Ser Gly Gly Phe
1 5

<210> 95

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 95

Glu Gly Gly Tyr Ser Tyr Gly Pro Gly Asp Tyr
1 5 10

<210> 96

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 96

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 Trp Tyr
20 25 30

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

Ser Ser Ile Ser Ser Ser Gly Gly Phe Thr Met Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Lys Glu Gly Gly Tyr Ser Tyr Gly Pro Gly Asp Tyr Trp Gly Gln
100 105 110

Glu Thr Leu Val Thr Val Ser Ser

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 97

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 97

Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

<210> 98

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 98

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 99

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 99

Gln Gln Ala Asn Ser Phe Pro Tyr Thr
1 5

<210> 100

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 100

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
85 90 95

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

<210> 101

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 101

Trp Tyr Pro Met Thr
1 5

<210> 102

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 102

Gly Phe Thr Phe Ser Trp Tyr
1 5

<210> 103

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 103

Ser Ile Gly Ser Ser Gly Gly Phe Thr Leu Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

-

<210> 104
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 104
 Ile Gly Ser Ser Gly Gly Phe
 1 5

<210> 105
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 105
 Asp Val Trp Gly Ile Ala Ala Pro Tyr Phe Asp Tyr
 1 5 10

<210> 106
 <211> 121
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 106
 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 Trp Tyr
 20 25 30

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

Ser Ser Ile Gly Ser Ser Gly Gly Phe Thr Leu Tyr Ala Asp Ser Val
 50 55 60

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

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

Thr Arg Asp Val Trp Gly Ile Ala Ala Pro Tyr Phe Asp Tyr Trp Gly

- - 100 - - 105 - - 110 - -
 Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120
 <210> 107
 <211> 11
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Human antibody library
 <400> 107
 Arg Ala Ser Gln Gly Ile Gly Ser Trp Leu Gly
 1 5 10
 <210> 108
 <211> 7
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Human antibody library
 <400> 108
 Ala Ala Ser Asn Leu Gln Ser
 1 5
 <210> 109
 <211> 9
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Human antibody library
 <400> 109
 Gln Gln Val Asn Asn Phe Pro Arg Ala
 1 5
 <210> 110
 <211> 107
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Human antibody library
 <400> 110
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15

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

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

Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Val Asn Asn Phe Pro Arg
85 90 95

Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

$\langle 210 \rangle$ 111

$\langle 211 \rangle$ 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

$\langle 400 \rangle$ 111

Trp Tyr Ile Met Ala
1 5

$\langle 210 \rangle$ 112

 $\langle 211 \rangle$ 7

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 112

Gly Phe Thr Phe Ser Trp Tyr
1 5

<210> 113

<211> 17

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Human antibody library

<400> 113

Tyr Ile Ser Ser Ser Gly Gly Phe Thr Ala Tyr Ala Asp Ser Val Lys

1 5 10 15

Gly

<210> 114
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 114
 Ser Ser Ser Gly Gly Phe
 1 5

<210> 115
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 115
 Ile Gly Gly Thr Asp Val Phe Asp Ile
 1 5

<210> 116
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 116
 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 Trp Tyr
 20 25 30

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

Ser Tyr Ile Ser Ser Ser Gly Gly Phe Thr Ala Tyr Ala Asp Ser Val
 50 55 60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Trp Trp Cys

----- 85 ----- 90 ----- 95 -----
 Ala Arg Ile Gly Gly Thr Asp Val Phe Asp Ile Trp Gly Gln Gly Thr
 100 105 110

Leu Val Thr Val Ser Ser
 115

<210> 117

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 117

Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
 1 5 10

<210> 118

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 118

Lys Ala Ser Ser Leu Glu Ser
 1 5

<210> 119

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 119

Gln Gln Ser Tyr Ser Ser Pro Trp Thr
 1 5

<210> 120

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 120

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Thr	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Trp
		20						25					30		

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

Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Thr	Ser	Leu	Leu	Pro
65					70					75					80

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

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

<210> 121

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 121

Trp	Tyr	Leu	Met	Lys
1				5

<210> 122

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 122

Gly	Phe	Thr	Phe	Ser	Trp	Tyr
1				5		

<210> 123

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 123

Tyr	Ile	Gly	Ser	Ser	Gly	Gly	Phe	Thr	Ala	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 124

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 124

Gly	Ser	Ser	Gly	Gly	Phe
1				5	

<210> 125

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 125

Glu	Asp	Asp	Phe	Gly	Ala	Met	Asp	Val
1				5				

<210> 126

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 126

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	Trp	Tyr
			20					25					30		

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

Ser	Tyr	Ile	Gly	Ser	Ser	Gly	Gly	Phe	Thr	Ala	Tyr	Ala	Asp	Ser	Val
	50					55					60				

Iys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asn	Asn	Ser	Iys	Asn	Thr	Leu	Tyr
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

65 70 75 80

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

Ala Arg Glu Asp Asp Phe Gly Ala Met Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 127

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 127

Arg Ala Ser Gln Thr Val Ser Lys Tyr Phe Asn
1 5 10

<210> 128

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 128

Ala Thr Ser Thr Leu Gln Ser
1 5

<210> 129

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 129

Gln Gln Ser Tyr Thr Thr Pro Trp Thr
1 5

<210> 130

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 130

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	Thr	Val	Ser	Lys	Tyr
		20						25					30		

Phe	Asn	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Glu	Ala	Pro	Lys	Leu	Leu	Ile
	35					40						45			

Tyr	Ala	Thr	Ser	Thr	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				

Ser	Gly	Tyr	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	

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

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

<210> 131

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 131

Ser	Tyr	Gln	Met	Gly
1			5	

<210> 132

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 132

Gly	Phe	Thr	Phe	Ser	Ser	Tyr
1				5		

<210> 133

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 133

Trp	Ile	Val	Pro	Ser	Gly	Gly	Phe	Thr	His	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 134

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 134

Val	Pro	Ser	Gly	Gly	Phe
1			5		

<210> 135

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 135

Asp	Ala	Gly	Tyr	Arg	Ser	Gly	Tyr	Tyr	Tyr	Tyr	Tyr	Gly	Met	Asp	Val
1				5					10					15	

<210> 136

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 136

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		

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

Ser Trp Ile Val Pro Ser Gly Gly Phe Thr His Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg Asp Ala Gly Tyr Arg Ser Gly Tyr Tyr Tyr Tyr Tyr Gly Met
 100 105 110

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

<210> 137

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 137

Arg Ala Ser Gln Ser Ile Ala Ser Tyr Leu Asn
 1 5 10

<210> 138

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 138

Gly Ala Ser Ser Leu Gln Ser
 1 5

<210> 139

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 139

Gln Gln Ser Tyr Gly Ile Ser Tyr Thr
 1 5

<210> 140

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 140

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ala	Ser	Tyr
			20					25					30		

Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			

Tyr	Gly	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				

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

Glu	Asp	Ile	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Gly	Ile	Ser	Tyr
				85					90					95	

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

<210> 141

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 141

His	Tyr	Pro	Met	Ser
1				5

<210> 142

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 142

Gly	Phe	Thr	Phe	Ser	His	Tyr
1				5		

<210> 143

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 143

Arg	Ile	Trp	Ser	Ser	Gly	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 144

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 144

Ile	Trp	Ser	Ser	Gly	Gly	Asn
1				5		

<210> 145

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 145

Gly	Gly	Tyr	Phe	Asp	Trp	Leu	Tyr	Pro	His	Asp	Tyr
1				5				10			

<210> 146

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 146

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

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

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

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

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

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

Ala Arg Gly Gly Tyr Phe Asp Trp Leu Tyr Pro His Asp Tyr Trp Gly
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 147

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 147

Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ser
 1 5 10

<210> 148

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 148

Ala Ala Ser Ser Leu Gln Ser
 1 5

<210> 149

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 149

Gln Gln Gly Asn Ser Phe Pro Pro Thr
 1 5

<210> 150

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 150

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ala Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Arg Glu Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro
 65 70 75 80

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

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 151

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 151

Arg Tyr Glu Met Leu
 1 5

<210> 152

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 152

Gly Phe Thr Phe Ser Arg Tyr

1 5

<210> 153

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 153

Ser	Ile	Tyr	Ser	Ser	Gly	Gly	Trp	Thr	Trp	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 154

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 154

Tyr	Ser	Ser	Gly	Gly	Trp
1			5		

<210> 155

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 155

His	Ser	Val	Thr	Gly	Val	Ala	Phe	Asp	Tyr
1			5					10	

<210> 156

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 156

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 Arg Tyr
 20 25 30

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

Ser Ser Ile Tyr Ser Ser Gly Gly Trp Thr Trp Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Arg His Ser Val Thr Gly Val Ala Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 157

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 157

Arg Ala Ser Gln Asn Ile Asp Thr Tyr Leu Ser
 1 5 10

<210> 158

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 158

Ala Ala Ser Ser Leu Gln Ser
 1 5

<210> 159

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 159

Gln Gln Ser Tyr Tyr Thr Pro Thr
 1 5

<210> 160

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 160

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 Asn Ile Asp Thr Tyr
 20 25 30

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50

55

60

Ser Arg 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 Ser Tyr Tyr Thr Pro Thr
 85 90 95

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

<210> 161

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 161

Pro Tyr Asp Met Gly
 1 5

<210> 162

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 162

Gly	Phe	Thr	Phe	Ser	Pro	Tyr
1				5		

<210> 163

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 163

Ser	Ile	Tyr	Ser	Ser	Gly	Gly	Trp	Thr	Lys	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 164

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 164

Tyr	Ser	Ser	Gly	Gly	Trp
1				5	

<210> 165

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 165

Asp	Asn	Trp	Asn	Asp	Gly	Ala	Phe	Asp	Val
1				5					10

<210> 166

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 166

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 Pro Tyr
 20 25 30

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

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

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

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

Ala Arg Asp Asn Trp Asn Asp Gly Ala Phe Asp Val Trp Gly Gln Gly
 100 105 110

Thr Met Val Thr Val Ser Ser
 115

<210> 167

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 167

Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
 1 5 10

<210> 168

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 168

Ala Ala Ser Arg Leu Gln Thr
 1 5

<210> 169

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 169

Gln Gln Ala Lys Thr Phe Pro Leu Thr
1 5

<210> 170

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 170

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

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

Phe Ala Ala Ser Arg Leu Gln 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 Ser Ala Thr Tyr Tyr Cys Gln Gln Ala Lys Thr Phe Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Arg Val Glu Ile Lys
100 105

<210> 171

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 171

Phe Tyr Asp Met Ser
1 5

<210> 172

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 172

Gly Phe Thr Phe Ser Phe Tyr
1 5

<210> 173

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 173

Ser Ile Val Pro Ser Gly Gly Trp Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 174

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 174

Val Pro Ser Gly Gly Trp
1 5

<210> 175

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 175

Asp Ser Trp Asn Asp Gly Ala Ser Asp Ile
1 5 10

<210> 176

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 176

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

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

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

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

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

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

Ala Arg Asp Ser Trp Asn Asp Gly Ala Ser Asp Ile Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ser
115

<210> 177

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 177

Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

<210> 178

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 178

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 179

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 179

Gln	Gln	Ala	Asn	Ser	Phe	Pro	Phe	Thr
1				5				

<210> 180

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 180

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly
1				5					10					15	

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

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

Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asn	Ser	Leu	Gln	Pro
65					70					75				80	

Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ala	Asn	Ser	Phe	Pro	Phe
				85					90					95	

Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Phe	Lys
			100					105		

<210> 181

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 181

Pro	Tyr	Gly	Met	Arg
1			5	

- ~

<210> 182
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 182
 Gly Phe Thr Phe Ser Pro Tyr
 1 5

<210> 183
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 183
 Ser Ile Ser Pro Ser Gly Gly Asn Thr Asp Tyr Ala Asp Ser Val Lys
 1 5 10 15

Gly

<210> 184
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 184
 Ser Pro Ser Gly Gly Asn
 1 5

<210> 185
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Human antibody library

<400> 185
 Arg Ala Ser His Ser Val Ser Ser Asp Tyr Leu Ala
 1 5 10

<210> 186

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 186

Ile	Arg	Tyr	Cys	Gly	Ser	Ala	Tyr	Cys	Tyr	Thr	Asp	Ala	Phe	Asp	Ile
1				5					10					15	

<210> 187

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 187

Ser	Gly	Glu	Lys	Leu	Gly	Asp	Arg	Tyr	Val	Ser
1				5					10	

<210> 188

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> from human Fab library

<400> 188

His	Asp	Lys	Lys	Arg	Pro	Pro
1				5		

<210> 189

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 189

Gln	Ala	Trp	Asp	Ser	Pro	Thr	Glu	Val
1				5				

<210> 190

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 190

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

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

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

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

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

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

Phe	Gly	Pro	Gly	Thr	Lys	Leu	Thr	Val	Leu	Ser	Gln	Pro
			100					105				

<210> 191

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 191

Met	Tyr	Asp	Met	Ala
1				5

<210> 192

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> from human antibody library

<400> 192

Gly	Phe	Thr	Phe	Ser	Met	Tyr
1				5		

<210> 193

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 193

Gly	Ile	Trp	Pro	Ser	Gly	Gly	Pro	Thr	Met	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 194

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 194

Trp	Pro	Ser	Gly	Gly	Pro
1			5		

<210> 195

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 195

Gly	Tyr	Ser	Tyr	Gly	Asp	Ala	Leu	Asp	Tyr
1				5				10	

<210> 196

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 196

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	Met	Tyr
			20					25					30		

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

Ser Gly Ile Trp Pro Ser Gly Gly Pro Thr Met Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Gly Gly Tyr Ser Tyr Gly Asp Ala Leu Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 197

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 197

Ser Gly Thr Ser Ser Asn Ile Gly Arg Asn Tyr Val Ser
 1 5 10

<210> 198

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 198

Asp Asp Arg Asn Arg Pro Ser
 1 5

<210> 199

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 199

Gly Thr Trp Asp Thr Ser Leu Ser Val Val Val
 1 5 10

<210> 200

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 200

Gln	Ser	Ala	Leu	Thr	Gln	Pro	Pro	Ser	Ala	Ser	Gly	Ser	Pro	Gly	Gln
1				5					10					15	

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

Tyr	Val	Ser	Trp	Tyr	Arg	His	Leu	Pro	Gly	Thr	Ala	Pro	Lys	Leu	Leu
		35					40					45			

Ile	Tyr	Asp	Asp	Arg	Asn	Arg	Pro	Ser	Gly	Ile	Val	Asp	Arg	Phe	Ser
	50					55						60			

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

Thr	Gly	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gly	Thr	Trp	Asp	Thr	Ser	Leu
				85					90					95	

Ser	Val	Val	Val	Phe	Gly	Gly	Gly	Thr	Lys	Val	Thr	Val	Leu	Ser	Gln
			100					105					110		

Pro

<210> 201

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 201

Glu	Tyr	Arg	Met	Ile
1				5

<210> 202

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 202

Gly	Phe	Thr	Phe	Ser	Glu	Tyr
1				5		

<210> 203

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 203

Gly	Ile	Tyr	Pro	Ser	Gly	Gly	Trp	Thr	Asn	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 204

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 204

Tyr	Pro	Ser	Gly	Gly	Trp
1				5	

<210> 205

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 205

Ile	Gly	Gly	Ala	Asn	Ala	Phe	Asp	Ile
1				5				

<210> 206

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 206

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

[illegible]

<210> 207

<211> 14

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Human antibody library

<400> 207

Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 208

 $\langle 211 \rangle$ 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 208

Glu Val Ser Asn Arg Pro Ser
1 5

<210> 209

$\langle 211 \rangle$ 11

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Human antibody library

<400> 209

Ser Ser Tyr Thr Ser Gly Ser Thr Arg Tyr Val
1 5 10

<210> 210

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 210

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 Ile 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 Glu 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 Gly
85 90 95

Ser Thr Arg Tyr Val Phe Gly Pro Gly Thr Lys Val Thr Val Leu Gly
100 105 110

Gln Pro

<210> 211

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 211

Lys Tyr Arg Met Ala
1 5

<210> 212

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 212

Gly Phe Thr Phe Ser Lys Tyr
1 5

<210> 213

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 213

Tyr Ile Tyr Pro Ser Gly Gly Phe Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 214

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 214

Tyr Pro Ser Gly Gly Phe
1 5

<210> 215

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 215

Asp Ile Gly Gln Trp Leu Phe Val Phe Asp Tyr
1 5 10

<210> 216

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 216

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

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

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

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

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

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

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

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 217

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 217

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 218

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 218

Asp Val Ser Asn Arg Pro Ser
1 5

<210> 219

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 219

Ser	Ser	Tyr	Thr	Asn	Thr	Ile	Thr	Val	Val
1				5					10

<210> 220

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 220

Gln	Ser	Glu	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	Asn	Thr
				85					90					95	

