(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 February 2020 (27.02.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/038379 A1

(51) International Patent Classification:
C07K 16/30 (2006.01) *A61P 35/00* (2006.01)
A61K 39/395 (2006.01)

(21) International Application Number:
PCT/CN2019/101659

(22) International Filing Date:
20 August 2019 (20.08.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/720,015 20 August 2018 (20.08.2018) US

(71) Applicants: **1GLOBE BIOMEDICAL CO., LTD.** [CN/CN]; 8F, Block B, Techart Plaza, No. 30 Xueyuan Road, Haidian District, Beijing 100083 (CN). **1GLOBE HEALTH INSTITUTE LLC** [US/US]; 333 Providence Hwy, Norwood, MA, 02062 (US).

(72) Inventors: **LI, Chiang J.**; Cambridge, MA, 02140 (US). **UNNIRAMAN, Shyam**; Newton, MA, 02465 (US). **BADER, Hannah**; Waltham, MA, 02154 (US). **JHA, Mithilesh**; Sharon, MA, 02067 (US).

(74) Agent: **CHOFN INTELLECTUAL PROPERTY**; Room 1215-1218, Floor 12, Left Bank Community No.68 Beisihuanxilu, Haidian District, Beijing 100080 (CN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: NOVEL CANCER IMMUNOTHERAPY ANTIBODY COMPOSITIONS

(57) Abstract: Provided are compositions and methods relating to or derived from anti-PD-L1 antibodies with ADCC and/or CDC activities. More specifically, provided are fully human antibodies that bind PD-L1, PD-L1-binding antibody fragments, derivatives of such antibodies, and PD-L1-binding polypeptides comprising such fragments.

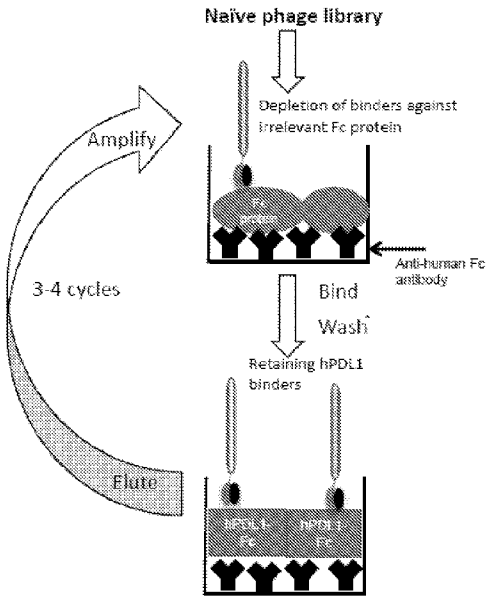


FIG. 1

WO 2020/038379 A1

[Continued on next page]

Published:
— *with international search report (Art. 21(3))*

NOVEL CANCER IMMUNOTHERAPY ANTIBODY COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of copending United States Provisional Patent Application Serial No. 62/720,015 filed August 20, 2018, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to antigen-binding polypeptides that bind human PD-L1, pharmaceutical compositions and uses thereof. Aspects of the invention also relate to expression system producing such antigen-binding polypeptides or antibodies. The described antigen-binding polypeptides or pharmaceutical compositions of the invention are useful for treating a subject in need thereof for a pathological condition, such as a mammalian cancer, an infection, and so on.

BACKGROUND OF INVENTION

[0003] Immune cells have costimulatory and inhibitory receptors on their cell surfaces that interact with membrane-bound and soluble ligands. These receptors serve to regulate the potency, duration, and type of the immune response by altering thresholds and the durations of immune cell activation or inhibition. These are often referred collectively to as immune checkpoints. Many of these checkpoint molecules are members of either the B7 superfamily or tumor necrosis factor (TNF) superfamily of molecules.

[0004] The B7 family includes both inhibitory and stimulatory co-receptors. For example, on the one hand, ligation of Programmed (Cell) Death Protein 1 (PD-1) and Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) with their respective ligands (PD-L1, PD-L2 and B7-1, B7-2, respectively) leads to suppression of the activation or generation of regulatory T cells, anergy, exhaustion and apoptosis. On the other hand, ligation of Cluster of Differentiation (CD28) and Inducible T-cell COStimulator (ICOS) receptors with their respective ligands results in increased proliferation and production of cytokine. In contrast, the TNF family of costimulatory receptors includes only stimulatory molecules such as OX40, 4-1BB, CD40, CD27 and their ligands that favor proliferation and effector function differentiation. In addition, there are other co-receptors that do belong to either of these families e.g., Tim-3, LAG-3, Ceacam-1, etc.

[0005] For the past couple of decades, it has become clear that many types of cancer generate an immunosuppressive environment within the tumor through a variety of mechanisms. A recurrent theme is the ectopic expression of an inhibitory immune checkpoint ligand (especially PDL1) that suppresses intratumoral T cells. There is also increasing evidence that blocking this tumor mediated immunity suppression can de-repress intratumoral T cells and allow them to kill the tumor (Adachi K, Tamada K. *Cancer Sci.* 2015;106(8):945-50; Rafiq S, et al., *Nat Biotechnol.* 2018 Aug 13;Hargadon KM, et al., *Int Immunopharmacol.* 2018;62:29-39). Blocking can be done through an antibody or a variety of other methods. This is different from traditional anti-cancer antibody therapy where the antibody binds to the cancer cell and recruits complement dependent cytotoxicity (CDC) as well as antibody-dependent cellular cytotoxicity (ADCC) to directly kill the tumor cells.

[0006] CTLA-4 antibodies were the first of a class of immunotherapeutics based on immune checkpoint blockade to win FDA approval. Other blockade targets, such as PD1 and its associated molecules, offer more and different opportunities for enhancing the antitumor immunity in a clinical setting.

BRIEF SUMMARY OF THE INVENTION

[0007] The present invention provides antigen-binding polypeptides that bind PD-L1 (or, interchangeably, "anti-PD-L1 polypeptide(s)," "PD-L1-binding polypeptides"), preferably, the human PD-L1; the polypeptide has one or both of the following features: (a) binds to PD-L1 and inhibits its ability to interact with PD1; and (b) has an isotype or constant region that can trigger ADCC and/or CDC. The resulting antibody can kill tumor cells through two synergistic pathways--T cell de-repression and direct cytotoxicity. The polypeptides of the present invention can be used to treat tumors by itself or in combination with (a) antibodies targeting other immunosuppressive pathways; (b) chemotherapy or radiation therapy; (c) other mechanisms of blocking immunosuppressive pathways, e.g., aptamers or RNAi; or (d) other immunotherapy agents, e.g. cytokines, targeted therapeutics, etc.

[0008] In one aspect, the present invention provides an antigen-binding polypeptide, e.g., an antibody, fragment, derivative or analog thereof, that is of the IgG1 isotype and binds to a PD-L1 epitope, preferably with a binding affinity of at least 10^{-6}M, and having a heavy chain variable domain sequence "consisting essentially of," meaning herein, that is at least 80%, or, more preferably, 85%, 90%, 95%, or even 100%, identical to the amino acid sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, SEQ ID NO:18,

SEQ ID NO:22, SEQ ID NO:26, SEQ ID NO:30, SEQ ID NO:34, SEQ ID NO:38, SEQ ID NO:42, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:54, SEQ ID NO:58, SEQ ID NO:62, SEQ ID NO:66, SEQ ID NO:70, SEQ ID NO:74, SEQ ID NO:78, SEQ ID NO:82, SEQ ID NO:86, SEQ ID NO:90, SEQ ID NO:94, SEQ ID NO:98, SEQ ID NO:102, SEQ ID NO:106, and combinations thereof, and that having a light chain variable domain sequence consisting essentially of, meaning, that is at least 80%, or, more preferably, 85%, 90%, 95%, or even 100%, identical to the amino acid sequences selected from the group consisting of SEQ ID NO:4, SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NO:32, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:44, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:56, SEQ ID NO:60, SEQ ID NO:64, SEQ ID NO:68, SEQ ID NO:72, SEQ ID NO: 76, SEQ ID NO:80, SEQ ID NO:84, SEQ ID NO:88, SEQ ID NO:92, SEQ ID NO:96, SEQ ID NO:100, SEQ ID NO:104, SEQ ID NO:108, and combinations thereof.

[0009] In preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective sequences consist essentially of the following pairing: (a) SEQ ID NO:18 and SEQ ID NO:20; (b) SEQ ID NO:42 and SEQ ID NO:44; or (c) SEQ ID NO:34 and SEQ ID NO:36.

[00010] In other preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective sequences consist essentially of the following pairing: (a) SEQ ID NO:22 and SEQ ID NO:24; (b) SEQ ID NO:2 and SEQ ID NO:4; (c) SEQ ID NO:62 and SEQ ID NO:64; or (d) SEQ ID NO:82 and SEQ ID NO:84.

[00011] In other preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective sequences consist essentially of the following pairing: (a) SEQ ID NO:70 and SEQ ID NO:72; (b) SEQ ID NO:50 and SEQ ID NO:52; (c) SEQ ID NO:102 and SEQ ID NO:104; or (d) SEQ ID NO:30 and SEQ ID NO:32.

[00012] In other preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective variable region sequences consist essentially of the following pairing: (a) SEQ ID NO:6 and SEQ ID NO:8; (b) SEQ ID NO:10 and SEQ ID NO:12; (c) SEQ ID NO:14 and SEQ ID NO:16; (d) SEQ ID NO:26 and SEQ ID NO:28; (e) SEQ ID NO:38 and SEQ ID NO:40; (f) SEQ ID NO:46

and SEQ ID NO:48; (g) SEQ ID NO:54 and SEQ ID NO:56; or (h) SEQ ID NO:58 and SEQ ID NO:60.

[00013] In other preferred embodiments, an antigen-binding polypeptide or antibody of the invention includes a pair of heavy chain variable region and light chain variable region where their respective variable region sequences consist essentially of the following pairing: (a) SEQ ID NO:66 and SEQ ID NO:68; (b) SEQ ID NO:74 and SEQ ID NO:76; (c) SEQ ID NO:78 and SEQ ID NO:80; (d) SEQ ID NO:86 and SEQ ID NO:88; (e) SEQ ID NO:90 and SEQ ID NO:92; (f) SEQ ID NO:94 and SEQ ID NO:96; (g) SEQ ID NO:98 and SEQ ID NO:100; or (h) SEQ ID NO:106 and SEQ ID NO:108.

[00014] Preferably, the antigen-binding polypeptide is fully human or otherwise humanized. In a preferred embodiment, the antigen-binding polypeptide further comprising a human constant region. In one feature, the human constant region is IgG1. In some embodiments, the antibody of the invention further includes a second pair of heavy and light chain variable regions that are, e.g., substantially identical to the first pair.

[00015] In a preferred version, the binding of the anti-PD-L1 polypeptide to PD-L1 blocks PD-L1's interaction with PD1. This could be either because the epitope for the binding on PD-L1 is at or near the PD1 interaction interface or because there is an allosteric change in the conformation of the PD1 interaction interface.

[00016] In another aspect, the present invention provides nucleic acid molecules that encode the above mentioned polypeptides. The nucleic acid molecule can be a DNA molecule or RNA molecule. In a preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:17 and SEQ ID NO:19; (b) SEQ ID NO:33 and SEQ ID NO:35; (c) SEQ ID NO:41 and SEQ ID NO:43.

[00017] In other preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:21 and SEQ ID NO:23; (b) SEQ ID NO:1 and SEQ ID NO:3; (c) SEQ ID NO:61 and SEQ ID NO:63; or (d) SEQ ID NO:81 and SEQ ID NO:83.

[00018] In other preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding

polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:69 and SEQ ID NO:71; (b) SEQ ID NO:49 and SEQ ID NO:51; (c) SEQ ID NO:101 and SEQ ID NO:103; or (d) SEQ ID NO:29 and SEQ ID NO:31.

[00019] In other preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:5 and SEQ ID NO:7; (b) SEQ ID NO:9 and SEQ ID NO:11; (c) SEQ ID NO:13 and SEQ ID NO:15; (d) SEQ ID NO:25 and SEQ ID NO:27; (e) SEQ ID NO:37 and SEQ ID NO:39; (f) SEQ ID NO:45 and SEQ ID NO:47; (g) SEQ ID NO:53 and SEQ ID NO:55; or (h) SEQ ID NO:57 and SEQ ID NO:59.

[00020] In other preferred embodiments, the nucleic acid molecule is a DNA molecule that encodes a heavy chain variable region and a light chain variable region of an antigen-binding polypeptide or antibody of the invention, wherein the DNA sequences respectively consist essentially of the following pairing: (a) SEQ ID NO:65 and SEQ ID NO:67; (b) SEQ ID NO:73 and SEQ ID NO:75; (c) SEQ ID NO:77 and SEQ ID NO:79; (d) SEQ ID NO:85 and SEQ ID NO:87; (e) SEQ ID NO:89 and SEQ ID NO:91; (f) SEQ ID NO:93 and SEQ ID NO:95; (g) SEQ ID NO:97 and SEQ ID NO:99; or (h) SEQ ID NO:105 and SEQ ID NO:107.

[00021] In another aspect, the present invention provides a pharmaceutical composition that includes an antigen-binding polypeptide, e.g., the anti-PD-L1 antibody, fragment, derivative or analog, as disclosed herein. The pharmaceutical composition further includes a pharmaceutically acceptable excipient, carrier, or diluent.

[00022] In a related aspect, the present invention provides a method of treating a subject in need thereof for a pathological condition therapeutically, said method comprising administering to said subject a therapeutically effective amount of the anti-PD-L1 polypeptide or antibody disclosed herein. The method may further include a step of administering a second and different therapeutic antibody against at least one cell-surface antigen indicative of said condition. The condition being treated may be a mammalian cancer, an infection, and so on. In various embodiments, the anti-PD-L1 polypeptide may be an antibody, an antibody fragment, an antibody derivative or an antibody analog.

[00023] Preferably, the spectrum of mammalian cancers to be treated is selected from the group consisting of ovarian cancer, colon cancer, breast cancer, lung cancer, myelomas,

neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, melanoma, bladder cancer, gastric cancer, liver cancer, urothelial carcinoma, cutaneum carcinoma, renal cancer, head and neck cancer, pancreatic cancer, and combinations thereof. More broadly, any cancer where at least a significant fraction of the tumor cells express detectable amount of PD-L1 is contemplated as targets to be treated by the composition of the present invention.

[00024] In yet another aspect, the invention provides a method of treating a subject in need thereof for similar conditions prophylactically, said method comprising administering to said subject a prophylactically effective amount of the pharmaceutical composition of the invention. The method may further include a step of administering a vaccine against said condition. In one embodiment, the condition is a cancer.

[00025] In a further aspect, the invention provides a mammalian expression system that produces the antigen-binding polypeptide, e.g., an antibody, fragment, derivative or analog thereof, that binds to a PD-L1 epitope described herein.

BRIEF DESCRIPTION OF FIGURES

[00026] Figure 1 schematically depicts screening for antigen-binding polypeptides with solid phase phage panning technologies, specifically, using indirect coating of test proteins to the immunotubes, according to an embodiment of the present invention.

[00027] Figure 2 schematically depicts screening for antigen-binding polypeptides with solid phase phage panning technologies, specifically, using direct coating of test proteins to the immunotubes, according to an embodiment of the present invention.

[00028] Figure 3 is a chart listing data that characterize the ability to bind hPDL1 of representative single chain variable fragments (scfv) obtained through an embodiment of present invention in indirect ELISA binding assay. “NC” represents negative control.

[00029] Figure 4 is a chart listing data that characterize the ability to bind hPDL1 of representative single chain variable fragments (scfv) obtained through an embodiment of present invention in FACS binding assay. “PC” represents positive control using hPDL1/293T cells stained with anti-hPDL1-APC (10 μg/ml). “NC” represents negative control with unstained hPDL1/293T cells.

[00030] Figure 5 is a chart listing data that characterize the ability to block the interaction between hPD1 and hPDL1 of various single chain variable fragments (scfv) obtained through an

embodiment of present invention in receptor blocking assay (plates coated by hPDL1). "PC" represents positive control with added biotin-hPD1-Fc. "NC" represents negative control where only buffer was added.

[00031] Figure 6 is a chart listing data that characterize the ability to block the interaction between hPD1 and hPDL1 of various single chain variable fragments (scfv) obtained through an embodiment of present invention in receptor blocking assay (plates coated by hPD1). "PC" represents positive control with added biotin-hPDL1-Fc. "NC" represents negative control where only buffer was added.

[00032] Figure 7 depicts ability to bind hPDL1-Fc, mPDL1-Fc (mouse PDL1) and hIgG1 of the single chain variable fragments (scfv) obtained through embodiments of the present invention in direct ELISA assays.

[00033] Figures 8A and 8B show full-length antibody 4-1E8 characterized by SDS-PAGE (FIG. 8A) and size exclusion chromatography (FIG. 8B).

[00034] Figures 9A and 9B show full-length antibody 3-1B11 characterized by SDS-PAGE (FIG. 9A) and size exclusion chromatography (FIG. 9B).

[00035] Figures 10A and 10B show full-length antibody 3-1E4 characterized by SDS-PAGE (FIG. 10A) and size exclusion chromatography (FIG. 10B).

[00036] Figures 11B and 11C show results of quantitative binding analysis of some of the full-length antibody embodiments according to the present invention to hPDL1 in an ELISA format according to FIG. 11A.

[00037] Figures 12A and 12B show results of quantitative FACS for some of the full-length antibody embodiments according to the present invention where binding to hPDL1-expressing 293T cells (top graph), and hPDL1-negative 293T cells (bottom graph).

[00038] Figure 13B shows results in receptor blocking assay of the lead antibody candidates in the present invention in RBA Format 1 (FIG. 13A): coated with hPDL1-Fc and added with Biotin-hPD1-Fc.

[00039] Figure 14B shows results in receptor blocking assay of the lead antibody candidates in the present invention in RBA Format 2 (FIG. 14A): coated with hPD1-Fc and added with Biotin-hPDL1-Fc.

[00040] Figure 15 is a chart listing data that characterizes various full-length antibodies obtained through an embodiment of the present invention.

[00041] Figures 16A-16D depict affinities to PD-L1 of lead antibody candidates using BIAcore: FIG. 16A schematically depicts the BIAcore format utilized according to an example of the present invention; FIG. 16B lists results from testing lead antibody candidates' affinity to PD-L1 using BIAcore; FIG. 16C depicts the response curve of antibody coded 4-1E8 of BIAcore affinity testing; and FIG. 16D depicts the response curve of antibody coded 3-1B11 of BIAcore affinity testing.

[00042] Figure 17A schematically depicts an epitope-binning format utilized according to an example of the present invention. Figure 17B schematically depicts an epitope bins for lead antibody candidates according to an embodiment of the present invention. Figure 17C lists epitope-binning matrix for lead antibody candidates using the format represented in FIG. 17A.

[00043] Figures 18A-18D show binding abilities of: controls (FIG. 18A), antibodies of the invention coded "4-1E8" (FIG. 18B), "3-1E4" (FIG. 18C), and "3-1B11" (FIG. 18D) to Rhesus PDL1-GFP expressing construct transfected 293T cell (top) and parental 293T (bottom) cells through FACS assays.

[00044] Figures 19A-19D show binding abilities of: controls (FIG 19A), antibodies of the invention coded "4-1E8" (FIG. 19B), "3-1E4" (FIG. 19C), and "3-1B11" (FIG. 19D) to Rhesus PDL1 expressing construct transfected 293T cell (top) and parental 293T (bottom) cells through FACS assays.

[00045] Figure 20 shows representative EC50 results of IL-2 production experiment according to embodiments of the invention.

[00046] Figure 21 shows ADCC activity of the polypeptide embodiment coded "4-1E8" in comparison to commercially available anti-PDL1 antibody Atezolizumab.

[00047] Figures 22A-22C show ADCC activity of the polypeptide embodiment coded "4-1E8" in comparison to embodiments coded "3-1B11" (FIG. 22A) and "3-1E4" (FIG. 22B), with key data points summarized in a chart (FIG. 22C).

[00048] Figures 23A, 23B and 23C provide three sets of experimental data of IL-2 production ability of PBMCs co-cultured with PDL1+ MDA-MB-231 tumor cells in the presence of lead antibodies according to the invention in comparison to commercially available anti-PDL1 antibodies.

[00049] Figure 24 provides results of IFNγ production ability of CD8 T cells co-cultured with PDL1+ MDA-MB-231 tumor cells in the presence of lead antibodies according to the invention in comparison to commercially available anti-PDL1 antibodies.

[00050] Figures 25A and 25B show mixed lymphocyte reaction results of lead antibodies according to embodiments of the invention.

[00051] Figures 26A and 26B show the specificity of binding by antibodies of the invention coded "4-1E8" (FIG. 26A) and "3-1B11" (FIG. 26B).

[00052] Figures 27A and 27B show ability of the antibodies of the invention E8 (FIG. 27A) and B11 (FIG. 27B) to block CD80 from binding PD-L1-expressing cells (grey silled curves) compared to CD80 alone (solid line) and secondary alone (dashed line).

[00053] Figure 28 shows half-life measurement of the antibody embodiments of the invention using Tg32 mice.

DETAILED DESCRIPTION OF INVENTION

[00054] Unless otherwise noted, technical terms are used according to conventional usage.

[00055] As used herein, "a" or "an" may mean one or more. As used herein when used in conjunction with the word "comprising," the words "a" or "an" may mean one or more than one. As used herein "another" may mean at least a second or more. Furthermore, unless otherwise required by context, singular terms include pluralities and plural terms include the singular.