Ile	Thr	Val	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln
			100					105					110		

Pro

<210> 221

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 221

Lys	Tyr	Asp	Met	Tyr
1				5

<210> 222

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 222

Gly	Phe	Thr	Phe	Ser	Lys	Tyr
1				5		

<210> 223

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 223

Gly	Ile	Trp	Pro	Ser	Gly	Gly	Leu	Thr	Met	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 224

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 224

Trp	Pro	Ser	Gly	Gly	Leu
1				5	

<210> 225

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 225

Asp	Gly	Val	Val	Gly	Gly	Ser	Tyr	Ala	Phe	Asp	Ile
1				5						10	

<210> 226

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 226

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

<210> 227

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 227

Ser Gly Ala Ser Ser Asn Leu Gly Arg Asn Thr Val Asn

1 5 10

<210> 228

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 228

Thr Asn Asp His Arg Pro Ser
1 5

<210> 229

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 229

Ala Ala Trp Asp His Ser Leu Asn Gly Tyr Val
1 5 10

<210> 230

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 230

Gln Ser Ala Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

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

Thr Val Asn Trp Tyr Gln Gln Val Pro Gly Ser Ala Pro Lys Leu Leu
35 40 45

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

Gly Ser Arg Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp His Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Pro Gly Thr Lys Val Thr Val Leu Ser Gln
100 105 110

Pro

<210> 231

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 231

Ile Tyr Ser Met Asn

1

5

<210> 232

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 232

Gly Phe Thr Phe Ser Ile Tyr

1

5

<210> 233

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 233

Val Ile Tyr Pro Ser Gly Gly Phe Thr His Tyr Ala Asp Ser Val Lys

1

5

10

15

Gly

<210> 234

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 234

Tyr Pro Ser Gly Gly Phe

1

5

<210> 235

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 235

Gly	Arg	Lys	Thr	Thr	Val	Thr	Asp	Phe	Asp	Tyr
1				5					10	

<210> 236

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 236

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	Ile	Tyr
			20					25					30		

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

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

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

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

Ala	Arg	Gly	Arg	Lys	Thr	Thr	Val	Thr	Asp	Phe	Asp	Tyr	Trp	Gly	Gln
			100					105					110		

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser
		115				120	

<210> 237

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 237

Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr	Asn	Tyr	Val	Ser
1				5						10			

<210> 238

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 238

Glu	Val	Ser	His	Arg	Pro	Ser
1				5		

<210> 239

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 239

Ser	Ser	Tyr	Thr	Ser	Gly	Ser	Thr	Arg	Val
1				5				10	

<210> 240

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 240

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	Val
		35					40					45			

Met	Ile	Tyr	Glu	Val	Ser	His	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	Gly
				85					90					95	

Ser	Thr	Arg	Val	Phe	Gly	Gly	Gly	Thr	Lys	Val	Thr	Val	Leu	Gly	Gln
			100					105					110		

Pro

<210> 241

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 241

Met	Tyr	Met	Met	Met
1				5

<210> 242

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 242

Gly	Phe	Thr	Phe	Ser	Met	Tyr
1				5		

<210> 243

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 243

Ser	Ile	Tyr	Pro	Ser	Gly	Gly	Ile	Thr	Phe	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 244

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 244

Tyr	Pro	Ser	Gly	Gly	Ile
1				5	

<210> 245

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 245

Ile	Lys	Leu	Gly	Thr	Val	Thr	Thr	Val	Asp	Tyr
1			5						10	

<210> 246

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 246

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	Met	Tyr
		20						25					30		

Met	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	Ser	Val
	50					55					60				

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

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

Ala	Arg	Ile	Lys	Leu	Gly	Thr	Val	Thr	Thr	Val	Asp	Tyr	Trp	Gly	Gln
			100					105						110	

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser
		115				120	

<210> 247

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 247

Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Tyr Val Ser
 1 5 10

<210> 248

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 248

Asp Val Ser Asn Arg Pro Ser
 1 5

<210> 249

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 249

Ser Ser Tyr Thr Ser Ser Ser Thr Arg Val
 1 5 10

<210> 250

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 250

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 Ala 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 Gly Asp Gly Ala Asp Thr Thr Cys Ser Ser Thr Thr Ser Ser

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

<210> 251

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 251

Ala Tyr Arg Met Val
1 5

<210> 252

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 252

Gly Phe Thr Phe Ser Ala Tyr
1 5

<210> 253

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 253

Arg Ile Tyr Pro Ser Gly Gly Phe Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 254

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 254

```

Tyr Pro Ser Gly Gly Phe
1             5

```

<210> 255

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 255

```

Ala Leu Gly Pro Leu Ser Pro Leu Asp Ser
1             5             10

```

<210> 256

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 256

```

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 Ala Tyr
      20             25             30

```

```

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

```

```

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

```

```

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

```

```

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

```

```

Ala Arg Ala Leu Gly Pro Leu Ser Pro Leu Asp Ser Trp Gly Gln Gly
      100             105             110

```

```

Thr Leu Val Thr Val Ser Ser
      115

```

<210> 257

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 257

Thr	Gly	Thr	Ser	Ser	Asp	Val	Gly	Gly	Tyr	Asn	Tyr	Val	Ser
1				5					10				

<210> 258

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 258

Glu	Val	Ser	Asn	Arg	Pro	Ser
1				5		

<210> 259

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 259

Ser	Ser	Tyr	Arg	Ser	Gly	Asn	Thr	Leu	Val
1				5					10

<210> 260

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Human antibody library

<400> 260

Gln	Ser	Glu	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 Glu Val Ser Asn Arg Pro Ser Gly Val Pro Asp 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 Gly Asp Tyr Tyr Cys Ser Ser Tyr Arg Ser Gly
85 90 95

Asn Thr Leu Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Gln
100 105 110

Pro

<210> 261

<211> 209

<212> PRT

<213> Artificial Sequence

<220>

<223> SD15 fusion protein

<220>

<221> DOMAIN

<222> (1)..(61)

<223> human ILL-15Ra Sushi domain (NM-002189)

<220>

<221> DOMAIN

<222> (62)..(75)

<223> IRD-11exone3

<220>

<221> DOMAIN

<222> (76)..(95)

<223> linker

<220>

<221> DOMAIN

<222> (96)..(209)

<223> human IL-15 (NM-000585-3)

<400> 261

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
1 5 10 15

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

Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn Lys Ala
-- -- --

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

Ser

<210> 262

<211> 659

<212> PRT

<213> Artificial Sequence

<220>

<223> Fusion protein

<400> 262

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 Met Tyr
 20 25 30
 Met 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 Ser Val
 50 55 60

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

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

Ala Arg 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 Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

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

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

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

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

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

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

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

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

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

<210> 263

<211> 659

<212> PRT

<213> Artificial Sequence

<220>

<223> Fusion protein

<400> 263

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 Met Tyr
 20 25 30

Met 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 Ser Val
 50 55 60

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

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

Ala Arg 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 Arg Val Glu Pro Lys Ser Cys Asp
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
 225 230 235 240

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

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      530      535      540
Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu
545      550      555      560

Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val
      565      570      575

His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu
      580      585      590

Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val
      595      600      605

Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn
      610      615      620

Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn
625      630      635      640

Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile
      645      650      655

Asn Thr Ser

<210> 264
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 264
Ala Tyr Ala Met Ala
1      5

<210> 265
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic

<400> 265
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 Ala Tyr
      20      25      30

Ala Met Ala 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 Ser Val
50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 266

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 266

Ala Tyr Arg Met Phe
1 5

<210> 267

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 267

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 Ala Tyr
20 25 30

Arg Met Phe 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 Ser Val
50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 268

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 268

Ala Tyr Leu Met Val
 1 5

<210> 269

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 269

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 Ala Tyr
 20 25 30

Leu Met Val 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 Ser Val
 50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser

115

120

<210> 270

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 270

Ala	Tyr	Val	Met	Phe
1				5

<210> 271

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 271

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	Ala	Tyr
			20					25					30		

Val	Met	Phe	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	Ser	Val
	50					55					60				

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

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

Ala	Arg	Ile	Lys	Leu	Gly	Thr	Val	Thr	Thr	Val	Asp	Tyr	Trp	Gly	Gln
			100					105					110		

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser
		115				120	

<210> 272

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 272

Ala Tyr Val Met Ser
1 5

<210> 273

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 273

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

<210> 274

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 274

Gly Tyr Leu Met Val

1 5

<210> 275

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 275

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

<210> 276

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 276

Gly	Tyr	Gln	Met	Leu	1	5
-----	-----	-----	-----	-----	---	---

<210> 277

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 277

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 Gly Tyr
20 25 30

Gln Met Leu 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 Ser Val
50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 278

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 278

Gly Tyr Ser Met Phe
1 5

<210> 279

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 279

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 Gly Tyr
20 25 30

Ser Met Phe 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 Ser Val

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

<210> 280

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 280

Gly Tyr Trp Met Ala
 1 5

<210> 281

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 281

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 Gly Tyr
 20 25 30

Trp Met Ala 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 Ser Val
 50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln

100

105

110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 282

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 282

Gln Tyr Leu Met Tyr
1 5

<210> 283

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 283

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 Gln Tyr
20 25 30

Leu Met Tyr 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 Ser Val
50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 284

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 284

Gln Tyr Val Met Phe
1 5

<210> 285

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 285

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 Gln Tyr
20 25 30

Val Met Phe 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 Ser Val
50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 286

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 286

Gln Tyr Tyr Met Tyr
1 5

<210> 287

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 287

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 Gln Tyr
 20 25 30

Tyr Met Tyr 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 Ser Val
 50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser

115

120

<210> 288

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 288

Ser Tyr Leu Met Ser
 1 5

<210> 289

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 289

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

Leu Met Ser 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 Ser Val
 50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 290

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 290

Ser Tyr Leu Met Val
 1 5

<210> 291

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 291

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

Leu Met Val 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 Ser Val
50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 292

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 292

Ser Tyr Leu Met Thr Thr Cys Cys Leu Asp His Lys

1 5 10

<210> 293

$\langle 211 \rangle$ 120

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> synthetic

<400> 293

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

Leu Met Thr 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 Ser Val
50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 294

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 294

Ser Tyr Gln Met Val
1 5

<210> 295

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 295

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

Gln Met Val 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 Ser Val
50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

115 120
 <210> 296
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> synthetic

<400> 296
 Ser Tyr Ser Met Ala
 1 5

<210> 297
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> synthetic

<400> 297
 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
 Ser Met Ala 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 Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95
 Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 298
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>

<223> synthetic

<400> 298

Ser	Tyr	Val	Met	Phe
1				5

<210> 299

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 299

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		

Val	Met	Phe	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	Ser	Val
	50					55					60				

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

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

Ala	Arg	Ile	Lys	Leu	Gly	Thr	Val	Thr	Thr	Val	Asp	Tyr	Trp	Gly	Gln
			100					105					110		

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser
		115				120	

<210> 300

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 300

Ser	Tyr	Val	Met	Ser
1				5

<210> 301

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 301

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

Val Met Ser 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 Ser Val
 50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 302

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 302

Ser Tyr Val Met Tyr
 1 5

<210> 303

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 303

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

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

<210> 304

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 304

Ser Tyr Tyr Met Phe
 1 5

<210> 305

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 305

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

Tyr Met Phe 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 Ser Val
 50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser

115 120

<210> 306

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 306

Ser Tyr Tyr Met Val
 1 5

<210> 307

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 307

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

Tyr Met Val 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 Ser Val
 50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 308

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 308

Tyr Tyr Ser Met Val
 1 5

<210> 309

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 309

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 Tyr Tyr
 20 25 30

Ser Met Val 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 Ser Val
 50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 310

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 310

Trp Tyr Leu Met Ala

1 5

<210> 311

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 311

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	Trp	Tyr
		20						25					30		

Leu	Met	Ala	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	Ser	Val
50					55					60					

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

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

Ala	Arg	Ile	Lys	Leu	Gly	Thr	Val	Thr	Thr	Val	Asp	Tyr	Trp	Gly	Gln
		100					105						110		

Gly	Thr	Leu	Val	Thr	Val	Ser	Ser
	115					120	

<210> 312

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 312

Trp Tyr Gln Met Ser
1 5

<210> 313

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 313

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 Trp Tyr
20 25 30

Gln Met Ser 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 Ser Val
50 55 60

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

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

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 314

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 314

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

Gly Ser Leu Gln
20

<210> 315

<211> 198

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<220>

<221> DOMAIN

<222> (1)..(61)

<223> human IL-15Ra Sushi domain (NM-002189)

<220>

<221> DOMAIN

<222> (62)..(64)

<223> IRD-11exone3

<220>

<221> DOMAIN

<222> (65)..(84)

<223> linker1

<220>

<221> DOMAIN

<222> (85)..(198)

<223> human IL-15 (NM-000585-3)

<400> 315

Cys	Pro	Pro	Pro	Met	Ser	Val	Glu	His	Ala	Asp	Ile	Trp	Val	Lys	Ser
1				5					10					15	

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

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

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

Ser	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly
65				70					75					80	

Gly	Ser	Leu	Gln	Asn	Trp	Val	Asn	Val	Ile	Ser	Asp	Leu	Lys	Lys	Ile
			85						90					95	

Glu	Asp	Leu	Ile	Gln	Ser	Met	His	Ile	Asp	Ala	Thr	Leu	Tyr	Thr	Glu
		100						105					110		

Ser	Asp	Val	His	Pro	Ser	Cys	Lys	Val	Thr	Ala	Met	Lys	Cys	Phe	Leu
		115					120					125			

Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His
 130 135 140

Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser
 145 150 155 160

Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu
 165 170 175

Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln
 180 185 190

Met Phe Ile Asn Thr Ser
 195

<210> 316

<211> 25

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 316

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

Gly Gly Gly Gly Ser Gly Gly Gly Gly
 20 25

<210> 317

<211> 203

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

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<221> DOMAIN

<222> (1)..(61)

<223> human ILL-15Ra Sushi domain (NM-002189)

<220>

<221> DOMAIN

<222> (62)..(64)

<223> human IL-15Ra Sushi domain (NM-002189) IRD-11exone3

<220>

<221> DOMAIN

<222> (65)..(89)

<223> linker2

<220>

<221> DOMAIN

<222> (90)..(203)

<223> human IL-15 (NM-000585-3)

<400> 317

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser

1 5 10 15

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

<210> 318

<211> 30

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 318

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

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

<210> 319

<211> 208

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<220>

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<223> human ILL-15Ra Sushi domain (NM-002189)

<220>

<221> DOMAIN

<222> (62)..(64)

<223> IRD-11exone3

<220>

<221> DOMAIN

<222> (65)..(94)

<223> linker3

<220>

<221> DOMAIN

<222> (95)..(208)

<223> human IL-15 (NM-000585-3)

<400> 319

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
1 5 10 15

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

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

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

00 10 20 30
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Asn Trp
 85 90 95
 Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser
 100 105 110
 Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
 115 120 125
 Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
 130 135 140
 Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu
 145 150 155 160
 Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu
 165 170 175
 Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu
 180 185 190
 Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
 195 200 205

<210> 320

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 320

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

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

Gly Gly Gly Ser Gly Gly Gly Gly
 35 40

<210> 321

<211> 218

<212> PRT

<213> Artificial Sequence

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<223> synthetic

<220>

<221> DOMAIN

<222> (1)..(61)

<223> human ILL-15Ra Sushi domain (NM-002189)

<220>

<221> DOMAIN

<222> (62)..(64)

<223> IRD-11exone3

<220>

<221> DOMAIN

<222> (65)..(104)

<223> linker4

<220>

<221> DOMAIN

<222> (105)..(218)

<223> human IL-15 (NM-000585-3)

<400> 321

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
1 5 10 15

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

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

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
85 90 95

Gly Gly Gly Ser Gly Gly Gly Gly Asn Trp Val Asn Val Ile Ser Asp
100 105 110

Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr
115 120 125

Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met
130 135 140

Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp
145 150 155 160

Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn
165 170 175

Asp Thr Ser Ser Ser Glu Ser Met Thr Glu Ser Gly Ser Ser Ser Ser Ser Ser

Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys
 180 185 190

Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val
 195 200 205

His Ile Val Gln Met Phe Ile Asn Thr Ser
 210 215

<210> 322

<211> 50

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 322

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

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

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

Gly Gly
 50

<210> 323

<211> 228

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<220>

<221> DOMAIN

<222> (1)..(61)