[00056] As used herein, "about" refers to a numeric value, including, for example, whole numbers, fractions, and percentages, whether or not explicitly indicated. The term "about" generally refers to a range of numerical values (e.g., +/-5 to10% of the recited value) that one of ordinary skill in the art would consider equivalent to the recited value (e.g., having the same function or result). In some instances, the term "about" may include numerical values that are rounded to the nearest significant figure. Unless indicated otherwise, "about" is +/-10% of the recited value(s).

[00057] An "antigen-binding polypeptide" is a polypeptide comprising a portion that binds to an antigen. Examples of antigen-binding polypeptides include antibodies, antibody fragments (e.g., an antigen binding portion of an antibody), antibody derivatives, and antibody analogs.

[00058] An antigen binding polypeptide or protein can have, for example, the structure of a naturally occurring antibody (also known as "immunoglobulin". Each naturally occurring antibody is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The variable regions of each light/heavy chain pair form the antibody-binding site such that an intact antibody has two binding sites.

[00059] The variable regions of naturally occurring antibody chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper-variable regions,

also called complementarity determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat et al. in *Sequences of Proteins of Immunological Interest*, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. Other numbering systems for the amino acids in immunoglobulin chains include IMGT (international ImMunoGeneTics information system; Lefranc et al., *Dev. Comp. Immunol.* 29:185-203; 2005) and AHo (Honegger and Pluckthun, *J. Mol. Biol.* 309(3):657-670; 2001).

[00060] Antibodies can be obtained from sources such as serum or plasma that contain immunoglobulins having varied antigenic specificity. If such antibodies are subjected to affinity purification, they can be enriched for a particular antigenic specificity. Such enriched preparations of antibodies usually are made of less than about 10% antibody having specific binding activity for the particular antigen. Subjecting these preparations to several rounds of affinity purification can increase the proportion of antibody having specific binding activity for the antigen. Antibodies prepared in this manner are often referred to as "monospecific." Monospecific antibody preparations can be made up of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, or 99.9% antibody having specific binding activity for the particular antigen.

[00061] The term "antibody" or "Ab" (and their plural forms), as used herein, broadly refers to any immunoglobulin (Ig) molecule comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment(s), mutant(s), variant(s), derivative(s) or analog(s) thereof, which retains the essential and specific epitope-binding features of an Ig molecule. Such fragment, mutant, variant, derivative or analog antibody formats are known in the art, and include, inter alia, Fab, F(ab'), $F(ab')_2$, Fv, single-chain antibodies (scFv), single-domain antibodies (sdAbs), complementarity determining region (CDR) fragments, chimeric antibodies, diabodies, triabodies, tetrabodies, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. Antibody fragments, derivatives and analogs may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies.

[00062] A Fab fragment is a monovalent fragment having the V_L, V_H, C_L and C_{H1} domains; a $F(ab')_2$ fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the V_H and C_{H1} domains; an Fv fragment has the V_L and V_H domains of a single arm of an antibody; and a dAb fragment has a V_H domain, a V_L domain, or an

antigen-binding fragment of a V_H or V_L domain (*see, e.g.,* U.S. Pat. Nos. 6,846,634; 6,696,245, US App. Pub. 20/0202512; 2004/0202995; 2004/0038291; 2004/0009507; 2003/0039958, and Ward et al., *Nature* 341:544-546, 1989).

[00063] A single-chain antibody (scFv) is an antibody in which a V_L and a V_H region are joined via a linker (e.g., a synthetic sequence of amino acid residues) to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site (see, e.g., Bird et al., 1988, *Science* 242:423-26 and Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-83). Diabodies are bivalent antibodies comprising two polypeptide chains, where each polypeptide chain comprises V_H and V_L domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, e.g., Holliger et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:6444-48, and Poljak et al., 1994, *Structure* 2:1121-23). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen-binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.

[00064] Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody may be identified using the system described by Kabat et al. *supra*; Lefranc et al., *supra* and/or Honegger and Pluckthun, *supra*. One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein. An antigen binding polypeptide may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest.

[00065] An antigen binding polypeptide may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a “bispecific” or “bifunctional” antibody has two different binding sites.

[00066] The term “human antibody” or “humanized antibody” as used herein includes all antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and constant domains are derived from human

immunoglobulin sequences (a fully human or humanized antibody). These antibodies may be prepared in a variety of ways, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes. A humanized antibody has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies may be found in U.S. Pat. Nos. 6,054,297, 5,886,152 and 5,877,293.

[00067] The term "chimeric antibody" as used herein refers to an antibody that contains one or more regions from one antibody and one or more regions from at least another antibody. In an embodiment, the CDRs from more than one human anti-PD-L1 antibodies are mixed and matched in a chimeric antibody.

[00068] Activated T cells express PD1 on their cell surface. Binding of PD-L1 to PD1 activates PD1 and suppresses the $PD1^+$ T cells. A "neutralizing antibody" or an "inhibitory antibody" as used herein refers to an antibody that blocks the activation of PD1 when an excess of the anti-PD-L1 antibody reduces the amount of said activation by at least about 20% using an assay such as those described herein in the Examples. In various embodiments, the antigen binding protein reduces the amount of activation of PD1 by at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, and 99.9%.

[00069] Fragments or analogs of antibodies can be readily prepared by those of ordinary skill in the art following the teachings of this specification and using techniques known in the art.

Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Computerized comparison methods can be used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. See, Bowie et al., 1991, *Science* 253:164.

[00070] As used herein, an antigen-binding polypeptide "specifically binds" to an antigen (e.g., human PD-L1) if it binds to the antigen with a dissociation constant of 100 nanomolar or less.

[00071] An "antigen binding domain," "antigen binding region," or "antigen binding site," as used herein, is a portion of an antigen binding protein that contains amino acid residues (or other moieties) that interact with an antigen and contribute to the antigen binding protein's specificity and affinity for the antigen. For an antibody to specifically bind to its antigen, it will include at least part of at least one of its CDR domains.

[00072] An "epitope" as used herein is the portion of a molecule that is bound by an antigen binding protein (e.g., by an antibody). An epitope can comprise non-contiguous portions of the molecule (e.g., in a polypeptide, amino acid residues that are not contiguous in the polypeptide's primary sequence but that, in the context of the polypeptide's tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein).

[00073] As used herein, the terms "polynucleotide," "oligonucleotide" and "nucleic acid" are used interchangeably throughout and include DNA molecules (e.g., cDNA or genomic DNA), RNA molecules (e.g., mRNA), analogs of the DNA or RNA generated using nucleotide analogs (e.g., peptide nucleic acids and non-naturally occurring nucleotide analogs), and hybrids thereof. The nucleic acid molecule can be single-stranded or double-stranded. In one embodiment, the nucleic acid molecules of the invention comprise a contiguous open reading frame encoding an antibody, or a fragment, derivative, mutant, or variant thereof.

[00074] A "vector" as used herein is a nucleic acid that can be used to introduce another nucleic acid linked to it into a cell. One type of vector is a "plasmid," which refers to a linear or circular double stranded DNA molecule into which additional nucleic acid segments can be ligated. Another type of vector is a viral vector (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), wherein additional DNA segments can be introduced into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are

introduced (e.g., bacterial vectors comprising a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. An "expression vector" is a type of vector that can direct the expression of a chosen polynucleotide.

[00075] As used herein, a nucleotide sequence is "operably linked" to a regulatory sequence if the regulatory sequence affects the expression (e.g., the level, timing, or location of expression) of the nucleotide sequence. A "regulatory sequence" is a nucleic acid that affects the expression (e.g., the level, timing, or location of expression) of a nucleic acid to which it is operably linked. The regulatory sequence can, for example, exert its effects directly on the regulated nucleic acid, or through the action of one or more other molecules (e.g., polypeptides that bind to the regulatory sequence and/or the nucleic acid). Examples of regulatory sequences include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Further examples of regulatory sequences are described in, for example, Goeddel, 1990, Gene Expression Technology: *Methods in Enzymology* 185, Academic Press, San Diego, Calif. and Baron et al., 1995, *Nucleic Acids Res.* 23:3605-06.

[00076] Preferably, the broad spectrum of mammalian cancers to be treated by compositions of the present invention is selected from the group consisting of ovarian cancer, colon cancer, breast cancer, lung cancer, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, melanoma, bladder cancer, gastric cancer, liver cancer, urothelial carcinoma, cutaneum carcinoma, renal cancer, head and neck cancer, pancreatic cancer, and combinations thereof. More broadly, any cancer where at least a fraction of the tumor cells express detectable amount of PD-L1 can potentially be treated by the composition of the invention.

[00077] Polypeptides of the present disclosure can be produced using any standard methods known in the art. In one example, the polypeptides are produced by recombinant DNA methods by inserting a nucleic acid sequence (e.g., a cDNA) encoding the polypeptide into a recombinant expression vector and expressing the DNA sequence under conditions promoting expression.

[00078] Nucleic acids encoding any of the various polypeptides disclosed herein may be synthesized chemically. Codon usage may be selected so as to improve expression in a cell. Such codon usage will depend on the cell type selected. Specialized codon usage patterns have been developed for E. coli and other bacteria, as well as mammalian cells, plant cells, yeast cells and

insect cells. See for example: Mayfield et al., *Proc. Natl. Acad. Sci. USA*. 2003 100(2):438-42; Sinclair et al. *Protein Expr. Purif.* 2002 (1):96-105; Connell N D. *Curr. Opin. Biotechnol.* 2001 12(5):446-9; Makrides et al. *Microbiol. Rev.* 1996 60(3):512-38; and Sharp et al. *Yeast.* 1991 7(7):657-78.

[00079] General techniques for nucleic acid manipulation are described for example in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Vols. 1-3, Cold Spring Harbor Laboratory Press, 2 ed., 1989, or F. Ausubel et al., *Current Protocols in Molecular Biology* (Green Publishing and Wiley-Interscience: New York, 1987) and periodic updates, herein incorporated by reference. The DNA encoding the polypeptide is operably linked to suitable transcriptional or translational regulatory elements derived from mammalian, viral, or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants is additionally incorporated.

[00080] The recombinant DNA of the present invention can also include any type of protein tag sequence that may be useful for purifying the protein. Examples of protein tags include but are not limited to a histidine tag, a FLAG tag, a myc tag, an HA tag, or a GST tag. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts can be found in *Cloning Vectors: A Laboratory Manual*, (Elsevier, N.Y., 1985).

[00081] The expression construct of the present invention is introduced into the host cell using a method appropriate to the host cell. A variety of methods for introducing nucleic acids into host cells are known in the art, including, but not limited to, electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (where the vector is an infectious agent). Suitable host cells include prokaryotes, yeast, mammalian cells, or bacterial cells.

[00082] Proteins disclosed herein can also be produced using cell-translation systems. For such purposes the nucleic acids encoding the polypeptide must be modified to allow in vitro transcription to produce mRNA and to allow cell-free translation of the mRNA in the particular cell-free system being utilized (eukaryotic such as a mammalian or yeast cell-free translation system or prokaryotic such as a bacterial cell-free translation system.

[00083] PD-L1-binding polypeptides can also be produced by chemical synthesis (e.g., by the methods described in *Solid Phase Peptide Synthesis*, 2nd ed., 1984, The Pierce Chemical Co., Rockford, Ill.). Modifications to the protein can also be produced by chemical synthesis.

[00084] The polypeptides of the present disclosure can be purified by isolation/purification methods for proteins generally known in the field of protein chemistry. Non-limiting examples include extraction, recrystallization, salting out (e.g., with ammonium sulfate or sodium sulfate), centrifugation, dialysis, ultrafiltration, adsorption chromatography, ion exchange chromatography, hydrophobic chromatography, normal phase chromatography, reversed-phase chromatography, gel filtration, gel permeation chromatography, affinity chromatography, electrophoresis, countercurrent distribution or any combinations of these. After purification, polypeptides may be exchanged into different buffers and/or concentrated by any of a variety of methods known to the art, including, but not limited to, filtration and dialysis.

[00085] The purified polypeptide is preferably at least 85% pure, more preferably at least 90% or 95% pure, and most preferably at least 98% pure. Regardless of the exact numerical value of the purity, the polypeptide is sufficiently purified for use as a pharmaceutical product.

Post-Translational Modifications of Polypeptides

[00086] In certain embodiments, the binding polypeptides of the invention may further comprise post-translational modifications. Exemplary post-translational protein modifications include phosphorylation, acetylation, methylation, ADP-ribosylation, ubiquitination, glycosylation, carbonylation, sumoylation, biotinylation or addition of a polypeptide side chain or of a hydrophobic group. As a result, the modified soluble polypeptides may contain non-amino acid elements, such as lipids, poly- or mono-saccharide, and phosphates. A preferred form of glycosylation is sialylation, which conjugates one or more sialic acid moieties to the polypeptide. Sialic acid moieties improve solubility and serum half-life while also reducing the possible immunogeneticity of the protein. See Raju et al. *Biochemistry*. 2001 31; 40(30):8868-76. Effects of such non-amino acid elements on the functionality of a polypeptide may be tested for its antagonizing role in PD-L1 or PD-1 function, e.g., its inhibitory effect on angiogenesis or on tumor growth.

[00087] In one embodiment, modified forms of the subject polypeptides comprise linking the subject soluble polypeptides to nonproteinaceous polymers. In one specific embodiment, the polymer is polyethylene glycol ("PEG"), polypropylene glycol, or polyoxyalkylenes, in the manner as set forth in U.S. Pat. No. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

[00088] In one feature, the pegylated embodiments of binding polypeptides of the invention preferably retain at least 25%, 50%, 60%, 70%, 80%, 90%, 95% or 100% of the biological activity associated with the unmodified protein. In one embodiment, biological activity refers to its ability to bind to PD-L1, as assessed by KD, k_{on} or k_{off} rates. In one specific embodiment, the pegylated binding polypeptide protein shows an increase in binding to human PD-L1 relative to the unpegylated counterpart. In another embodiment, the biological activity refers to blockage of PD-L1/PD1 interaction.

Therapeutics, Vaccines & Administration

[00089] The present disclosure further features methods for treating conditions or preventing pre-conditions which respond to inhibition of an PD-L1 biological activity. Preferred examples are conditions that are characterized by cellular hyperproliferation and sustained infection. Techniques and dosages for administration vary depending on the type of specific polypeptide and the specific condition being treated. Because regulatory agencies require that a protein reagent to be used as a therapeutic be formulated with acceptably low levels of pyrogens, therapeutic formulations of the present invention can be distinguished from other formulations for being substantially pyrogen free, or at least contain no more than acceptable levels of pyrogen as determined by the appropriate regulatory agency (e.g., U.S. FDA).

[00090] Pharmaceutical formulations of the present invention may include at least one pharmaceutically acceptable diluent, carrier, or excipient. Excipients included in the formulations will have different purposes depending, for example, on the kind of gene construct or effector cells used, and the mode of administration. Examples of generally used excipients include, without limitation: saline, buffered saline, dextrose, water-for-infection, glycerol, ethanol, and combinations thereof, stabilizing agents, solubilizing agents and surfactants, buffers and preservatives, tonicity agents, bulking agents, and lubricating agents.

[00091] In another embodiment of the invention, a pharmaceutical formulation of the invention is administered into the patient. Exemplary administration modes include, but are not limited to, intravenous injection. Other modes include, without limitation, intratumoral, intradermal, subcutaneous (s.c., s.q., sub-Q, Hypo), intramuscular (i.m.), intraperitoneal (i.p.), intra-arterial, intramedullary, intracardiac, intra-articular (joint), intrasynovial (joint fluid area), intracranial, intraspinal, and intrathecal (spinal fluids). Any known device useful for parenteral injection or infusion of the formulations can be used to effect such administration. As used herein, the terms "treat", "treating", and "treatment" have their ordinary and customary meanings, and include one or

more of: blocking, ameliorating, or decreasing in severity and/or frequency a symptom of a disease (e.g., cancer) in a subject, and/or inhibiting the growth, division, spread, or proliferation of cancer cells, or progression of cancer (e.g., emergence of new tumors) in a subject. Treatment means blocking, ameliorating, decreasing, or inhibiting by about 5% to about 100% versus a subject in which the methods of the present invention have not been practiced. Preferably, the blocking, ameliorating, decreasing, or inhibiting is about 100%, 99%, 95%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, or 5% versus a subject in which the methods of the present invention have not been practiced.

[00092] The invention also provides a kit comprising one or more containers filled with quantities of gene constructs encoding the polypeptides of the invention, with pharmaceutically acceptable excipients. The kit may also include instructions for use. Associated with the kit may further be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

EXAMPLES

[00093] *Screening of Antigen-binding Polypeptide Employing Phage Display Techniques:*

[00094] Indirect coating: Referring to FIG. 1, PDL1-binding single chain variable fragments (scFv) were identified by standard phage display technique. Human naïve scFv libraries were generated through PCR-based reconstruction from B cells from 50 healthy donors. Solid phase immunotube-based panning was performed using hPDL1-Fc fusion protein and irrelevant Fc fusion protein indirectly immobilized onto immunotube coated with anti-human IgG Fc antibody. To pan for strong binders, Fc-binding scFvs were first depleted using the irrelevant Fc fusion proteins and then the unbound phages were selected for binding with the hPDL1-Fc fusion protein. Eluted phages were amplified in bacteria. These rounds were repeated 3-4 times and the phage titers and complexity was determined after the second round onwards. Once, convergence in sequence was seen (rounds 3 and 4), individual phage clones were tested for their ability to bind hPDL1 in ELISA assays.

[00095] Direct coating: This was conducted by directly coating the Fc proteins onto the immunotube without the use of the anti-human Fc antibody (FIG. 2).

[00096] *Phage Binding ELISAs:*

[00097] ELISAs were performed using the same strategy as the panning. For clones from the indirect panning, plates were first coated with anti-human Fc antibody and then the Fc protein. For clones from the direct panning, plates were directly coated with the Fc protein. In indirect ELISA assays, phages were tested for their ability to bind hPDL1-Fc and an irrelevant Fc protein (or hIgG1) in parallel assays. Phages that showed low binding to the irrelevant Fc protein and high binding to the hPDL1 were selected for further sequencing and secondary screening. Data were shown in FIG. 3. Non-specific binding of most clones is low (signal value against Fc protein (1:10 dilution) is less than 0.2). In direct ELISA assays, phages were tested for their ability to bind hPDL1-Fc, mPDL1-Fc (mouse PDL1) and hIgG1 in parallel assays. Phages showed that there was no significant binding to mouse PDL1 by any of the lead molecules in the present invention, namely, none of the lead molecules show significant cross-reactivity with mouse PDL1. Data are shown in FIG. 7.

[00098] *Sequencing:*

[00099] Unique clones were identified by initially sequencing the CDR3 region of the heavy chain. This was later confirmed by the complete sequence as well. A small subset of clones shared the same CDR3 but had significant divergence in other parts of their sequences.

[000100] *Secondary Screening by FACS:*

[000101] Phages, phage lysates or lysates from bacteria expressing scFvs were tested for their ability to preferentially bind to 293T cells expressing hPDL1 but not parental 293T cells. The ratio of the mean fluorescence intensity (MFI) was used as the basis for identifying positive clones. Data were shown in FIG. 4. Most clones showed high ratio that could be identified as positive clones.

[000102] *Blocker Identification:*

[000103] Phages, phage lysates or lysates from bacteria expressing scFvs were tested for their ability to block the interaction between hPD1 and hPDL1. The binding assays were set up by either coating the plates with hPD1-Fc or hPDL1-Fc. Binding of the biotinylated ligand (hPDL1 or hPD1) was detected using streptavidin-HRP using standard methods. The loss of binding in the presence of the scFv was used to identify potential blockers. Results are shown in FIGS. 5 and 6.

[000104] *Generation and Characterization of Fc fusion proteins:*

[000105] Since scFvs are relatively unstable, some scFvs were converted to Fc fusions and expressed in mammalian cells. These were purified using Protein A columns and tested for their ability to block PD1-PDL1 interaction as well as their ability to bind PDL1-expressing 293T cells.

[000106] *Generation of Full-Length Antibodies:*

[000107] Full-length antibody genes were constructed by PCR-amplifying the VH and VL regions from individual scFv clones and cloned into appropriate expression vectors using standard methods familiar to one skilled in the art. Full-length antibody proteins were generated by transiently transfecting suspension-grown 293T cells and purified using a Protein A column by standard methods familiar to one skilled in the art.

[000108] *Characterization of Full-length Antibodies:*

[000109] Exemplary full length antibodies were characterized by SDS-PAGE and size exclusion chromatography (result was shown in FIGS. 8A, 8B, 9A, 9B, 10A, and 10B), as well as quantification of their potency in (a) specifically binding hPDL1 by ELISA (result was shown in FIGS. 11B and 11C); (b) specifically binding hPDL1-expressing 293T cells and unstrained 293T cells (results were shown in FIGS. 12A and 12B); and (c) blocking PD1-PDL1 interaction in both versions of the blocking assay. Resulting data for exemplary lead antibody candidates in Format 1 and Format 2 are shown in FIGS. 13B and 14B. Resulting data for 27 antibody embodiments in the present invention are shown in FIG. 15.

[000110] *Affinity of PD-L1 Interaction by BIAcore:*

[000111] The lead antibody candidates were tested for their affinities to PD-L1 using BIAcore (FIGS. 16B-16D). Briefly, biotinylated hPDL1 was captured through streptavidin onto the sensor chip surface. Antibody was made to flow over the chip and the reaction parameters were calculated using a single cycle kinetics method based on the stability of the interaction. KD values were evaluated using BIAcore X100 evaluation software 2.0 with bivalent analyte binding model.

[000112] *Rhesus PD-L1 binding by FACS*

[000113] (A) 293T cells were transiently transfected with Rhesus PDL1-GFP expression construct. Embodiments 4-1E8, 3-1E4 and 3-1B11 were tested and compared to control. Results are shown in FIGS. 18A-18D: all three antibodies bound rhesus PDL1

[000114] (B) 293T cells were transiently transfected with Rhesus PDL1 expression construct. Embodiments 4-1E8, 3-1E4 and 3-1B11 were tested and compared to control. Results are shown in FIGS. 19A-19D: all three antibody embodiments bound rhesus PDL1.