<223> human ILL-15Ra Sushi domain (NM-002189)

<220>

<221> DOMAIN

<222> (62)..(64)

<223> IRD-11exone3

<220>

<221> DOMAIN

<222> (65)..(114)

<223> linker5

<220>

<221> DOMAIN

<222> (115)..(228)

<223> human IL-15 (NM-000585-3)

<400> 323

Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser
1 5 10 15

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

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

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
85 90 95

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp
115 120 125

Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp
130 135 140

Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu
145 150 155 160

Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr
165 170 175

Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly
180 185 190

Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys
195 200 205

Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe
210 215 220

Ile Asn Thr Ser
225

<210> 324

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 324

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

Gly Ser

<210> 325

<211> 646

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<220>

<221> DOMAIN

<222> (1)..(120)

<223> tccLD7-102 heavy chain variable domain

<220>

<221> DOMAIN

<222> (121)..(449)

<223> IgG1 CH1-CH2-CH3 domain

<220>

<221> DOMAIN

<222> (450)..(646)

<223> deSD15-20

<400> 325

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	Ala	Tyr
			20						25					30	

Arg	Met	Phe	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	Ser	Val
	50					55					60				

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95
 Ala Arg 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 Arg Val Glu Pro Lys Ser Cys Asp
 210 215 220
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 225 230 235 240
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 245 250 255
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 260 265 270
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 290 295 300
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 305 310 315 320
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 325 330 335
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 340 345 350
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
 355 360 365
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380
 Glu Ser Asn Gly Glu Pro Gly Asn Asn Thr Thr Thr Thr Thr Thr Val

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

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

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

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

Gly Ser Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
450 455 460

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
465 470 475 480

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
485 490 495

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
500 505 510

Arg Asp Ser Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
515 520 525

Gly Gly Gly Ser Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile
530 535 540

Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu
545 550 555 560

Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu
565 570 575

Leu Glu Leu Gln Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His
580 585 590

Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser
595 600 605

Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu
610 615 620

Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln
625 630 635 640

Met Phe Ile Asn Thr Ser
645

<210> 326

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<220>

<221> DOMAIN

<222> (1)..(113)

<223> VL

<220>

<221> DOMAIN

<222> (114)..(216)

<223> CL

<400> 326

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	Ala	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> 327

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<220>

<221> DOMAIN

<222> (1)..(113)

<223> VL

<220>

<221> DOMAIN

<222> (114)..(215)

<223> CL w/ C-terminal serine deleted

<400> 327

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 Ala 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

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140          150          160          170
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
          210          215

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<210> 328

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<220>

<221> VARIANT

<222> (1)..(1)

<223> residue is A G M Q S Y or W

<220>

<221> VARIANT

<222> (3)..(3)

<223> residue is A L M Q R S V W or Y

<220>

<221> VARIANT

<222> (5)..(5)

<223> residue is A F L M S T V or Y

<400> 328

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Xaa Tyr Xaa Met Xaa
1          5

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Patentkrav

1. Fusionsprotein, som omfatter:

(i) et første domæne, der omfatter et antistof mod PD-L1, hvor
5 antistoffet omfatter

(a) en CDR-1H af tung kæde, der omfatter SEQ ID NO: 121; en CDR-
2H af tung kæde, der omfatter SEQ ID NO: 123; en CDR-3H af tung
kæde, der omfatter SEQ ID NO: 125; en CDR-1L af let kæde, der
omfatter SEQ ID NO: 127; en CDR-2L af let kæde, der omfatter SEQ
10 ID NO: 128; og en CDR-3L af let kæde, der omfatter SEQ ID
NO: 129;

(b) en CDR-1H af tung kæde, der omfatter SEQ ID NO: 241, en CDR-
2H, der omfatter SEQ ID NO: 243, og en CDR-3H, der omfatter SEQ
ID NO: 245; og en CDR-1L af let kæde, der omfatter SEQ ID
15 NO: 247, en CDR-2L, der omfatter SEQ ID NO: 248, og en CDR-3L,
der omfatter SEQ ID NO: 249; eller

(c) en CDR-1H af tung kæde, der omfatter SEQ ID NO: 266, en CDR-
2H, der omfatter SEQ ID NO: 243, og en CDR-3H, der omfatter SEQ
ID NO: 245; og en CDR-1L af let kæde, der omfatter SEQ ID
20 NO: 247, en CDR-2L, der omfatter SEQ ID NO: 248, og en CDR-3L,
der omfatter SEQ ID NO: 249;

og hvor antistoffet binder til PD-L1 og blokerer dets
interaktion med PD-1,

(ii) et andet domæne, der binder til IL-15-receptor ("IL-15R"),
25 hvor det andet domæne omfatter IL-15 eller et IL-15R-bindende
fragment deraf, og

(iii) et IL-15-receptor-alfa-sushi-domæne.

2. Fusionsprotein ifølge krav 1, som yderligere omfatter en
30 fleksibel linker, der forbinder sushi-domænet af IL-15R-alfa til
IL-15 eller det IL-15R-bindende fragment, eventuelt hvor den
fleksible linker omfatter 15-20 aminosyrer, der overvejende er
serin og glycin.

3. Fusionsprotein ifølge krav 2, hvor fusionsproteinet
omfatter SEQ ID NO: 315, SEQ ID NO: 317, SEQ ID NO: 319, SEQ ID
35 NO: 321, SEQ ID NO: 323 eller SEQ ID NO: 261.

4. Fusionsprotein ifølge et hvilket som helst af kravene 1 til 3, hvor antistoffet mod PD-L1 omfatter en CDR-1H af tung kæde, der omfatter SEQ ID NO: 121; en CDR-2H af tung kæde, der omfatter SEQ ID NO: 123; en CDR-3H af tung kæde, der omfatter SEQ ID NO: 125; en CDR-1L af let kæde, der omfatter SEQ ID NO: 127; en CDR-2L af let kæde, der omfatter SEQ ID NO: 128; og en CDR-3L af let kæde, der omfatter SEQ ID NO: 129.

5. Fusionsprotein ifølge et hvilket som helst af kravene 1 til 3, hvor antistoffet mod PD-L1 omfatter et variabelt domæne af tung kæde, der er mindst 95 % identisk med SEQ ID NO: 126, og/eller et variabelt domæne af let kæde, der er mindst 95 % identisk med SEQ ID NO: 130.

6. Fusionsprotein ifølge krav 5, hvor antistoffet mod PD-L1 omfatter et variabelt domæne af tung kæde, der har sekvensen ifølge SEQ ID NO: 126, og et variabelt domæne af let kæde, der har sekvensen ifølge SEQ ID NO: 130.

7. Fusionsprotein ifølge et hvilket som helst af kravene 1 til 3, hvor antistoffet mod PD-L1 omfatter en CDR-1L af let kæde, der omfatter SEQ ID NO: 247, en CDR-2L, der omfatter SEQ ID NO: 248, og en CDR-3L, der omfatter SEQ ID NO: 249; og en CDR-1H af tung kæde, der omfatter SEQ ID NO: 241, en CDR-2H, der omfatter SEQ ID NO: 243, og en CDR-3H, der omfatter SEQ ID NO: 245.

8. Fusionsprotein ifølge et hvilket som helst af kravene 1 til 3, hvor antistoffet mod PD-L1 omfatter en CDR-1L af let kæde, der omfatter SEQ ID NO: 247, en CDR-2L, der omfatter SEQ ID NO: 248, og en CDR-3L, der omfatter SEQ ID NO: 249; og en CDR-1H af tung kæde, der omfatter SEQ ID NO: 266, en CDR-2H, der omfatter SEQ ID NO: 243, og en CDR-3H, der omfatter SEQ ID NO: 245.

9. Fusionsprotein ifølge et hvilket som helst af kravene 1 til 3, hvor antistoffet mod PD-L1 omfatter et variabelt domæne af tung kæde, der er mindst 85 % identisk med SEQ ID NO: 246,

og/eller et variabelt domæne af let kæde, der er mindst 85 % identisk med SEQ ID NO: 250.

- 5 10. Fusionsprotein ifølge krav 9, hvor antistoffet mod PD-L1 omfatter et variabelt domæne af tung kæde, der har sekvensen ifølge SEQ ID NO: 246 eller SEQ ID NO: 267, og et variabelt domæne af let kæde, der har sekvensen ifølge SEQ ID NO: 250.
- 10 11. Fusionsprotein ifølge et hvilket som helst af kravene 4 eller 6 til 10, hvor fusionsproteinet omfatter SEQ ID NO: 261.
12. Fusionsprotein ifølge et hvilket som helst af kravene 1 til 11 til anvendelse til behandling af cancer.
- 15 13. Nukleinsyremolekyle, som omfatter en nukleotidsekvens, der koder for fusionsproteinet ifølge et hvilket som helst af kravene 1-11.