[000115] *IL2 Induction and EC50 Determination*

[000116] Peripheral Blood Mononuclear Cells (PBMCs) were isolated from human blood with a Ficoll gradient, followed by red blood cell lysis, using standard protocols. For the assay, RPMI+ medium was prepared as follows: 10% FBS, 1% anti-anti (Gibco) and 1% non-essential amino acids (Gibco) were added to RPMI medium with ATCC modification (Gibco). After isolation from blood,

PBMCs were resuspended in 10-20 ml RPMI$^+$ and were cultured overnight at 37°C with 5% CO_2. Next, PBMCs were seeded into 96 well tissue culture plates (Corning) at a concentration of 100 000 PBMCs/96 well; the final volume per well was 200 ul. Staphylococcal Enterotoxin B (SEB) was added at a concentration of 1 ng/ml, and lead antibodies were added at 20 ug/ml (for screening) or at a range of concentrations from 50 ug/ml to 0.003 ug/ml. As controls, cells without SEB (e.g. no stimulation); with SEB alone or with SEB and isotype control (e.g., baseline).

[000117] After a 76-hour incubation at 37°C with 5% CO_2, PBMCs were spun down at 1200 rpm for 15 minutes at room temperature, and supernatants were collected and stored at -20°C. IL2 ELISA was performed using a commercially available IL2-ELISA kit (Biolegend or Thermofisher), following instructions from the manufacturer. Supernatants were diluted 1/20 – 1/80 for the ELISA. The absorbance was measured using a Spectramax3 M3 microplate reader (Molecular Devices), and data were analyzed using Graphpad software. The lead antibody candidates were compared to commercially available anti-PD1 antibodies. Results are shown in FIG. 20. In the tumor co-culture experiments with MDA-MB-231 cells (see FIGS. 23A-23C), the 4-1E8 was consistently better than 3-1B11 and 3-1E4 in de-repressing IL2 (see FIGS. 23A-23C) and IFNγ (see FIG. 24). However, all three antibodies were as good or better than commercial PDL1 antibodies such as atezolizumab (Atezo) and durvalumab (Durva) production in similar co-culture experiments with T cells and MDA-MB-231 cells.

[000118] *ADCC activity*

[000119] As shown in FIGS. 21 and 22, all three lead antibodies showed robust ADCC activity while atezolizumab (which is engineered to be ADCC-negative) showed no activity. Among the three embodiments of the invention, 4-1E8 showed the most amount of ADCC activity.

[000120] *Mixed Lymphocyte Reaction*

[000121] Peripheral Blood Mononuclear Cells (PBMCs) were isolated from human blood with a Ficoll gradient, followed by red blood cell lysis, using standard protocols. Cells were cultured in serum-free RPMI 1640 for 1 hour at 37°C. Non-adherent cells were removed, and remaining monocytes were cultured in RPMI 1640 supplemented with 5% human AB serum, 2 ng/mL GM-CSF, and 10 ng/mL IL4 (BD Biosciences). Fresh media with cytokine supplements were added every 2 to 3 days. Mature dendritic cells were induced by addition of 20 ng/mL TNFa (BD Biosciences) on day 6 and cultured for 24 hours.

[000122] Dendritic cells were harvested, phenotyped, and frozen for later use. CD4 T cells were isolated from PBMCs using magnetic beads (Dynal) as per manufacturer's instructions. CD4 T

cells were cultured in 96 well-flat bottom plates (Costar) together with allogeneic dendritic cells at a ratio of 1:2.5, using RPMI 1640 supplemented with 10% human AB serum. Dendritic cells were treated with 100 mg/mL of mitomycin C (Sigma) before addition. Proliferation was measured by CFSE (or similar dye) dilution in T cells. IFNg release was measured using a commercially available IFNg-ELISA kit, following instructions of the manufacturer. The absorbance was measured using a Spectramax3 M3 microplate reader (Molecular Devices), and data were analyzed using graphpad software. In these studies, the lead antibody candidates according to embodiments of the present invention performed comparably to other commercially available anti-PD1 and anti-PDL1 antibodies. Exemplary results are shown in FIGS. 25A and 25B.

[000123] *Binding specificity*

[000124] Lines of Expi293 cells were generated that stably expressed a variety of B7 family members and their receptors. The ability of anti-PDL1 antibodies was tested by FACS using fluorescent anti-human IgG. Resulting data for exemplary lead antibody candidates are shown in FIGS. 26A and 26B.

[000125] *Blocking CD80-PDL1 binding*

[000126] DLD1 cells engineered to express PDL1 bind were used to detect binding of biotinylated CD80-Fc in the presence or absence of anti-PDL1 Abs, followed by fluorescent streptavidin. Resulting data for exemplary lead antibody candidates of the present invention are shown in FIGS. 27A and 27B.

[000127] *Half-life measurement*

[000128] Serum half-life was measured using male homozygous Tg32 mice (B6.Cg-Fcgrttm1Dcr Tg(FCGRT)32Dcr/DcrJ, Jackson labs). 2 mg/kg of antibody was injected IV on Day 0 and blood was drawn on Day 1 and various later time points. Plasma was prepared and antibody titers were measured using a sandwich ELISA. Titers were normalized to Day 1 titers. Anti-antibody response was also measured and samples with high titers were removed from the analysis because they often showed sudden changes in the ELISA. Resulting data for exemplary lead antibody candidates of the present invention are shown in FIG. 28. Half-life for different antibodies ranged from 6.9 days (3-1E4, see Example 9 below for sequence details) to 10.5 days (3-1B11, see Example 11 below for sequence details) and 12.3 days (4-1E8, see Example 5 below for sequence details).

[000129] *Polypeptide Sequences*

[000130] Examples of PD-L1 binding polypeptide sequences according to the present inventions are listed as follows:

Example 1: Antibody code: 4-1A2

VH

[000131] DNA (SEQ ID NO:1)

CAGGTTCAGCTGGTGCAGTCTGGGACTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGGCTTCTGGATACACCTTCACCAGTTATGATATCAACTGGGTGCGACAGGCC
ACTGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTAACAGTGGTGGCACAAACTAT
GCACAGAAGTTTCAGGGCAGGGTCACCATGACCACAGACACTTCTACGGGCACAGCCTAC
ATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGATTTTTA
TGGGGTTCGGGGAGTTATGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000132] AMINO ACID (SEQ ID NO:2)

QVQLVQSGTEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWMGWINPNSGGTNY
AQKFQGRVTMTTDTSTGTAYMELRSLRSDDTAVYYCARFLWGSGSYDYWGQGTLVTVSS

VL

[000133] DNA (SEQ ID NO:3)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTCGCAACTTACTACTGTCAACAGACTTACACATTCCCGCACACTTTTGCCCAG
GGGACCAACCTGGAGATCAAA

[000134] AMINO ACID (SEQ ID NO:4)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGT
DFTLTISSLQPEDFATYYCQQTYTFPHTFAQGTNLEIK

Example 2: Antibody code: 4-1A12

VH

[000135] DNA (SEQ ID NO:5)

CAAGTCCAGCTGGTACAATCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTAT
GCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTAC

ATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGATTGG
ATACAGCTATGGTTACCCCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000136] AMINO ACID (SEQ ID NO:6)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNY
AQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDWIQLWLPLDYWGQGTLVTVSS

VL

[000137] DNA (SEQ ID NO:7)

GACATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAACAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCAGTTTGGAAAGTGGGGTCCCATCA
AGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTCACAGTTCCCCCCTCACTTTCGGCGGA
GGGACCAAGGTGGACATCAAA

[000138] AMINO ACID (SEQ ID NO:8)

DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYGASSLESGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQSHSSPLTFGGGTKVDIK

Example 3: Antibody code: 4-1B9

VH

[000139] DNA (SEQ ID NO:9)

GAAGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAGCCTGGGAGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCT
CCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTAT
GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATTTG
ATCCCGTTGCGAGATAGTAGGGGGGGGTACTACTACGGTATGGACGTCTGGGGCCAAGGG
ACCACGGTCACCGTCTCCTCAGGGAGT

[000140] AMINO ACID (SEQ ID NO:10)

EVQLVQSGGGLVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYY
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDLIPLRDSRGGYYYGMDVWGQG
TTVTVSS

VL

[000141] DNA (SEQ ID NO:11)

TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCTGTGGCCTTGGGACAGACAGTCAGGATC
ACATGCCAAGGAGACAGCCTCAGAGACTATTATGCAAGCTGGTACCAGCAGAAGCCAGGA
CAGGCCCCTGTACTTGTCATCTATGGTAAAAACAACCGGCCCTCAGGAATCCCAGACCGA
TTCTCTGGCTCCAGCTCAGGAAACACAGCTTCCTTGACCATCACTGGGACTCAGGCGGAA
GATGAGGCTGACTATTACTGTAACTCCCGTGACAGCGGTGCTTACCATTATGTCTTCGGA
ACTGGGACCAAGGTCACCGTCCTA

[000142] AMINO ACID (SEQ ID NO:12)

SSELTQDPAVSVALGQTVRITCQGDSLRDYYASWYQQKPGQAPVLVIYGKNNRPSGIPDR
FSGSSSGNTASLTITGTQAEDEADYYCNSRDSGAYHYVFGTGTKVTVL

Example 4: Antibody code: 4-1B12

VH

[000143] DNA (SEQ ID NO:13)

CAAATCCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCT
CCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTAT
GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGGAAGT
ATTATAGGGGATGGTGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

[000144] AMINO ACID (SEQ ID NO:14)

QIQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYY
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSIIGDGAFDIWGQGTMVTVSS

VL

[000145] DNA (SEQ ID NO:15)

GATATTGTGATGACCCAGTCTCCACTCTCCCTGCCCGTCACCCTTGGAGAGCCGGCCTCC
ATCTCCTGCAGGTCTAGTCAGACCCTCCTGCATAATGGATTCAACTTTTTGGATTGGTAC
CTGCAGAAGCCAGGGCAGTCTCCACAACTCCTGATGTATTTGGCCTCTAGCCGGGCCTCC
GGGGTCCCTGACAGGTTCAGTGGCAGTGGATCGGGCACAGATTTCACACTGAAAATCAGC
AGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGGTACACACTGGCCGTAC
ACTTTTGGCCAGGGGACCAAGCTGGATATCAAA

[000146] AMINO ACID (SEQ ID NO:16)

DIVMTQSPLSLPVTLGEPASISCRSSQTLLHNGFNFLDWYLQKPGQSPQLLMYLASSRAS
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPYTFGQGTKLDIK

Example 5: Antibody code: 4-1E8

VH

[000147] DNA (SEQ ID NO:17)

CAAATCCAGCTGGTACAATCTGGGGCTGAGGTGAAGATGCCTGGGGCCTCAGTGACGATT
TCCTGCGAGGCGTCTGGATACAACTTCATCAGCTACTATATACACTGGGTGCGACAGGCC
CCTGGACAAGGCCTTGAGTGGATGGGATTCGTCGTCCCTAGTGGTGGTGCCGCAGGCTAC
ACACAGAAGTTCCAGGGCAGACTCACCGTGACCAGGGACACGTCCACGAGCACAGTCTAC
ATGGACCTGAACAGCCTGACATCTGACGACACGGCCGTGTATTACTGTGTGCGAGAAATG
AGTGGTGGCTGGTTTGATTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCG

[000148] AMINO ACID (SEQ ID NO:18)

QIQLVQSGAEVKMPGASVTISCEASGYNFISYYIHWVRQAPGQGLEWMGFVVPSGGAAGY
TQKFQGRLTVTRDTSTSTVYMDLNSLTSDDTAVYYCVREMSGGWFDFWGQGTLVTVSS

VL

[000149] DNA (SEQ ID NO:19)

GACATCGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAAAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCACTTTGCAAAGTGGGGTCCCATCA
AGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCT
GAAGATGTGGCAGTTTATTACTGTCAGCAATATTATAGTACTCCTCTCACTTTCGGCCCT
GGGACCAAAGTGGATATCAAA

[000150] AMINO ACID (SEQ ID NO:20)

DIVMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYAASTLQSGVPS
RFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPLTFGPGTKVDIK

Example 6: Antibody code: 4-1G7

VH

[000151] DNA (SEQ ID NO:21)

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTAT
GCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTAC
ATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGCCTCA
CCGGTACAGCAGCCCATATGGTGGGCGGAGTACTGGGGCCAGGGAACCCTGGTCACCGTC
TCCTCA

[000152] AMINO ACID (SEQ ID NO:22)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNY
AQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARASPVQQPIWWAEYWGQGTLVTV
SS

VL

[000153] DNA (SEQ ID NO:23)

CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATC
TCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTATGTCTCCTGGTACCAACAG
CACCCAGGCAAAGCCCCCAAACTCATGATTTCTGATGTCAGTAAGCGGCCCTCAGGGGTT
TCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTC
CAGGCTGAGGACGAGGCTGATTATTACTGCAGCTCATATACAAGCAACTACACTTTGGTA
TTCGGCGGAGGGACCAAGCTGACCGTCCTA

[000154] AMINO ACID (SEQ ID NO:24)

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMISDVSKRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSNYTLVFGGGTKLTVL

Example 7: Antibody code: 4-1H10

VH

[000155] DNA (SEQ ID NO:25)

CAGCTGCAGCTACAGCAGTCCGGAGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTCCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAAGGATCATCCCTATCCTTGGTATAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAAGACACGGCCGTGTATTACTGTGCGAGTCATGGT
CGGGCAGCAGCTGGTAGGTACGCTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTC
TCCTCA

[000156] AMINO ACID (SEQ ID NO:26)

QLQLQQSGAEVKKPGSSVKVSCKAPGGTFSSYAISWVRQAPGQGLEWMGRIIPILGIANY
AQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCASHGRAAAGRYAMDVWGQGTTVTV
SS

VL

[000157] DNA (SEQ ID NO:27)

AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGATTCTCCGGGGAAGACGGTAACCATC

TCCTGCACCCGCAGCAGTGGCAGCATTGCCAGCAACTATGTGCAGTGGTACCAGCAGCGC
CCGGGCAGTGCCCCCACCACTGTGATCTATGACGATAAGCAAAGACCCTCTGGGGTCCCT
GATCGGTTCTCGGGCTCCATCGACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCTGGA
CTGACGACTGAGGACGAGGCTGACTACTACTGTCAGTCCTTTGATGGCAGCAGTGTCATC
TTCGGCGGAGGGACCAAGCTGACCGTCCTG

[000158] AMINO ACID (SEQ ID NO:28)

NFMLTQPHSVSDSPGKTVTISCTRSSGSIASNYVQWYQQRPGSAPTTVIYDDKQRPSGVP
DRFSGSIDSSSNSASLTISGLTTEDEADYYCQSFDGSSVIFGGGTKLTVL

Example 8: Antibody code: 3-1H2

VH

[000159] DNA (SEQ ID NO:29)

CAGGTTCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAAAGGAG
CGTTTCTATGATAGTAGTGGTTATTACGATGCTTTTGATATCTGGGGCCAAGGGACAATG
GTCACCGTCTCTTCA

[000160] AMINO ACID (SEQ ID NO:30)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARKERFYDSSGYYDAFDIWGQGTM
VTVSS

VL

[000161] DNA (SEQ ID NO:31)

CAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTCTCCTGGGCAGTCAGTCACCATC
TCCTGCACTGGAACCAGCAATGATGTTGGTGGTTATAACTATGTCTCCTGGTACCAACAG
CACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAAGCGGCCCTCAGGGGTC
CCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGCCTC
CAGCCTGAGGATGAGGCTGACTATTATTGCGCCTCTTATGGAGGCAGGAACAATTTGCTT
TTTGGCGGAGGGACTCAACTGACCGTCTTA

[000162] AMINO ACID (SEQ ID NO:32)

QSALTQPRSVSGSPGQSVTISCTGTSNDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV
PDRFSGSKSGNTASLTVSGLQPEDEADYYCASYGGRNNLLFGGGTQLTVL

Example 9: Antibody code: 3-1E4

VH

[000163] DNA (SEQ ID NO:33)

CAAATCCAGCTGGTACAATCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCCGGAGGGGGA
GCAGTGGCGGACAATAGTTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000164] AMINO ACID (SEQ ID NO:34)

QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCAGGGAVADNSYWGQGTLVTVSS

VL

[000165] DNA (SEQ ID NO:35)

GACATCCGGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTACAAAGTGGGGTCCCATCA
AGGTTCAGCGGCAGTGGATCTGGCACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT
GAAGATTTTGCAACTTATTACTGTCTACAAGATTACAATTACCCTCGAACGTTCGGCCAA
GGGACCAAGGTGGAAATCAAA

[000166] AMINO ACID (SEQ ID NO:36)

DIRMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYAASSLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCLQDYNYPRTFGQGTKVEIK

Example 10: Antibody code: 3-1A8

VH

[000167] DNA (SEQ ID NO:37)

CAAATCCAGCTGGTACAATCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACGGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGACGGT
TCGTATAGCAGCAGCTGGTACTCGTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTC

TCCTCA

[000168] AMINO ACID (SEQ ID NO:38)

QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDGSYSSSWYSFDYWGQGTLVTV
SS

VL

[000169] DNA (SEQ ID NO:39)

CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATC
TCCTGCACTGGAACCAGCAGTGACGTCGGTGGTTATAACTATGTCTCCTGGTACCAACAG
CACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAATCGGCCCTCAGGGGTT
TCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTC
CAGGCTGAGGACGAGGCTGATTATTACTGCTCCTCATATGCAGGTGATATTAGTTATGTA
CTGTTCGGCGGCGGGACCAAGCTGACCGTCCTA

[000170] AMINO ACID (SEQ ID NO:40)

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYAGDISYVLFGGGTKLTVL

Example 11: Antibody code: 3-1B11

VH

[000171] DNA (SEQ ID NO:41)

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGAGGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTCACTTTTAGTGACTATGACATGATCTGGGTCCGCCAGGCT
CCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTAT
GCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTAT
CTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGAGTTC
TTTGGTGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

[000172] AMINO ACID (SEQ ID NO:42)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYDMIWVRQAPGKGLEWVAVISYDGSNKYY
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKEFFGAFDIWGQGTMVTVSS

VL

[000173] DNA (SEQ ID NO:43)

TCTTCTGAGCTGACTCAGGACCCTGCTGTGTCGGTGGCCTTGGGACAGACAGTCACGATC
ACATGCCAAGGAGACAGCCTCAATTACTATTATGCAAACTGGTTCCAGCTGAAGCCAGGG

CAGGCCCCTGTACTTGTCCTCTTTGGTAAAAACAACCGGCCCTCAGGGATCCCAGACCGA
TTCTCTGGCTCCTACTCGGGAAGCACAGCTTCCTTGACCATCACTGGGGCTCAGGCGGAA
GATGACGCTGACTATTACTGTAATTCGCGGGACAGCGGTGGTAATCCTTGGGTGTTCGGC
GGAGGGACCAAGCTGACCGTCCTA

[000174] AMINO ACID (SEQ ID NO:44)

SSELTQDPAVSVALGQTVTITCQGDSLNYYYANWFQLKPGQAPVLVLFGKNNRPSGIPDR
FSGSYSGSTASLTITGAQAEDDADYYCNSRDSGGNPWVFGGGTKLTVL

Example 12: Antibody code: 4-1F3

VH

[000175] DNA (SEQ ID NO:45)

CAAATCCAGCTGGTACAATCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAAGGATCATCCCTATCCTTGGTATAGCAGACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
ATGGAACTGAGTAGCCTGGGATCTGAGGACACGGCCGTGTATTTTTGTGCGAGAGAGGGG
GGATCCTTTAGGCACTTTGACTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000176] AMINO ACID (SEQ ID NO:46)

QIQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPILGIADY
AQKFQGRVTITADKSTSTAYMELSSLGSEDTAVYFCAREGGSFRHFDFWGQGTLVTVSS

VL

[000177] DNA (SEQ ID NO:47)

CAGCCTGTGCTGACTCAGCCACCCTCAGTCTCTGGGGCCCCAGGGCAGAGGGTCACCATC
TCCTGCGCTGGGAGCGACCCCAACATCGGGACAGGTCATGATGTGCACTGGTACCAGCAA
CTTCCAGGAACAGCCCCCAAACTCGTCATCTATGGTAACACCAATCGGCCCTCAGGGGTC
CCTGAGCGATTCACTGCCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGGCTC
CAGGCTGAGGATGAGGCTGATTATTACTGCCAGGCCTACGACAGGAGCCTGCGTGGTTAT
GTCTTCGGGACTGGGACCAAGGTCACCGTCCTG

[000178] AMINO ACID (SEQ ID NO:48)

QPVLTQPPSVSGAPGQRVTISCAGSDPNIGTGHDVHWYQQLPGTAPKLVIYGNTNRPSGV
PERFTASKSGTSASLAITGLQAEDEADYYCQAYDRSLRGYVFGTGTKVTVL

Example 13: Antibody code: 4-1G5

VH

[000179] DNA (SEQ ID NO:49)

CAAATCCAGCTGGTACAGTCTGGTGCTGAAGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGACTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTAT
GCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTAC
ATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAACTACA
GGTGACGAGTGGCTACGATTGGCTATAAATGACTACTGGGGCCAGGGAACCCTGGTCACC
GTCTCCTCA

[000180] AMINO ACID (SEQ ID NO:50)

QIQLVQSGAEVKKPGASVKVSCKTSGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNY
AQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARTTGDEWLRLAINDYWGQGTLVT
VSS