DRAWINGS

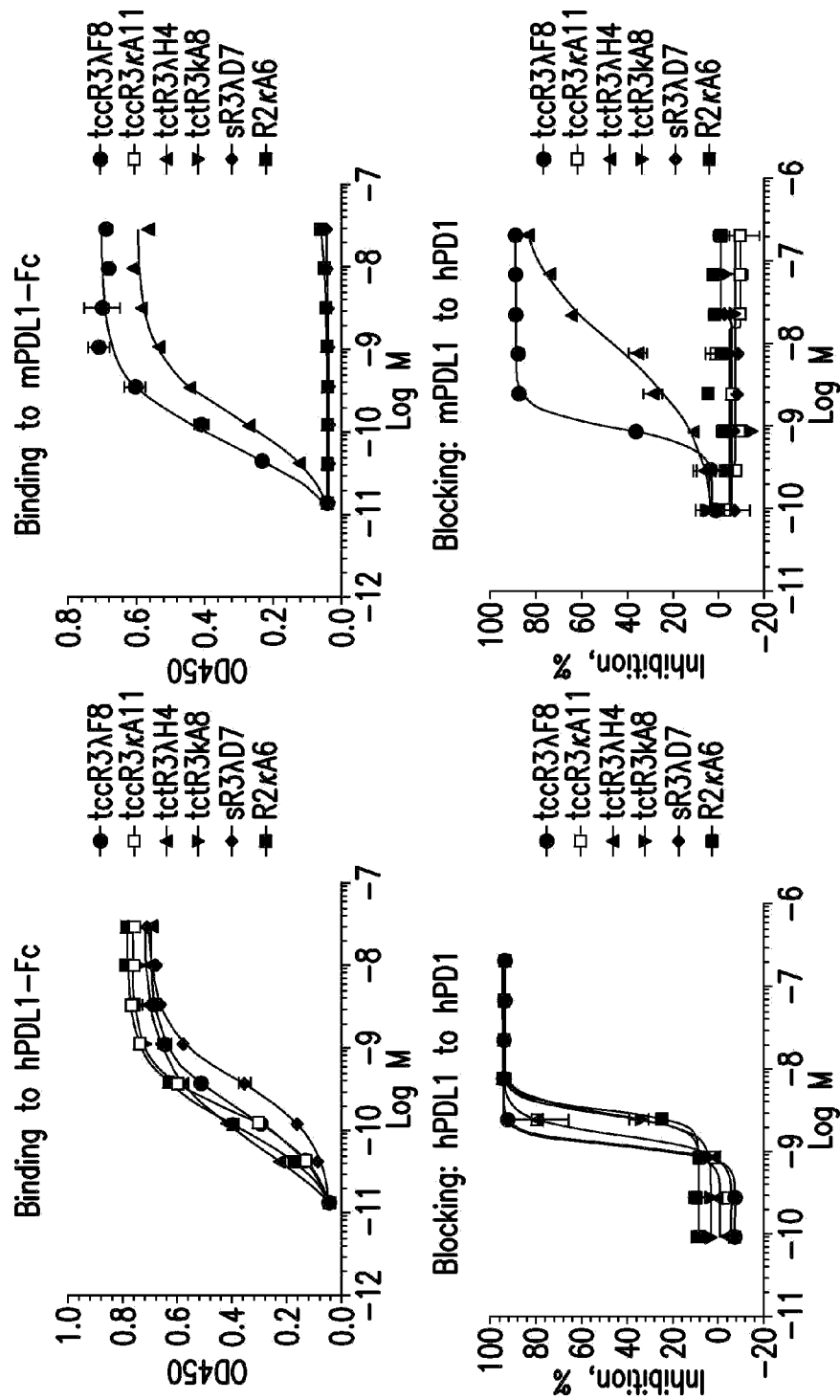


FIG. 1

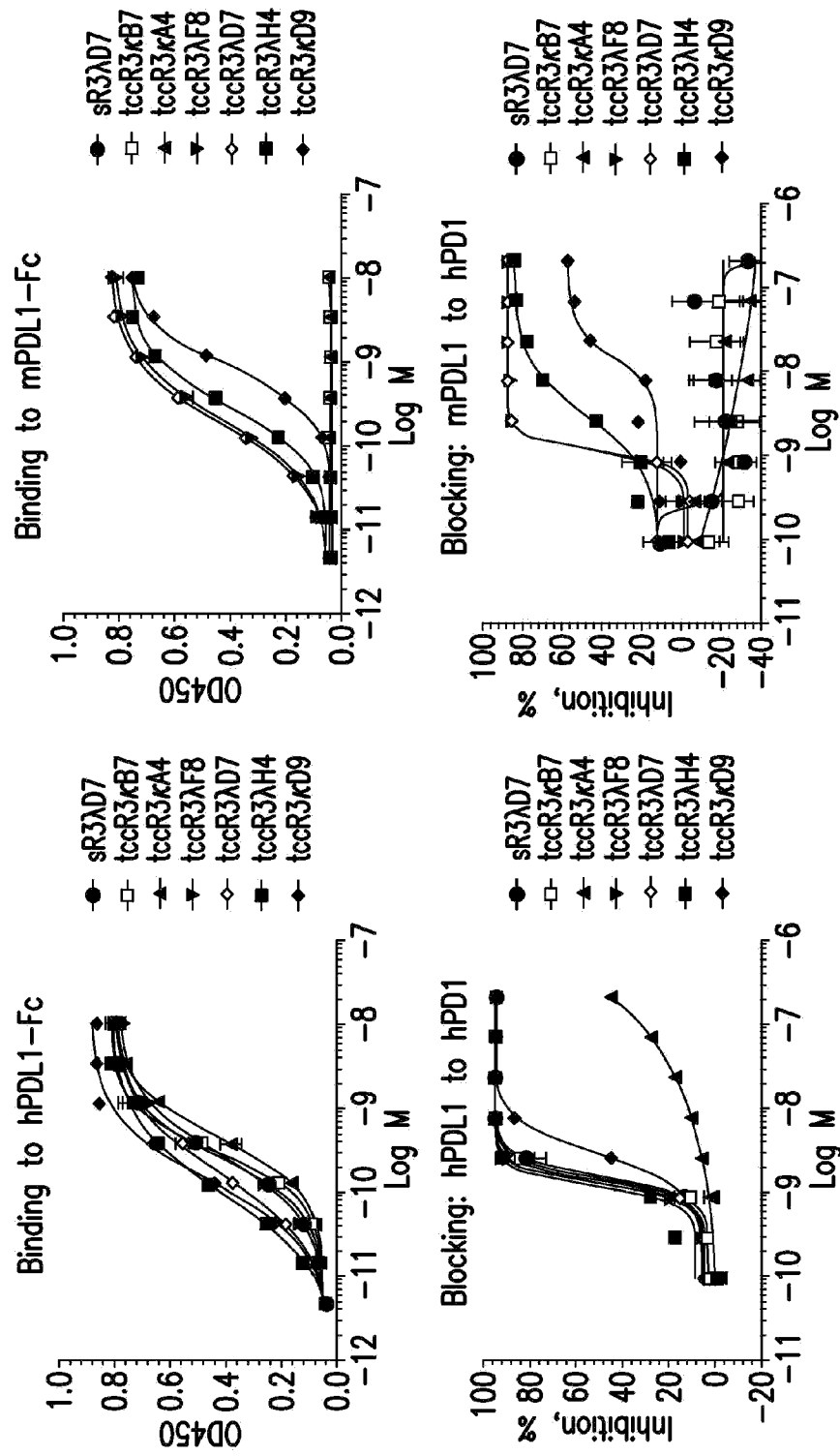


FIG. 2

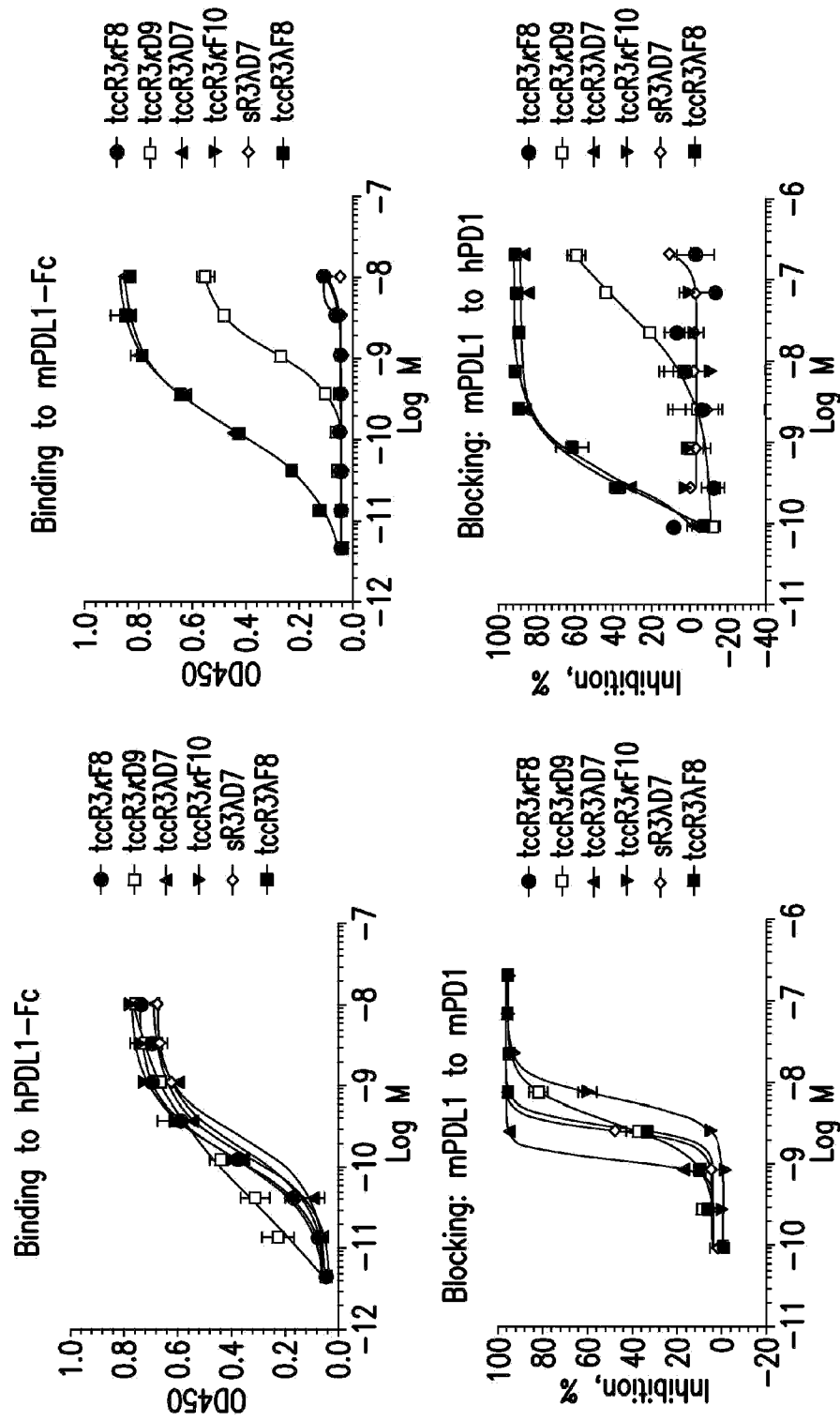


FIG. 3

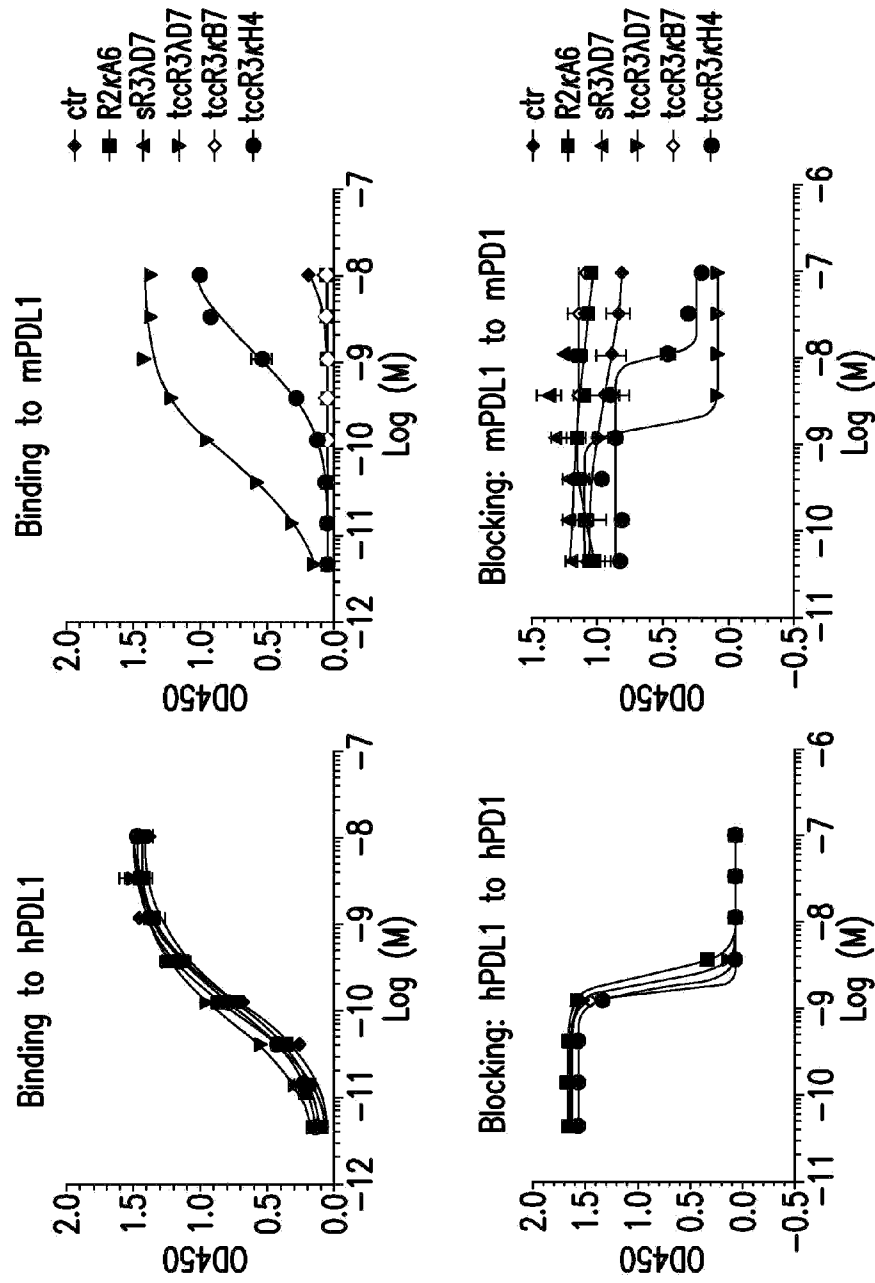


FIG. 4

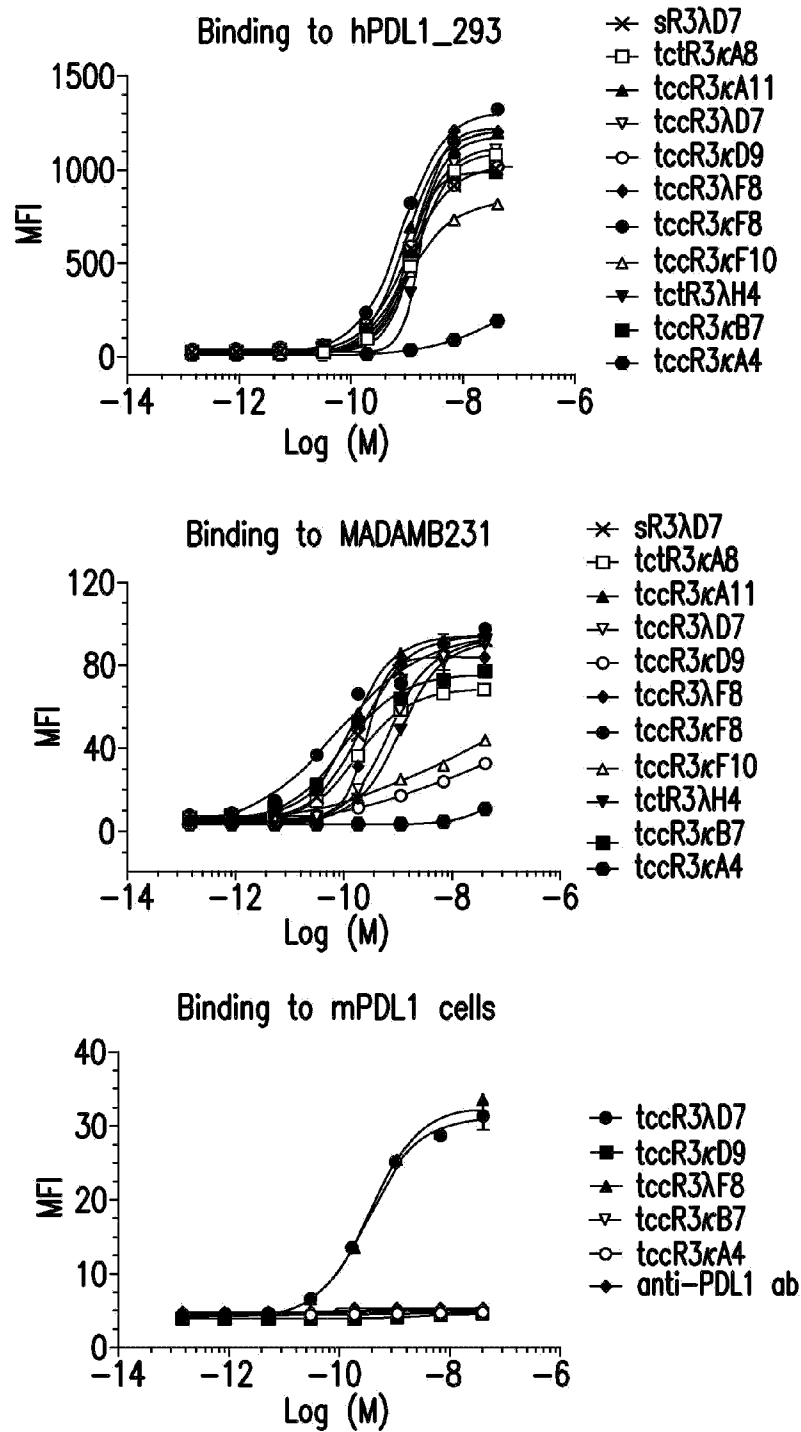


FIG. 5

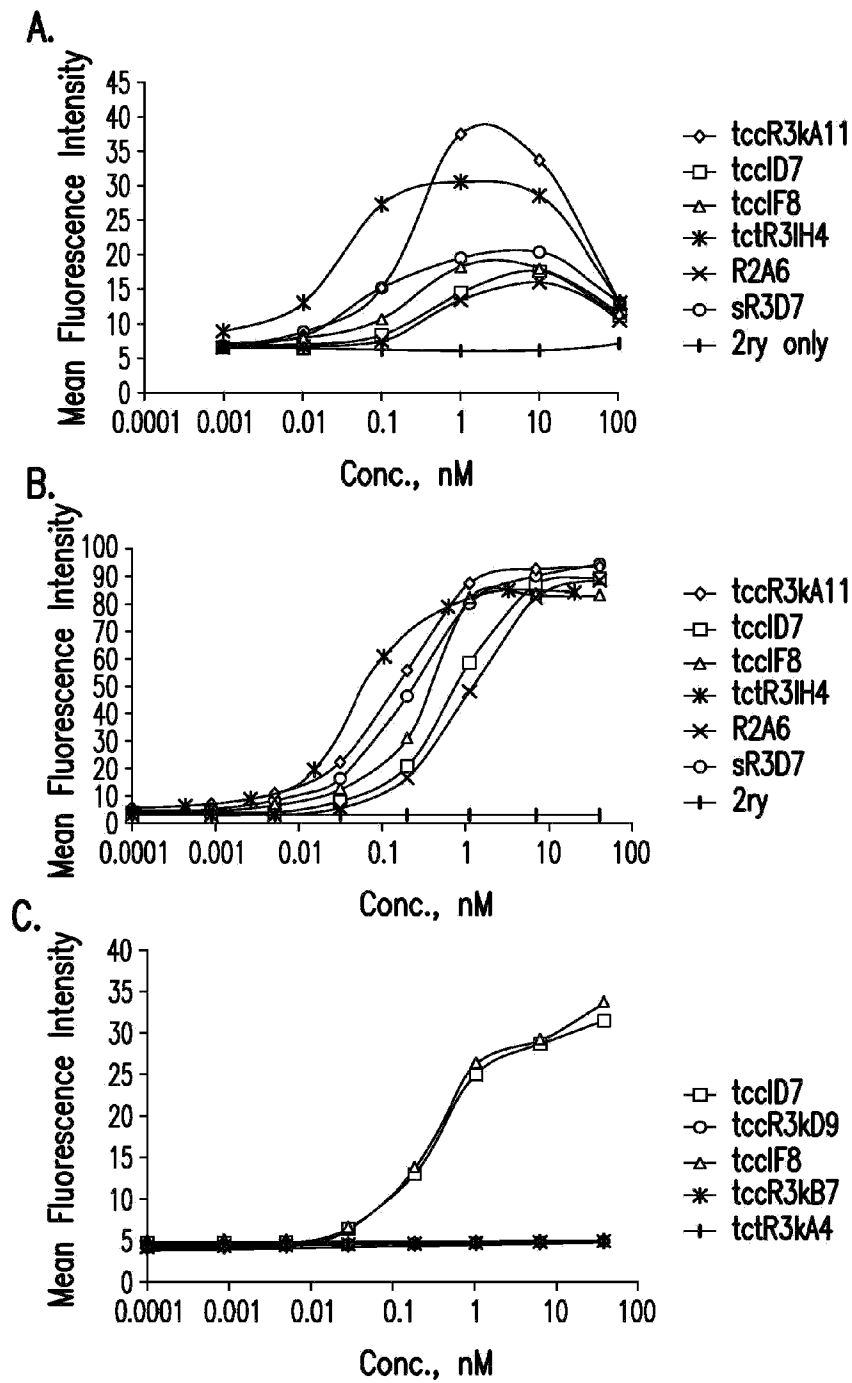


FIG. 6

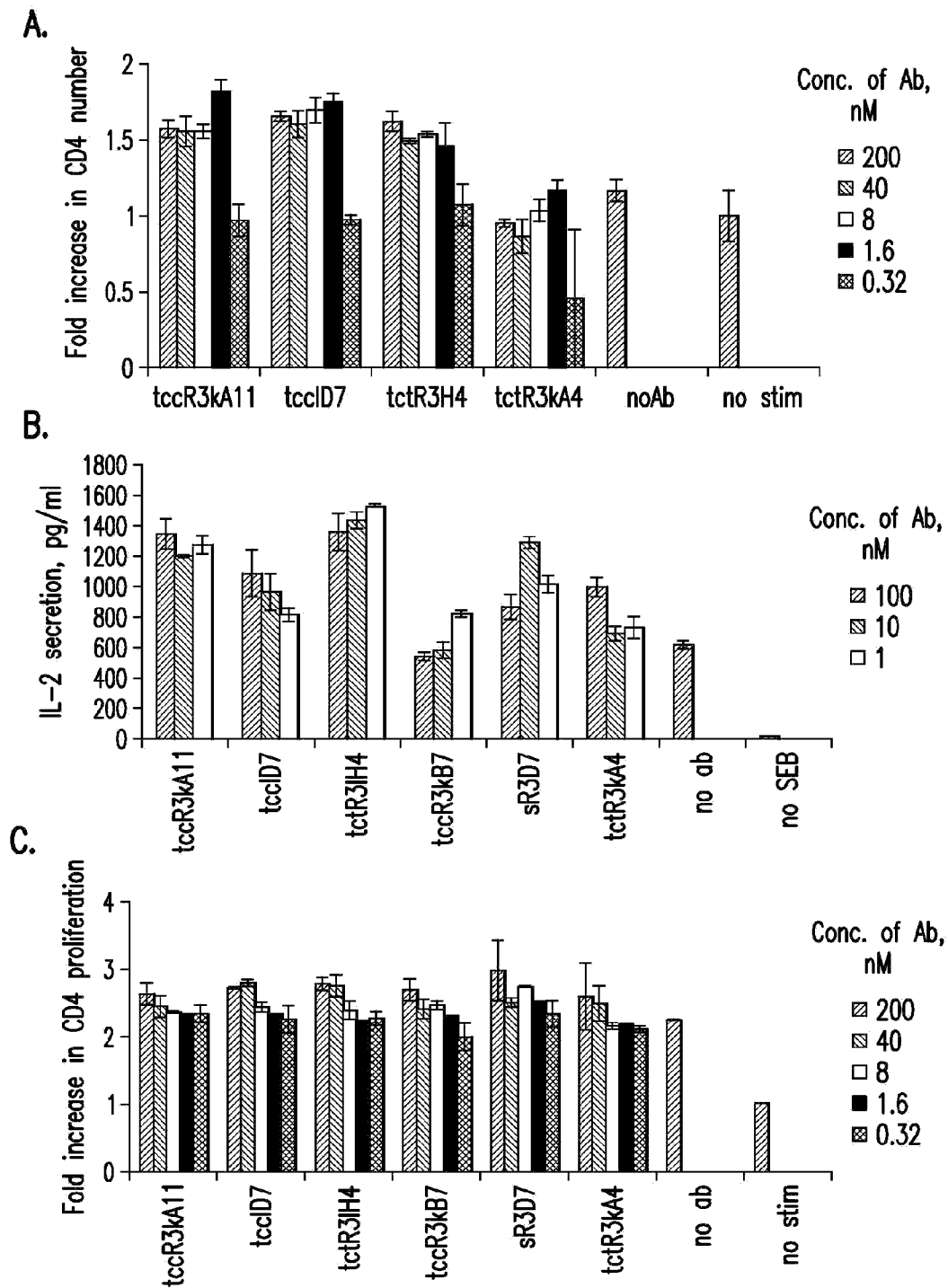
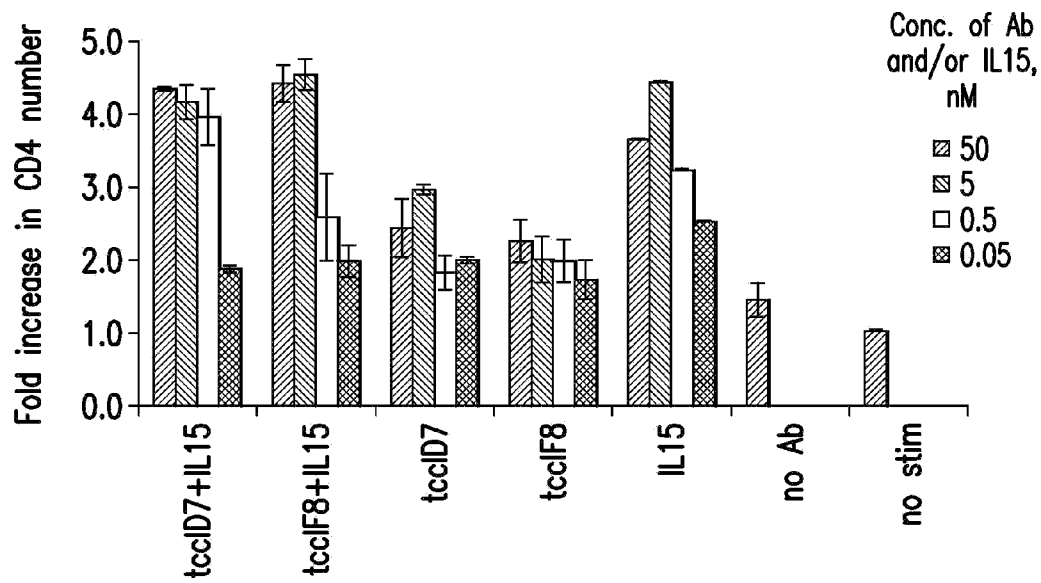


FIG. 7

A.



B.

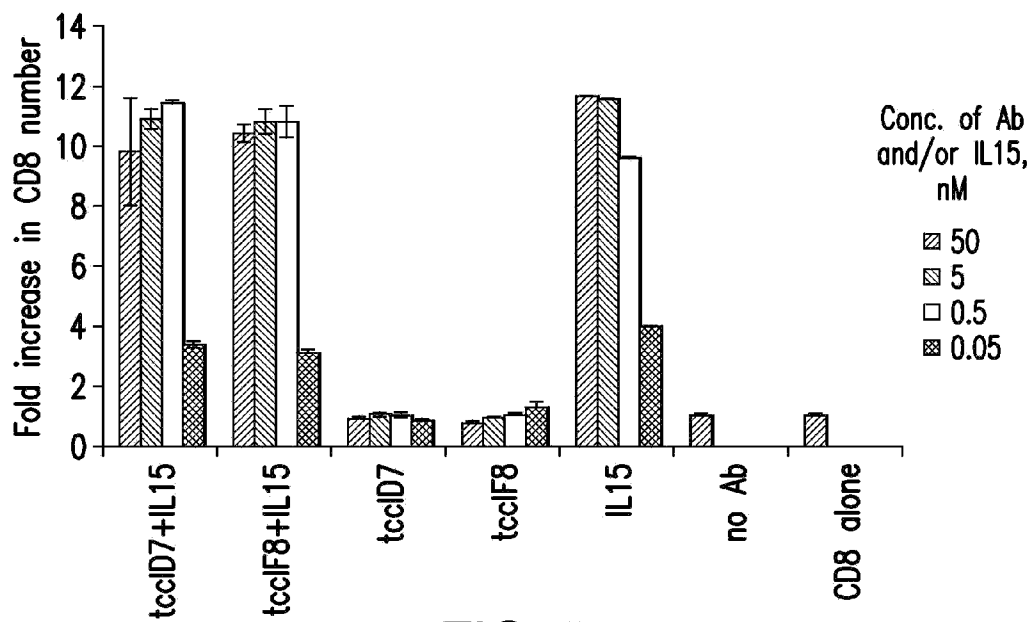


FIG. 8

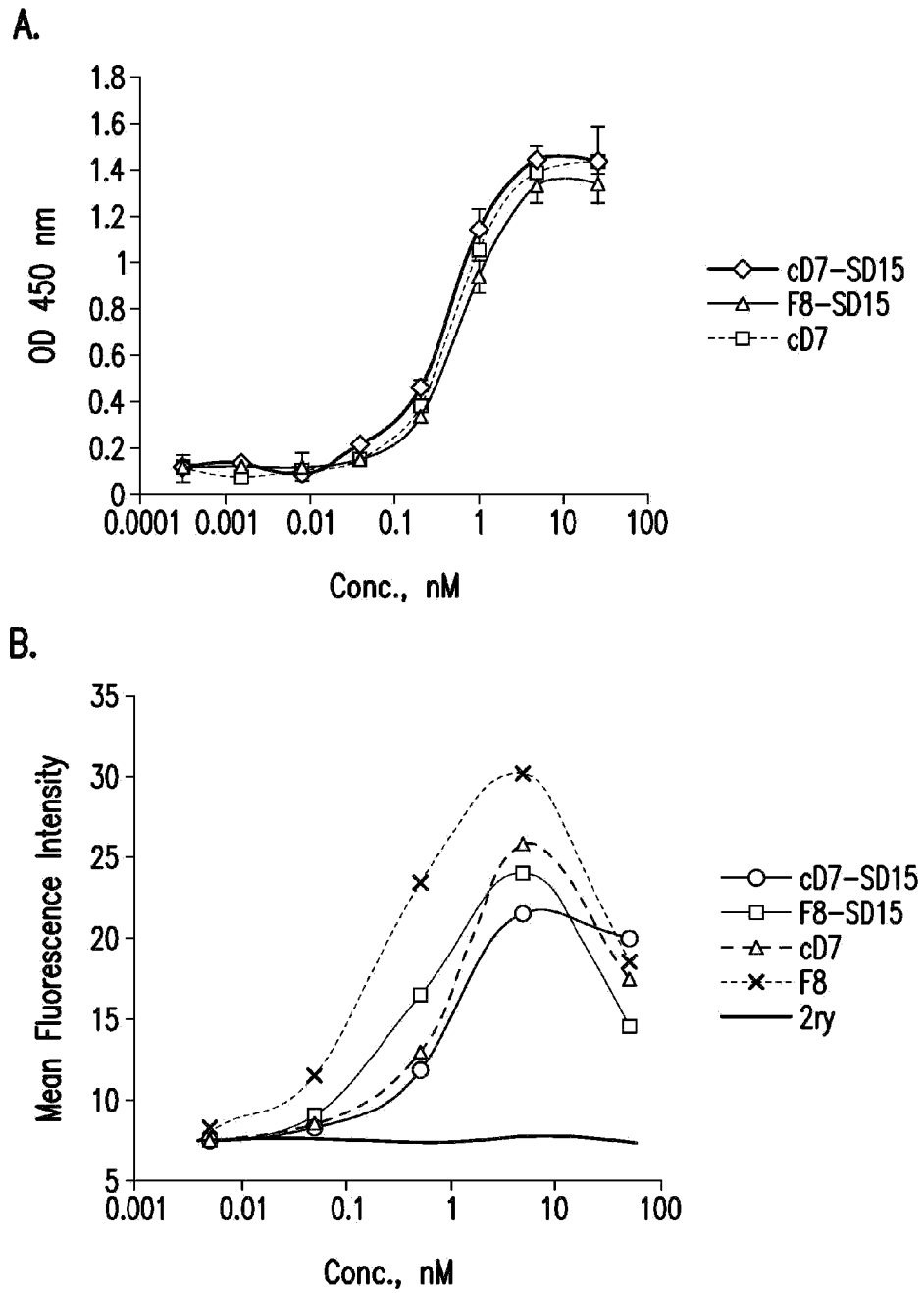


FIG. 9

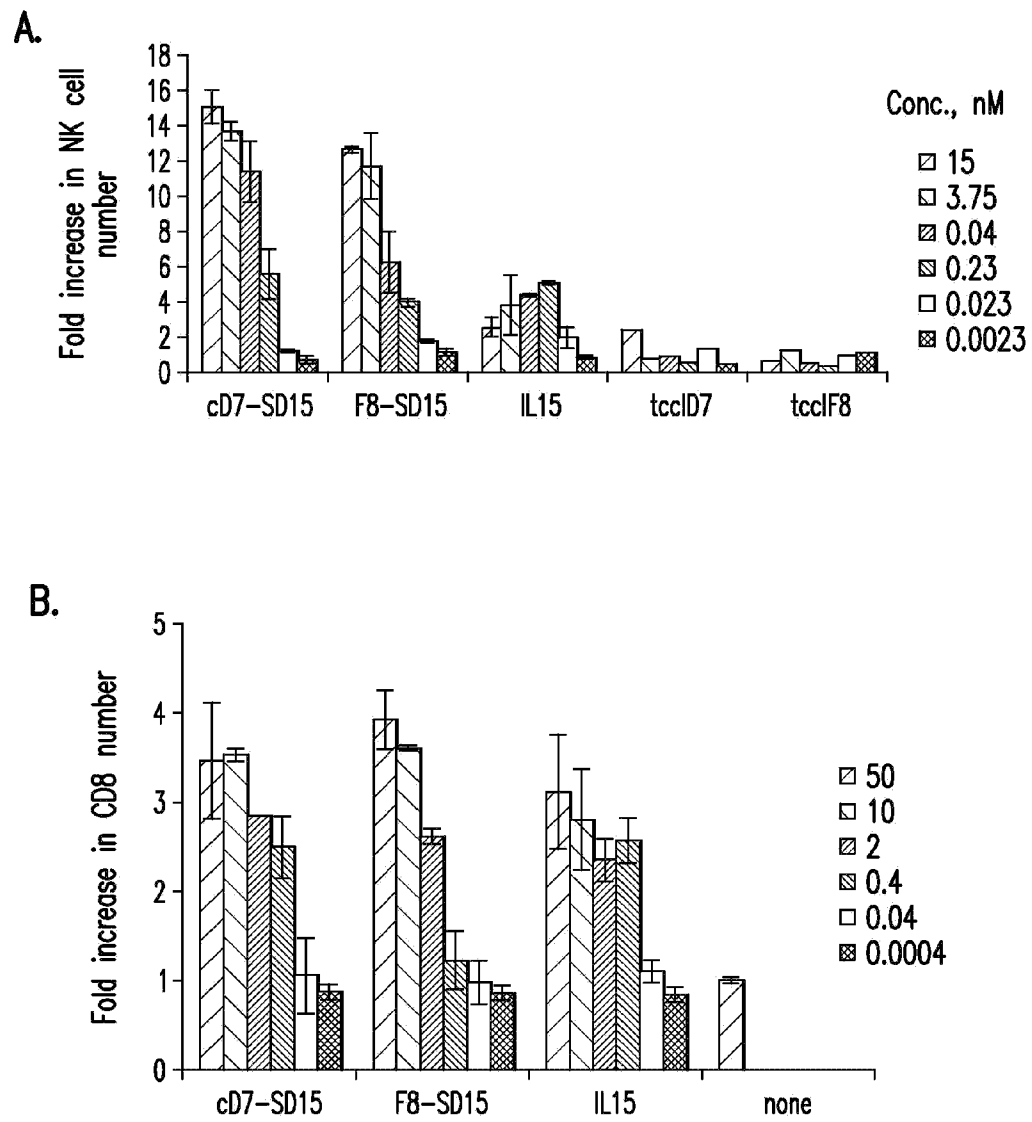


FIG. 10

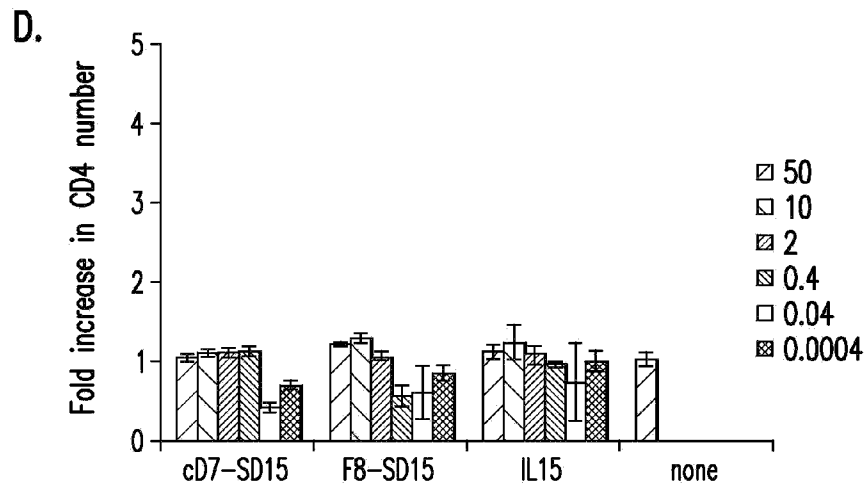
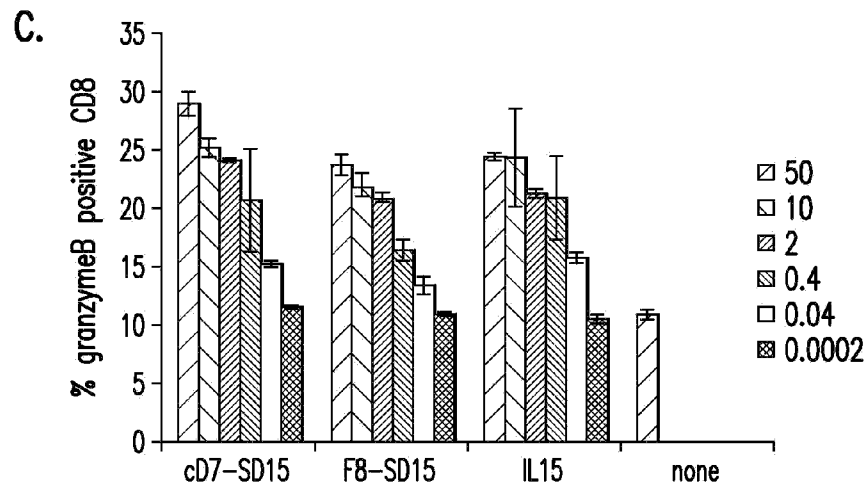
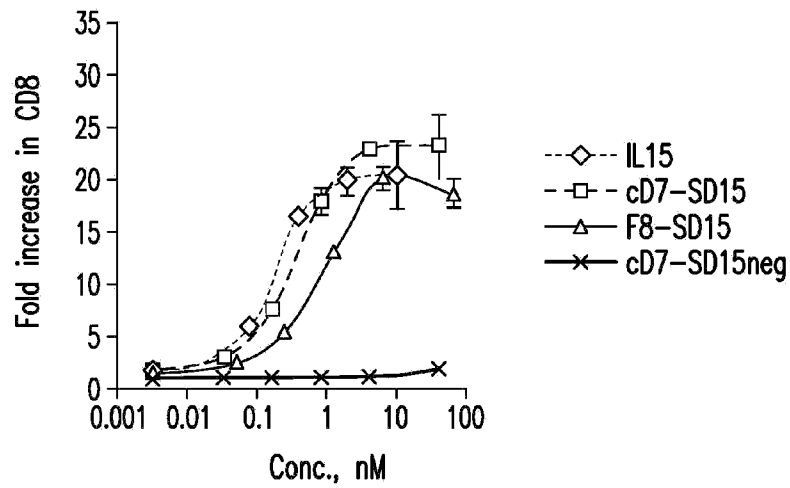
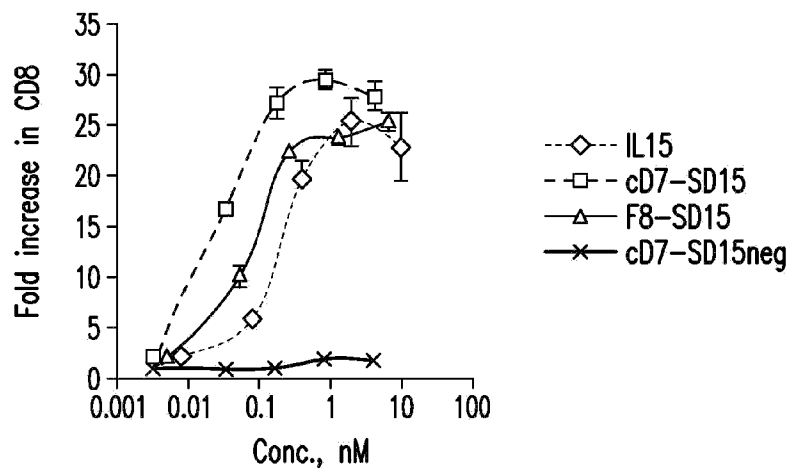