VL

[000181] DNA (SEQ ID NO:51)

GATATTGTGATGACACAGTCTCCCCTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCC
ATCTCCTGCAGGTCTAGTCTGCGCCTCATGCATCCTAATGGACTCAACTATTTGGATTGG
TACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTAATCTTTTTGGGTTCTCAGCGGGCC
TCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACACTGAAAATC
AGCAGAGTGGAGGCTGAGGATGTTGGCATTTATTACTGCATGCAAGCTCTAGAACCTCCG
TACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA

[000182] AMINO ACID (SEQ ID NO:52)

DIVMTQSPLSLPVTPGEPASISCRSSLRLMHPNGLNYLDWYLQKPGQSPQLLIFLGSQRA
SGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCMQALEPPYTFGQGTKLEIK

Example 14: Antibody code: 4-1C9

VH

[000183] DNA (SEQ ID NO:53)

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCCC
GGGTATAGCAGTGGCTGGAAAGATGATGCTTTTGATATCTGGGGCCAAGGGACAATGGTC
ACCGTCTCTTCA

[000184] AMINO ACID (SEQ ID NO:54)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDPGYSSGWKDDAFDIWGQGTMV
TVSS

VL

[000185] DNA (SEQ ID NO:55)

GAAATTGTGATGACACAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGATACAGCCTCC
CTCTCCTGCAGGGCCAGTCAGACTGTTAGCAGCAACTACTTAGCCTGGTACCAACAGAAA
CCTGGCCAGGCTCCCAGGCTCCTCATCTATGATACATCCAACAGGGCCGCTGGCATCCCG
GCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGTAGCCTAGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTACGGTAGCTCACTCTGGACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAA

[000186] AMINO ACID (SEQ ID NO:56)

EIVMTQSPGTLSLSPGDTASLSCRASQTVSSNYLAWYQQKPGQAPRLLIYDTSNRAAGIP
ARFSGSGSGTDFTLTISSLEPEDFAVYYCQQYGSSLWTFGQGTKVEIK

Example 15: Antibody code: 11-A4

VH

[000187] DNA (SEQ ID NO:57)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGCGGGG
CAGCAGCTGGTAGCCCTTTGGTACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000188] AMINO ACID (SEQ ID NO:58)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARAGQQLVALWYYWGQGTLVTVSS

VL

[000189] DNA (SEQ ID NO:59)

CAGTCTGCCCTGACTCAGCCTCCCTCCGCGTCCGGGTCTCGTGGACAGTCAGTCTCCATC
TCCTGCAGTGGAAGTCGCAGTGACATTGGATATTATAACTATGTCTCCTGGTATCAACAA
CACCCAGGCAAAGCCCCCAAACTCATCATTTTTGACGTCAATAAGCGGCCCTCAGGGGTC

CCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGCCTC
CAGCCTGAGGATGAGGCTGACTATTATTGCGCCTCTTATGGAGGCAGGAACAATTTGCTT
TTTGGCGGAGGGACTCAACTGACCGTCTTA

[000190] AMINO ACID (SEQ ID NO:60)

QSALTQPPSASGSRGQSVSISCSGSRSDIGYYNYVSWYQQHPGKAPKLIIFDVNKRPSGV
PDRFSGSKSGNTASLTVSGLQPEDEADYYCASYGGRNNLLFGGGTQLTVL

Example 16: Antibody code: 21-A1

VH

[000191] DNA (SEQ ID NO:61)

CAGGTGCAACTGCAGGAGTCGGGCCCAGGACTGGTGGAGCCTTCGGAGACCCTGTCCCTC
ACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTTCTACTGGAGCTGGATCCGGCAGCCC
CCAGGGAAGGGACTGGAGTGGATTGGCTATATCAATTACAGTGGGAGCACCAACTACAAC
CCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTG
AAGCTGAGCTCTGTGACCGCCGCAGACACGGCTGTGTATTACTGTGCGAGACAGATATTA
TGGTTCGGGGAGTTAAGGTGGTTCGACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCC
TCA

[000192] AMINO ACID (SEQ ID NO:62)

QVQLQESGPGLVEPSETLSLTCTVSGGSISSFYWSWIRQPPGKGLEWIGYINYSGSTNYN
PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARQILWFGELRWFDPWGQGTLVTVS
S

VL

[000193] DNA (SEQ ID NO:63)

CAGTCTGCCCTGACTCAGCCTCCCTCCGCGTCCGGGTCTCCTGGACAGTCAGTCACCATC
TCCTGCACTGGAACCAGCAGTGACATTGGTGGTTATAACTATGTCTCCTGGTACCAACTG
CGCCCAGGCAAAGCCCCCAAACTCATGATTTATGACGTCACCAAGCGGCCCTCAGGGGTC
CCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCGTCTCTGGGCTC
CAGGCTGAGGATGAGGCTGATTATTACTGCAGCTCATATGCAGGCAGCAACAATGTGGTA
TTCGGCGGAGGGACCAAGCTGACCGTCCTA

[000194] AMINO ACID (SEQ ID NO:64)

QSALTQPPSASGSPGQSVTISCTGTSSDIGGYNYVSWYQLRPGKAPKLMIYDVTKRPSGV
PDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNNVVFGGGTKLTVL

Example 17: Antibody code: 21-H12

VH

[000195] DNA (SEQ ID NO:65)

CAAGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAAATCCC
TACGGTTTCAACTGGTTCGACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000196] AMINO ACID (SEQ ID NO:66)

QVQLVQSGAEVKKPGASVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARNPYGFNWFDPWGQGTLVTVSS

VL

[000197] DNA (SEQ ID NO:67)

AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACCATC
TCCTGCACCCGCAGCAGTGGCAGCATTGCCAGCAACTATGTGCAGTGGTACCAGCAGCGC
CCGGGCAGTGCCCCCACCACTGTGATCTATGAGGATAACCAAAGACCCTCTGGGGTCCCT
GATCGGTTCTCTGGCTCCATCGACAGCTCCTCCAACTCTGCCTCCCTCACCATCTCCGGA
CTGAAGACTGAGGACGAGGCTGACTACTACTGTCAGTCTTATGATGGCTTCAATCAGGTG
TTCGGCGGAGGGACCAAGCTGACCGTCCTA

[000198] AMINO ACID (SEQ ID NO:68)

NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSAPTTVIYEDNQRPSGVP
DRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDGFNQVFGGGTKLTVL

Example 18: Antibody code: 7-D12

VH

[000199] DNA (SEQ ID NO:69)

CAAATGCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAACCGGT
AGTAGTGGTTATGTACGTTGGAGCAACTGGTTCGACCCCTGGGGCCAGGGAACCCTGGTC
ACCGTCTCCTCA

[000200] AMINO ACID (SEQ ID NO:70)

QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARTGSSGYVRWSNWFDPWGQGTLV
TVSS

VL

[000201] DNA (SEQ ID NO:71)

GACATCCAGATGACCCAGTCTCCCTCCACCCTGTCTGCATTTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCCAGTGAGAGTATTAGTAGGTGGTTGGCCTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAACTCCTAATCTCTAAGACGTCTAATTTAGAAAGCGGGGTCCCGTCA
AGGTTCAGTGGCGCTGGATCTGGGACAGATTTCACTCTCACCATTAGCAGTCTGCAACCT
GAGGATTTTGCAACTTACTTCTGTCAACAGGGTTCCAAAATGCCTCCGACTTTCGGCGGA
GGGACCAAGGTGGAGATCAAG

[000202] AMINO ACID (SEQ ID NO:72)

DIQMTQSPSTLSAFVGDRVTITCRASESISRWLAWYQQKPGKAPKLLISKTSNLESGVPS
RFSGAGSGTDFTLTISSLQPEDFATYFCQQGSKMPPTFGGGTKVEIK

Example 19: Antibody code: 9-E3

VH

[000203] DNA (SEQ ID NO:73)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGGGCC
TACGGTGGTAACTCCGCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000204] AMINO ACID (SEQ ID NO:74)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGAYGGNSAFDYWGQGTLVTVSS

VL

[000205] DNA (SEQ ID NO:75)

CAGTCTGTGCTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTCACCATC
TCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGGTTATGATGTACACTGGTACCAGCAG
CTTCCAGGAACAGCCCCCAAACTCCTCATGTACAGTAATGATCAGCGGCCCTCAGGGGTC

ACTGAGCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGGCTC
CAGTCTGAAGATGAGGGTGATTACTACTGCCAGTCCTATGACAGAAGCCTGAGAGGTTCG
GTCTTCGGCGGAGGGACCAAGCTGACCGTCCTC

[000206] AMINO ACID (SEQ ID NO:76)

QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLMYSNDQRPSGV
TERFSGSKSGTSASLAISGLQSEDEGDYYCQSYDRSLRGSVFGGGTKLTVL

Example 20: Antibody code: 10-A6

VH

[000207] DNA (SEQ ID NO:77)

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTT
TCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTAT
GCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTAC
ATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGATTCC
ATAGCAGCAGCTGGTACTCCGTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC
TCA

[000208] AMINO ACID (SEQ ID NO:78)

EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNY
AQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDSIAAAGTPFDYWGQGTLVTVS
S

VL

[000209] DNA (SEQ ID NO:79)

AATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTCACCATC
TCCTGCACCCGCAGCAGTGGCATCATTGCCAGCAAATATGTGCACTGGTACCAGCAGCGC
CCGGGCAGTGCCCCCACCACTGTGATCTATGAGGATAACCAAAGACCGTCTGGGGTCCCT
GATCGATTCTCTGGCTCCATCGACAACTCCTCCAACTCTGCCTCCCTCACCATCTCTGGA
CTGCAGACTGAGGACGAGGCTGACTACTACTGTCAGTCTCATGACGGCATCAATCAGGTT
TTCGGCGGAGGGACCAAGGTCACCGTCCTA

[000210] AMINO ACID (SEQ ID NO:80)

NFMLTQPHSVSESPGKTVTISCTRSSGIIASKYVHWYQQRPGSAPTTVIYEDNQRPSGVP
DRFSGSIDNSSNSASLTISGLQTEDEADYYCQSHDGINQVFGGGTKVTVL

Example 21: Antibody code: 12-A4

VH

[000211] DNA (SEQ ID NO:81)

GAGGTGCAGCTGGTGGAGTCCCGGGGAGGCTTGGTACAGCCGGGGGGGTCCCTGAGACTC
TCCTGTGTAACTTCTGGATTCAGCTTTAACAACTATGCCATGAACTGGGTCCGCCAGGCT
CCGGGGAAGGGGCTGGAGTGGGTCTCAGCTGTTAGTGGTAGTGGTGGTACCACATACTAC
GCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTTT
GTGCAGATGGACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGGACTT
TTCCCTACGATTTTTGGAGTAGGAGCAATGTTTGACTACTGGGGCCAGGGAACCCTGGTC
ACCGTCTCCTCA

[000212] AMINO ACID (SEQ ID NO:82)