FIG. 10 (Continued)

A.**B.****FIG. 11**

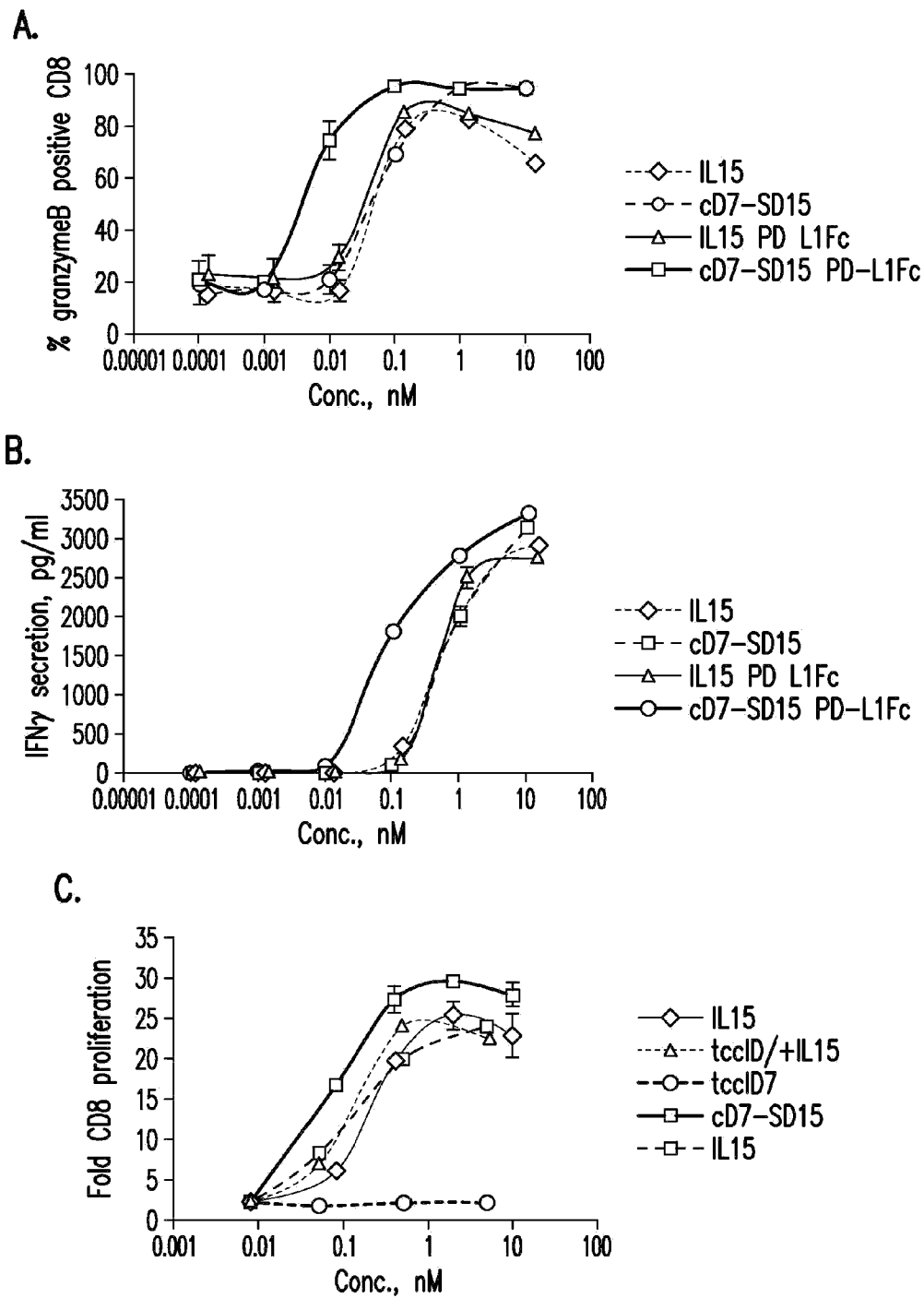


FIG. 12

Kabat No.	SEQ ID NO.	1	2	3	4
		1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3			
6		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SL ~~YW~~ MH--	WVRQA	PGK
16		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SP ~~YP~~ MW--	WVRQA	PGK
26		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SA ~~YI~~ MG--	WVRQA	PGK
36		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SM ~~YW~~ MA--	WVRQA	PGK
46		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SH ~~YP~~ MV--	WVRQA	PGK
56		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SE ~~YV~~ MI--	WVRQA	PGK
66		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SS ~~YEM~~ H--	WVRQA	PGK
76		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SR ~~YGM~~ G--	WVRQA	PGK
86		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SK ~~YV~~ MH--	WVRQA	PGK
96		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SW ~~YP~~ MH--	WVRQA	PGK
106		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SW ~~YP~~ MT--	WVRQA	PGK
116		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SW ~~YI~~ MA--	WVRQA	PGK
126		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SW ~~YL~~ MK--	WVRQA	PGK
136		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SS ~~YQM~~ G--	WVRQA	PGK
146		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SH ~~YP~~ MS--	WVRQA	PGK
156		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SR ~~YE~~ ML--	WVRQA	PGK
166		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SP ~~YD~~ MG--	WVRQA	PGK
176		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SS ~~FYD~~ MS--	WVRQA	PGK
186		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SP ~~YGM~~ R--	WVRQA	PGK
196		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SM ~~YD~~ MA--	WVRQA	PGK
206		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SE ~~YRM~~ I--	WVRQA	PGK
216		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SK ~~YRM~~ A--	WVRQA	PGK
226		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SK ~~YD~~ MY--	WVRQA	PGK
236		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SI ~~YS~~ MN--	WVRQA	PGK
246		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SM ~~YMM~~ M--	WVRQA	PGK
256		EVQLLESGGGGLVQPGGSLRLSCAAS	GF ~~TF~~ SA ~~YRM~~ V--	WVRQA	PGK

FIG. 13A1

Kabat No.	SEQ ID NO.	5	6	7	8
		0 1 2 A B C 3 4 5 6 7 8 9 0 1 2 3 4 5	6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 A B C		
6		S I Y S - - S G V M T F Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
16		S I S P - - S G G F T F Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
26		Y I S S - - S G G W T A Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
36		Y I V P - - S G G I T L Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
46		W I G S - - S G G F T M Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
56		S I S S - - S G G F T W Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
66		G I W P - - S G G V T L Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
76		S I S S - - S G G Q T S Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
86		Y I S S - - S G G F T V Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
96		S I S S - - S G G F T M Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
106		S I G S - - S G G F T L Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
116		Y I S S - - S G G F T A Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
126		Y I G S - - S G G F T A Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
136		W I V P - - S G G F T H Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
146		R I W S - - S G G N T Y Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
156		S I Y S - - S G G W T W Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
166		S I Y S - - S G G W T K Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
176		S I V P - - S G G W T F Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
186		S I S P - - S G G N T D Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
196		G I W P - - S G G P T M Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
206		G I Y P - - S G G W T N Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
216		Y I Y P - - S G G F T F Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
226		G I W P - - S G G L T M Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
236		V I Y P - - S G G F T H Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
246		S I Y P - - S G G I T F Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		
256		R I Y P - - S G G F T F Y A D S V K G	R F T I S R D N S K N T L Y L Q M N S L		

FIG. 13A2

Kabat No.	SEQ ID NO.	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3
6		RA	ED	TA	AV	YY	CA	RA	GS	RV	DA	FA	-	-	-	-	-	-	-	-	-	DI
16		RA	ED	TA	AV	YY	CA	RA	DR	VS	WN	DY	TG	M	-	-	-	-	-	-	-	DV
26		RA	ED	TA	AV	YY	CA	TA	DQ	DG	YN	DF	-	-	-	-	-	-	-	-	-	DY
36		RA	ED	TA	AM	YY	CA	RA	QV	RG	GA	FA	-	-	-	-	-	-	-	-	-	DI
46		RA	ED	TA	AV	YY	CT	TR	DS	FE	DH	YY	M	-	-	-	-	-	-	-	-	DV
56		RA	ED	TA	AV	YY	CA	RA	AR	AP	VGA	DA	FA	-	-	-	-	-	-	-	-	DI
66		RA	ED	TA	AV	YY	CA	RA	FR	TQ	PF	-	-	-	-	-	-	-	-	-	-	DI
76		RA	ED	TA	AV	YY	CT	TR	GG	LW	FG	L	-	-	-	-	-	-	-	-	-	DP
86		RA	ED	TA	AV	YY	CA	RA	VF	DS	GD	AF	-	-	-	-	-	-	-	-	-	DI
96		RA	ED	TA	AM	YY	CA	KA	EG	YS	YG	PG	-	-	-	-	-	-	-	-	-	DY
106		RA	ED	TA	AV	YY	CT	TR	DV	WG	IA	AP	YF	-	-	-	-	-	-	-	-	DY
116		RA	ED	TA	AV	YY	CA	RA	IG	GT	DV	F	-	-	-	-	-	-	-	-	-	DI
126		RA	ED	TA	AM	YY	CA	RA	ED	DF	GA	M	-	-	-	-	-	-	-	-	-	DV
136		RA	ED	TA	AV	YY	CA	RA	DA	GY	RS	GY	YY	YG	M	-	-	-	-	-	-	DV
146		RA	ED	TA	AV	YY	CA	RA	GG	YF	DW	LY	PH	-	-	-	-	-	-	-	-	DY
156		RA	ED	TA	AM	YY	CA	RA	HS	VT	GV	AF	-	-	-	-	-	-	-	-	-	DY
166		RA	ED	TA	AV	YY	CA	RA	DN	WN	DGA	FA	-	-	-	-	-	-	-	-	-	DV
176		RA	ED	TA	AV	YY	CA	RA	DS	WN	DGA	SA	-	-	-	-	-	-	-	-	-	DI
186		RA	ED	TA	AV	YY	CA	RA	IR	YC	GSA	YC	YT	DA	F	-	-	-	-	-	-	DI
196		RA	ED	TA	AV	YY	CA	GA	GY	SY	GD	AL	-	-	-	-	-	-	-	-	-	DY
206		RA	ED	TA	AV	YY	CA	RA	IG	GA	NA	FA	-	-	-	-	-	-	-	-	-	DI
216		RA	ED	TA	AV	YY	CA	KA	DI	GW	LF	VF	-	-	-	-	-	-	-	-	-	DY
226		RA	ED	TA	AM	YY	CA	RA	DG	VV	GG	SY	AF	-	-	-	-	-	-	-	-	DI
236		RA	ED	TA	AV	YY	CA	RA	GR	KT	TV	TD	F	-	-	-	-	-	-	-	-	DY
246		RA	ED	TA	I	YY	CA	RA	IK	LG	TV	TV	-	-	-	-	-	-	-	-	-	DY
256		RA	ED	TA	AV	YY	CA	RA	AL	GP	LS	PL	-	-	-	-	-	-	-	-	-	DS

FIG. 13A3

Kabat No.	SEQ ID NO:	4	5	6	7	8
10	89	QKPGQA	ASARA	GVPDR	GGSSG	TTISS
20	90	QKPGKAPT	SSLQS	VPSSR	SSRSG	TTISS
30	91	QKPGKAPN	SSLQS	VPSSR	SSRSG	TTISS
40	92	QKPGKAPK	ASNLET	VPSSR	SSRSG	TTISS
50	93	QKPGQSPQ	LGSNRRAS	VPDRR	SSRSG	TTKISR
60	94	QKPGQAPK	NAASLWN	VPSSR	SSRSG	TTITLMP
70	95	QKPGKVPK	AASLQS	VPSSR	SSRSG	TTISS
80	96	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
90	97	QKPGQPPK	WASTRES	VPDRR	SSRSG	TTISS
100	98	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
110	99	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
120	100	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
130	101	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
140	102	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
150	103	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
160	104	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
170	105	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
180	106	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
190	107	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
200	108	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
210	109	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
220	110	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
230	111	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
240	112	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
250	113	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS
260	114	QKPGKAPK	SSLQS	VPSSR	SSRSG	TTISS

FIG. 13B2

Kabat No.	SEQ ID NO:	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
10	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
20	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
30	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
40	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
50	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
60	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
70	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
80	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
90	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
100	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
110	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
120	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
130	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
140	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
150	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
160	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
170	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
180	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
190	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
200	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
210	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
220	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
230	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
240	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
250	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
260	EDFA	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9

FIG. 13B3

Sequence of IL-15Ra Sushi Domain and IL-15 Fusion Protein (called SD15)

<i>human IL-15Ra Sushi domain (NM-002189)</i>	IRD-11exone3 encoded AA	linker
CPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTCEVLKATNVAAHWTTPSLKC	IRDPALVHQRPAPP	SGSGGGGGGGGGGGSLQ
human IL-15 (NM_000585-3)		
NWNVVISDLKKIEDLIQSMHIDATLYTESDVHPCKVTAMKCFLELQVLSLESGDASIHDTVENLIILANNSLSNGNVTESGCKECELEEKNIKEFLQSFVHVIVQMFINTS		

Sequence Example of Fusion Heavy Chain

Wild Type Fusion Heavy Chain Sequence with *tc2D7* Variable Domain and SD15 (called *tc2D7HC-SD15*)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSIMYMMWVRQAPGKGLEWVSSIIYPSGGITFTADSVKGRFTISRDNKNTLIYLOMNSLRAEDTAIYYCARIKLGTVTITVDYWGQ
GTLVTVSS (*tc2D7 heavy chain variable domain*) ASTKGPVFPFLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVTVPS
TQYICNVNHEKPSNTKYVDKRVPEKSCDKTHTCTCPCPAPELGGPSVFLPFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRREEQYNSTYRVSVL
TVLHQDWLNGKEYCKVSNKALPAPIEKTIISKARQPREPQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYITTPVLDSDGSGFFLYSKLTVDKSRW
QQGNVFPSCSMHEALHNHYTQKSLSLSPG (*IgG1CH1-CH2-CH3 domain*) SCPPPMSEVHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTCEVLKATNVAAHWTTPSL
KCTRDPAIVHQRPAPPSGSGGGGGGGGSLQNWNVVISDLKKIEDLIQSMHIDATLYTESDVHPCKVTAMKCFLELQVLSLESGDASIHDTVENLIILANNSLS
NGNVTESGCKECELEEKNIKEFLQSFVHVIVQMFINTS (*IL-15Ra Sushi domain and IL-15*)

LALA Mutant Fusion Heavy Chain Sequence with *tc2D7* Variable Domain and SD15 (called LALA mutant *tc2D7HC-SD15*)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSIMYMMWVRQAPGKGLEWVSSIIYPSGGITFTADSVKGRFTISRDNKNTLIYLOMNSLRAEDTAIYYCARIKLGTVTITVDYWGQTLV
TVSS (*tc2D7 heavy chain variable domain*)

ASTKGPVFPFLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTTTPAVLQSSGLYSLSVTVPS
APEAAGGPSVFLFPFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRREEQYNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTIISKAKGQP
REFQVYITLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYITTPVLDSDGSGFFLYSKLTVDKSRWQQGNVFPSCSMHEALHNHYTQKSLSLSPG (*LALA mutant IgG1CH1-CH2-CH3 domain*) SCPPPMSEVHADIWVKSYSLSYRERYICNSG FKKAGTSSLTCEVLKATNVAAHWTTPSLKCTINDPALVHQRPAPPSGSGGGGGGGGGG
GSLQNWNVVISDLKKIEDLIQSMHIDATLYTESDVHPCKVTAMKCFLELQVLSLESGDASIHDTVENLIILANNSLSNGNVTESGCKECELEEKNIKEFLQSFVHVIVQMFINTS (*IL-15Ra Sushi domain and IL-15*)

FIG. 14

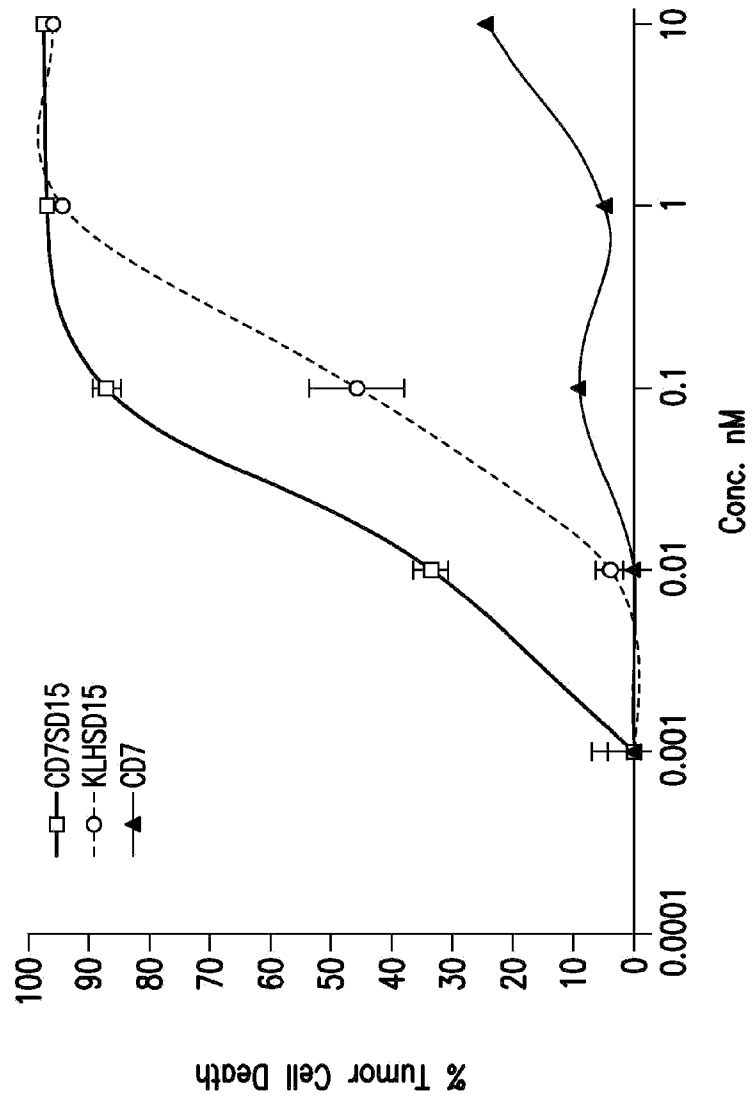


FIG. 15

CT26-e204 Kaplan-Meier Plot

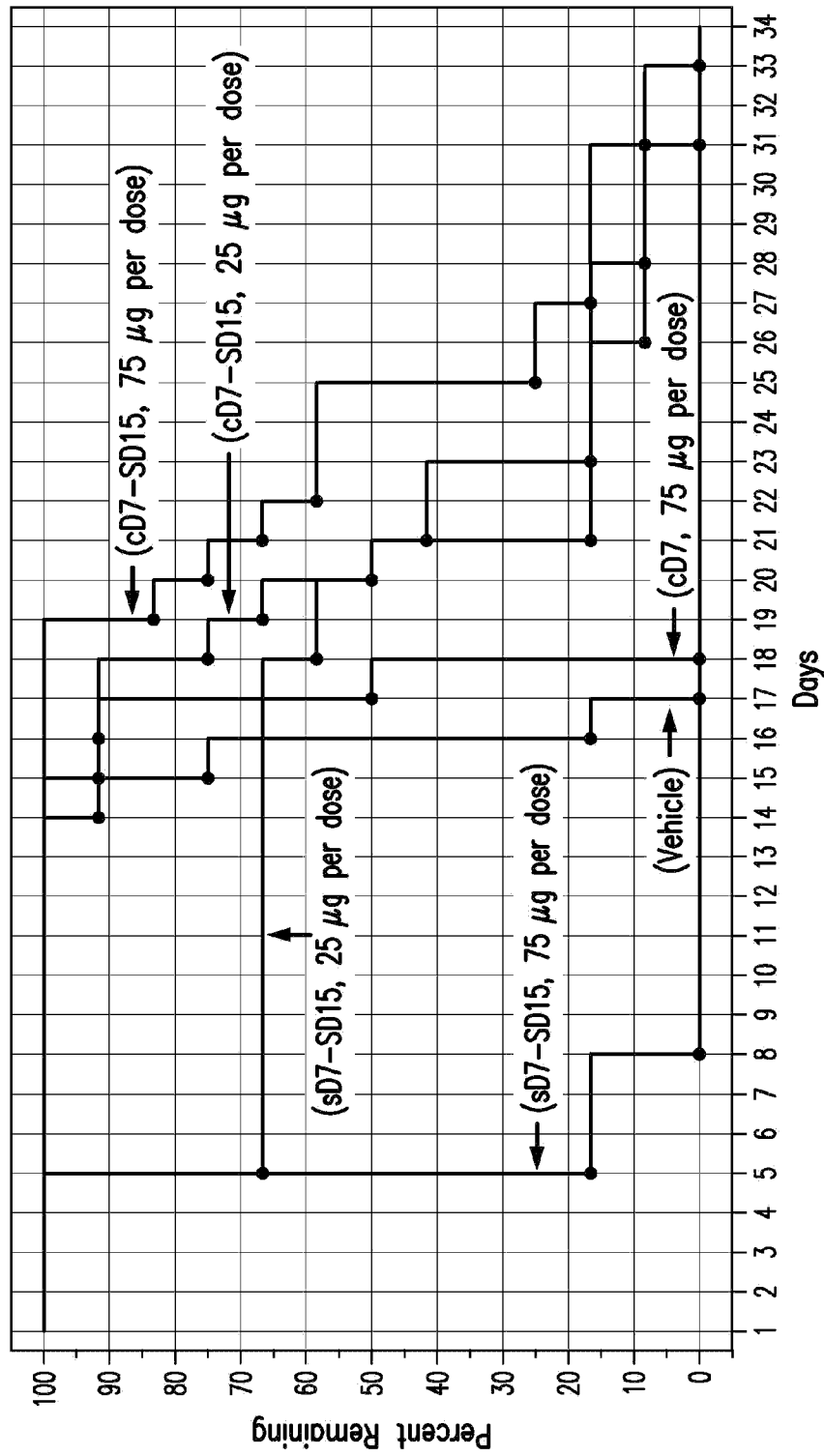


FIG. 16

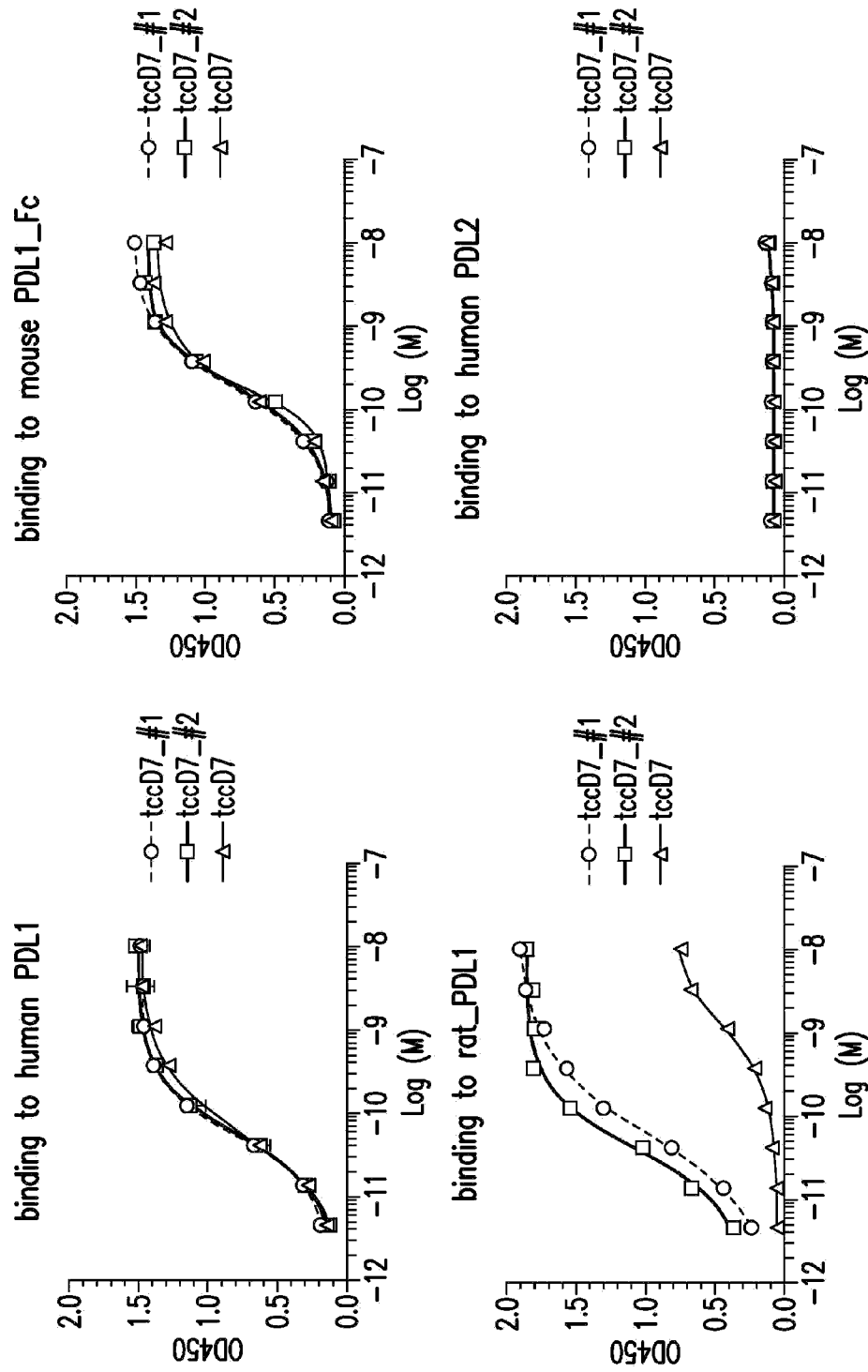


FIG. 17

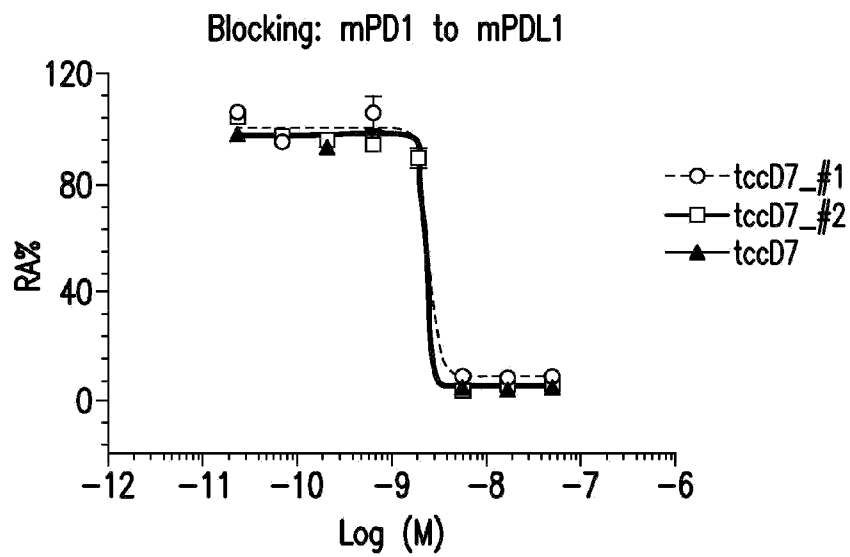
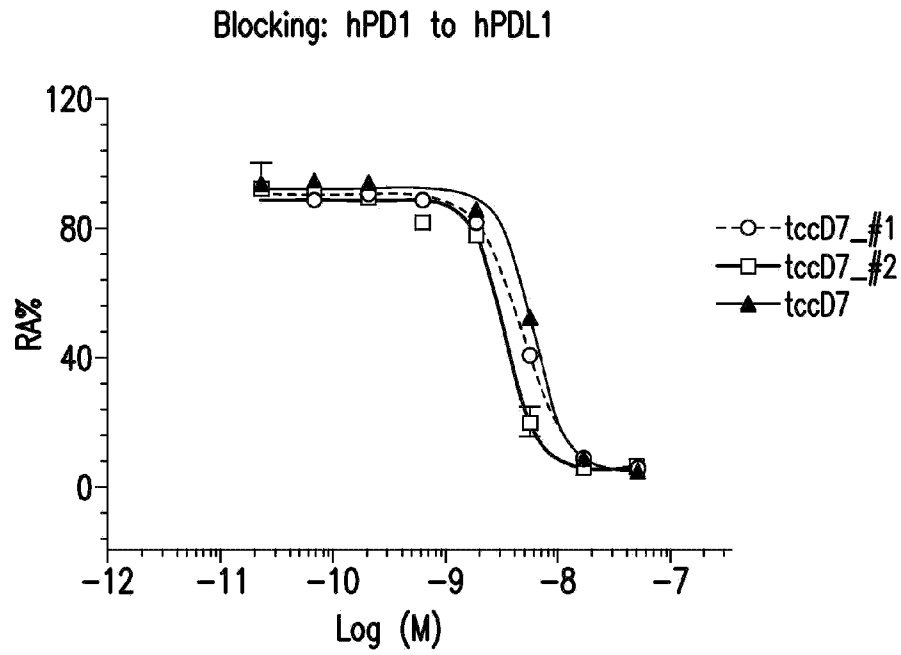


FIG. 18

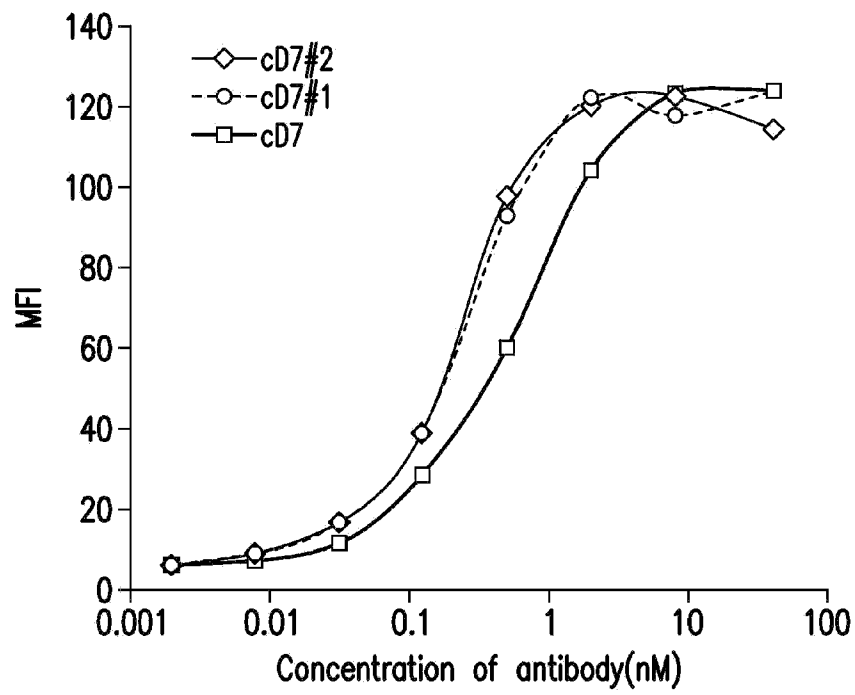


FIG. 19

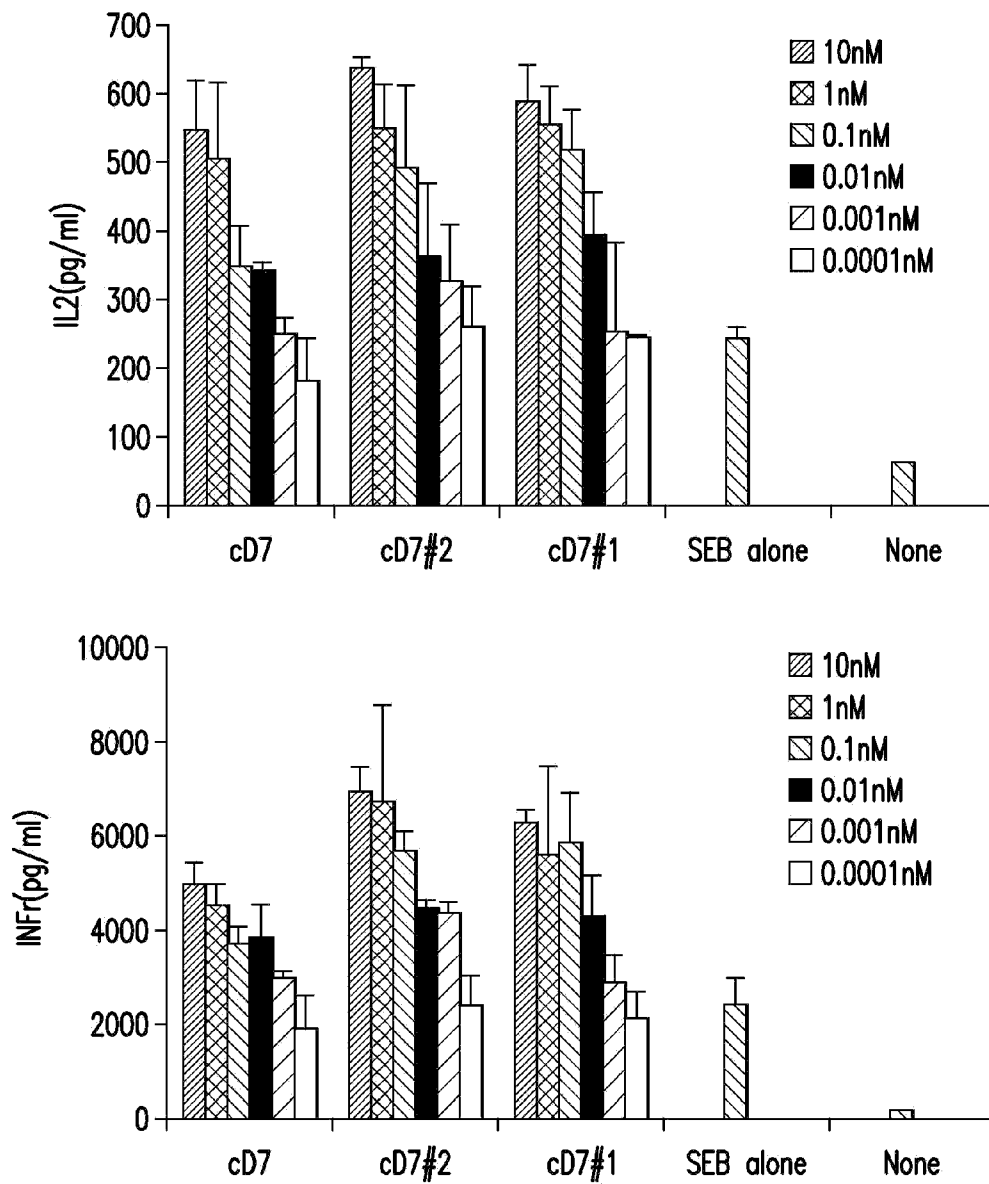


FIG. 20

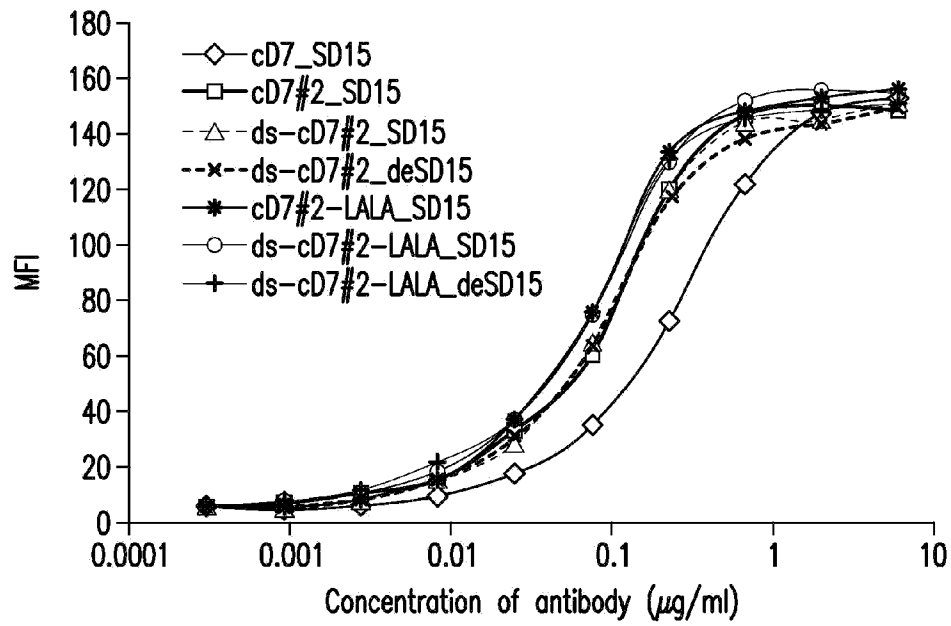


FIG. 21

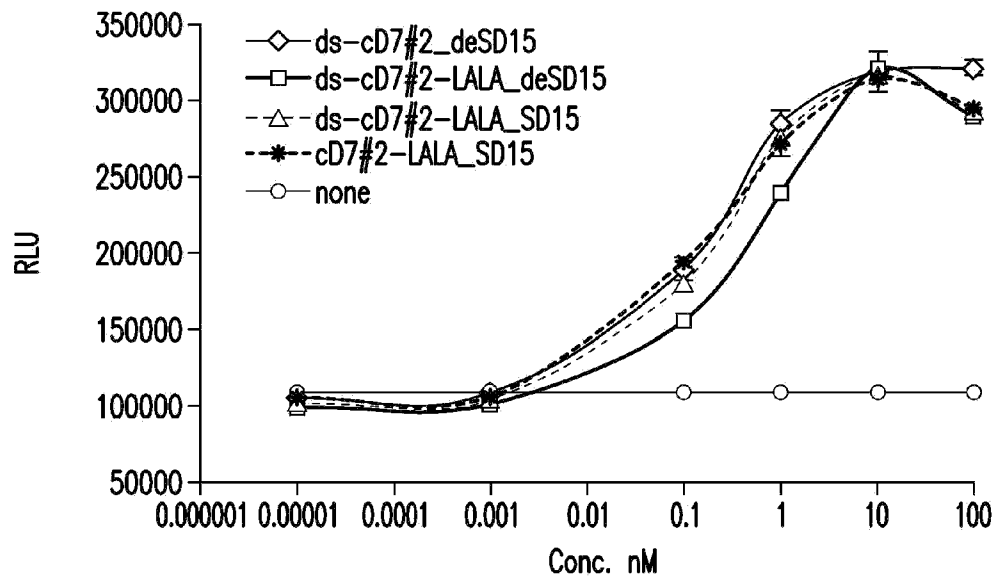


FIG. 22

—△— ds_cD7_#2 -△- ds_cD7_deSD15_#2 —▲— ds_cD7_SD15_#2

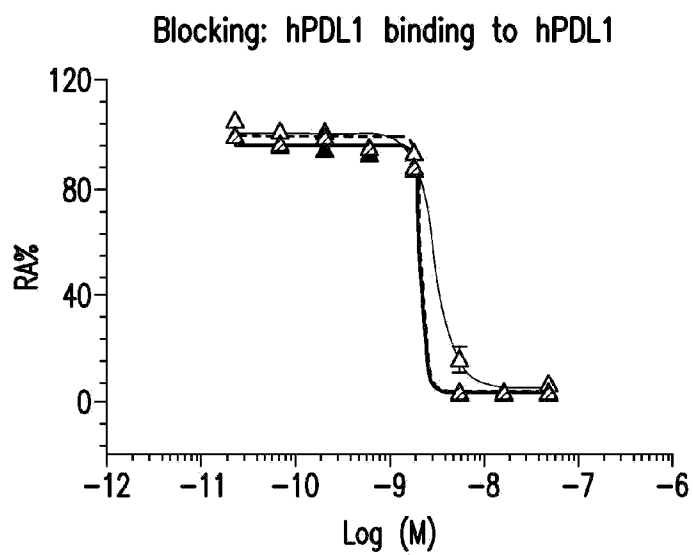
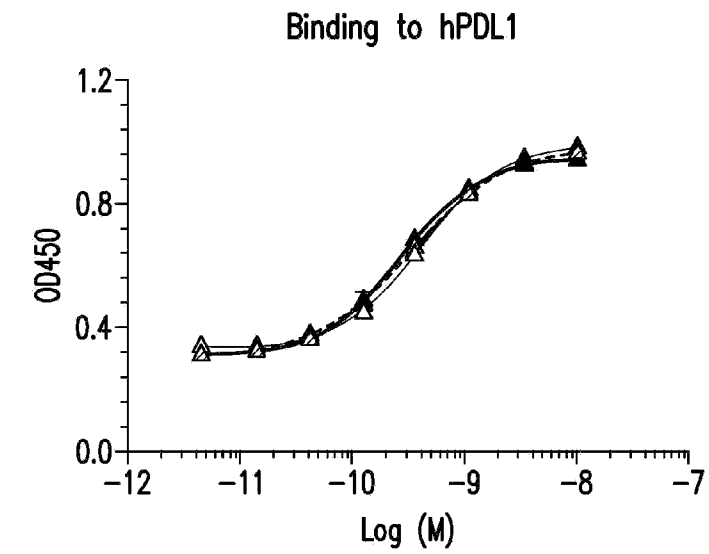


FIG. 23

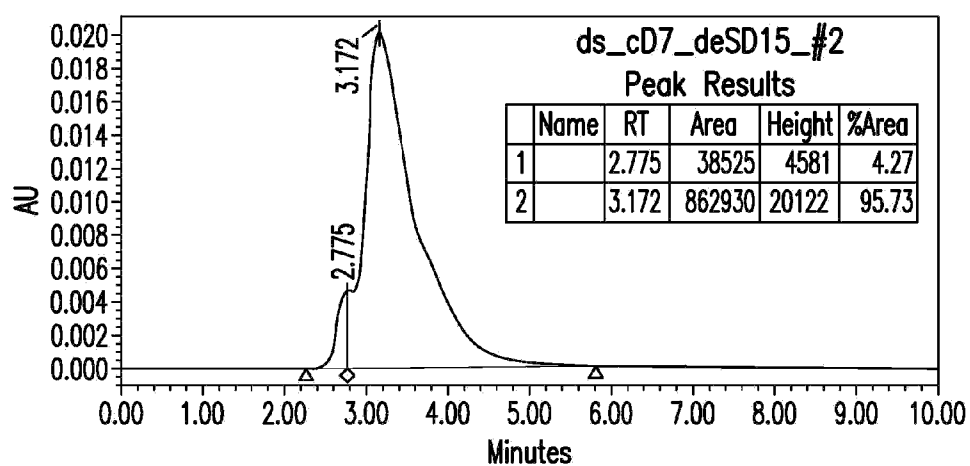
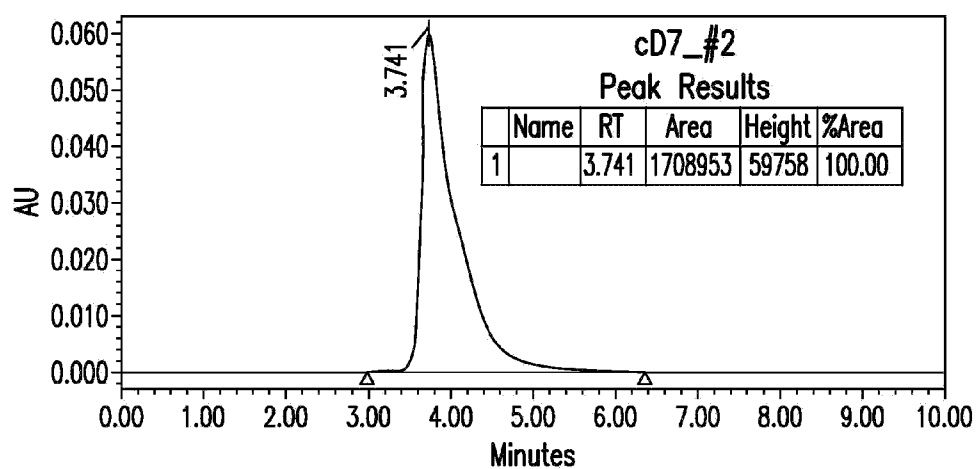
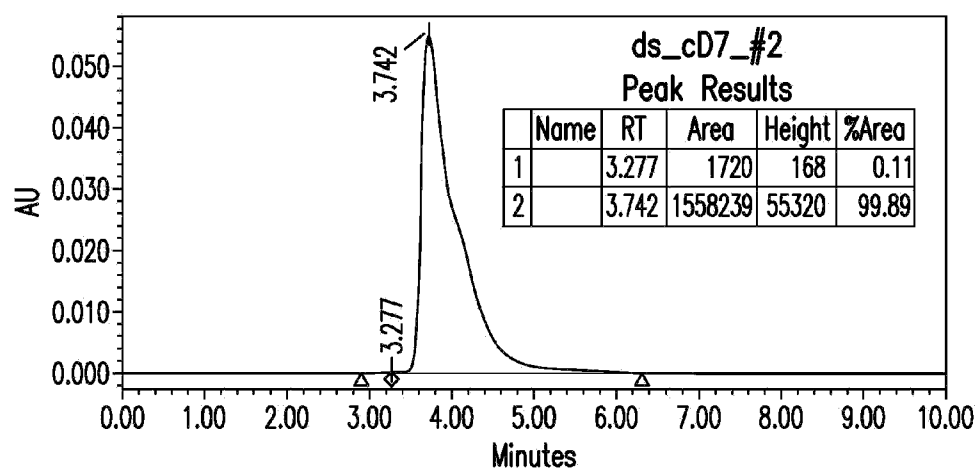


FIG. 24

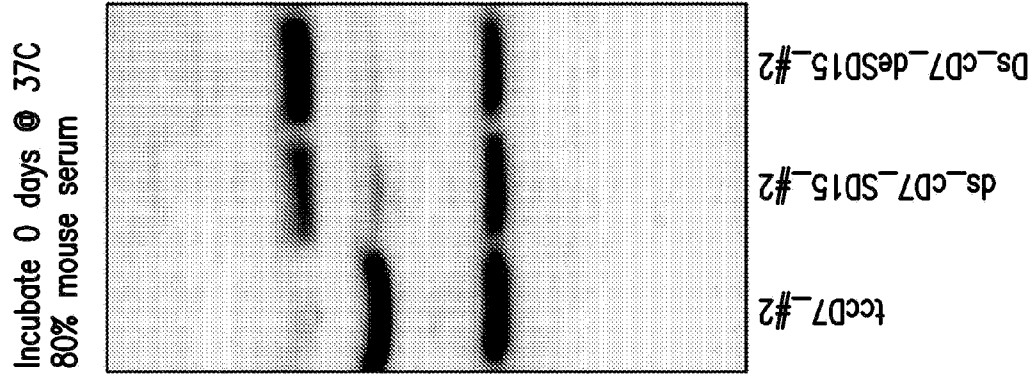


FIG. 25