EVQLVESRGGLVQPGGSLRLSCVTSGFSFNNYAMNWVRQAPGKGLEWVSAVSGSGGTTYY
ADSVKGRFTISRDNSKNTLFVQMDSLRAEDTAVYYCAKGLFPTIFGVGAMFDYWGQGTLV
TVSS

VL

[000213] DNA (SEQ ID NO:83)

TCTTCTGAGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACCATC
TCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATGCTGTTAACTGGTATCAGCAGCTC
CCAGGAACGGCCCCCAAACTCCTCATCTATGATAATAATCACCGGCCCTCAGGGGTCCCT
GACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGGCTCCAG
TCTGAGGATGAGGCTGATTATTATTGTGCAGCATGGGATGACACCATTCCTGGTGTGCTA
TTCGCCGGAGGGACCAAGCTGACCGTCCTA

[000214] AMINO ACID (SEQ ID NO:84)

SSELTQPPSASGTPGQRVTISCSGSSSNIGSNAVNWYQQLPGTAPKLLIYDNNHRPSGVP
DRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDTIPGVLFAGGTKLTVL

Example 22: Antibody code: 14-G10

VH

[000215] DNA (SEQ ID NO:85)

GAAGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGTGTT

TCTTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

[000216] AMINO ACID (SEQ ID NO:86)

EVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGVSYYYGMDVWGQGTTVTVSS

VL

[000217] DNA (SEQ ID NO:87)

CAGGCTGTGCTGACTCAGCCACCCTCGGTGTCCGTGTCCCCAGGACAGACAGCCATCATC
TCCTGTTCTGGACATAAATTGGGTGATAAGTATGTTTCCTGGTATCAACAGCAGCCAGGC
CAGTCCCCTGTGCTGGTCCTCTTTCAGGATACCAAGCGGCCCTCAGGGATCCCTGAGCGA
TTCTCTGGCTCCAACTCTGGGAACACAGCCACTCTGACCATCAGCGCGACCCAGGCTGCG
GATGAGGCTGACTATTACTGTCAGGCGGGGGACACCAAGTCTGTGATCTTCGGCGGCGGG
ACCAAGCTGACCGTCCTA

[000218] AMINO ACID (SEQ ID NO:88)

QAVLTQPPSVSVSPGQTAIISCSGHKLGDKYVSWYQQQPGQSPVLVLFQDTKRPSGIPER
FSGSNSGNTATLTISATQAADEADYYCQAGDTKSVIFGGGTKLTVL

Example 23: Antibody code: 22-A6

VH

[000219] DNA (SEQ ID NO:89)

CAGGTTCAGGTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGGCAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGATAC
AGCTATGGTTCAGGACACCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000220] AMINO ACID (SEQ ID NO:90)

QVQVVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGYSYGSGHLDYWGQGTLVTVSS

VL

[000221] DNA (SEQ ID NO:91)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCAGGCGAGTCAGGACATTAGCAACTATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGAAACAGGGGTCCCATCA

AGGTTCAGTGGCAGTGGATCTGGGACAGATTTCGCTCTCACCATCAGCAGTCTCCAACCT
GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCTCGGACTTTTGGCCAG
GGGACCAAGCTGGAGATCAAA

[000222] AMINO ACID (SEQ ID NO:92)

DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPS
RFSGSGSGTDFALTISSLQPEDFATYYCLQHNSYPRTFGQGTKLEIK

Example 24: Antibody code: 35-B1

VH

[000223] DNA (SEQ ID NO:93)

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATATGCACTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATGAACCCTAACAGTGGTGACACAGCCTAT
ACACAGAACTTCCAGGGCAGAGTCACCATGACCAGGAACCCCTCCATAAGCACAGCCTAC
ATGGAGCTGAGCAACCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCCGG
GGGTTCGCGGAGAAGCCCCTTGGGTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000224] AMINO ACID (SEQ ID NO:94)

EVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWMNPNSGDTAY
TQNFQGRVTMTRNPSISTAYMELSNLRSEDTAVYYCARGRGFAEKPLGYWGQGTLVTVSS

VL

[000225] DNA (SEQ ID NO:95)

GATATTGTGATGACTCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGGGAGGGCCACC
ATCAACTGCAAGTCCAGCCAGAGTATTTTATCCAGCTCCAATAATAAGAACTATTTAGCT
TGGTACCAGCAGAAACCAGGTCAGCCTCCTAAGCTGCTCATTTACTGGGCATCTACCCGG
GAATCCGGGGTCCCTGACCGGTTCAGCGGCAGCGGGTCTGGGACAGATTTCACTCTCACC
ATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATTATAGTACT
CCTCCGACATTCGGCCAAGGGACCAAGGTGGAAATCAAA

[000226] AMINO ACID (SEQ ID NO:96)

DIVMTQSPDSLAVSLGGRATINCKSSQSILSSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPPTFGQGTKVEIK

Example 25: Antibody code: 3-1F4

VH

[000227] DNA (SEQ ID NO:97)

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTC
TCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTAC
GCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTAC
ATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGGGCCCCT
CGAGGGCAGTGGCTGGTTCACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTC
TCCTCA

[000228] AMINO ACID (SEQ ID NO:98)

EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARAPRGQWLVHYFDYWGQGTLVTV
SS

VL

[000229] DNA (SEQ ID NO:99)

GAAATTGTGTTGACGCAGTCTCCAGCCACCCTCTCTCTGTCTCCAGGGGAAAGAGCCACC
CTCTCCTGCTGGGCCAGTCAGGATGTTAGCAACTACTTAGCCTGGTACCAACAGAAGCCT
GGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGCC
AGGTTCAGCGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGCCTAGAGCCT
GAAGATTTTGCAGTGTATTACTGTCAGCAACGTAGCAACTGGCCTCTCACTTTCGGCGGC
GGGACCAAGGTGGAGCTCAAA

[000230] AMINO ACID (SEQ ID NO:100)

EIVLTQSPATLSLSPGERATLSCWASQDVSNYLAWYQQKPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGGGTKVELK

Example 26: Antibody code: 4-1B3

VH

[000231] DNA (SEQ ID NO:101)

CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTC
TCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGGTGCGACAGGCC
CCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTAT
GCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGCACAGCCTAC
ATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGAGTCC
TACTCGTCCGCAGGTATTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

[000232] AMINO ACID (SEQ ID NO:102)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNY
AQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARESYSSAGIDYWGQGTLVTVSS

VL

[000233] DNA (SEQ ID NO:103)

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCC
ATCTCCTGCAGGTCTAGTCAGACCCTCCTGCATAGTAATGGATTCAACTATTTGGATTGG
TACCTGCAGAAGCCAGGGCAGTCTCCACAACTCCTGATGTATTTGGGCTCTAGCCGGGCC
TCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCGGGCACAGATTTCACACTGAAAATC
AGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAACTCTACAAACTCCT
CCGGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

[000234] AMINO ACID (SEQ ID NO:104)

DIVMTQSPLSLPVTPGEPASISCRSSQTLLHSNGFNYLDWYLQKPGQSPQLLMYLGSSRA
SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQTLQTPPAFGGGTKVEIK

Example 27: Antibody code: 21-G1

VH

[000235] DNA (SEQ ID NO:105)

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGACGATT
TCCTGCGAGGCGTCTGGATACAACTTCATCAGCTACTATATACACTGGGTGCGACAGGCC
CCTGGACAAGGCCTTGAGTGGATGGGATTCGTCGTCCCTAGTGGTGGTGCCGCAGGCTAC
ACACAGAAGTTCCAGGGCAGACTCACCGTGACCAGGGACACGTCCACGAGCACAGTCTAC
ATGGACCTGAACAGCCTGACATCTGACGACACGGCCGTGTATTACTGTGTGCGAGAAATG
AGTGGTGGCTGGTTTGATTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCG

[000236] AMINO ACID (SEQ ID NO:106)

QVQLVQSGAEVKKPGASVTISCEASGYNFISYYIHWVRQAPGQGLEWMGFVVPSGGAAGY
TQKFQGRLTVTRDTSTSTVYMDLNSLTSDDTAVYYCVREMSGGWFDFWGQGTLVTVSS

VL

[000237] DNA (SEQ ID NO:107)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC
ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCA
GGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCA
AGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT
GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCGATCACCTTCGGCCAA

GGGACACGACTGGAGATTAAA

[000238] AMINO ACID (SEQ ID NO:108)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQSYSTPITFGQGTRLEIK

[000239] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

[000240] Throughout this application, various publications, patents, and/or patent applications are referenced in order to more fully describe the state of the art to which this invention pertains. The disclosures of these publications, patents, and/or patent applications are herein incorporated by reference in their entireties to the same extent as if each independent publication, patent, and/or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

1. An antigen-binding polypeptide that binds to a human PD-L1 epitope, comprising a heavy chain variable domain and a light chain variable domain, wherein the respective sequences thereof consist essentially of:

   (a) SEQ ID NO: 18 and SEQ ID NO: 20;

   (b) SEQ ID NO: 42 and SEQ ID NO: 44;

   or

   (c) SEQ ID NO: 34 and SEQ ID NO: 36.

2. An antigen-binding polypeptide that binds to a human PD-L1 epitope, comprising a heavy chain variable domain and a light chain variable domain, wherein the respective sequences thereof consist essentially of:

   (a) SEQ ID NO: 22 and SEQ ID NO: 24;

   (b) SEQ ID NO: 2 and SEQ ID NO: 4;

   (c) SEQ ID NO: 62 and SEQ ID NO: 64;

   or

   (d) SEQ ID NO: 82 and SEQ ID NO: 84.

3. An antigen-binding polypeptide that binds to a human PD-L1 epitope, comprising a heavy chain variable domain and a light chain variable domain, wherein the respective sequences thereof consist essentially of:

   (a) SEQ ID NO: 70 and SEQ ID NO: 72;

   (b) SEQ ID NO: 50 and SEQ ID NO: 52;

   (c) SEQ ID NO: 102,and SEQ ID NO: 104;

   or

   (d) SEQ ID NO: 30 and SEQ ID NO: 32.

4. An antigen-binding polypeptide that binds to a human PD-L1 epitope, comprising a heavy chain variable domain and a light chain variable domain, wherein the respective sequences thereof consist essentially of:

(a) SEQ ID NO: 6 and SEQ ID NO: 8;

(b) SEQ ID NO: 10 and SEQ ID NO: 12;

(c) SEQ ID NO: 14 and SEQ ID NO: 16;

(d) SEQ ID NO: 26 and SEQ ID NO: 28;

(e) SEQ ID NO: 38 and SEQ ID NO: 40;

(f) SEQ ID NO: 46 and SEQ ID NO: 48;

(g) SEQ ID NO: 54 and SEQ ID NO: 56;

or

(h) SEQ ID NO: 58 and SEQ ID NO: 60.

5. An antigen-binding polypeptide that binds to a human PD-L1 epitope, comprising a heavy chain variable domain and a light chain variable domain, wherein the respective sequences thereof consist essentially of:

(a) SEQ ID NO: 66 and SEQ ID NO: 68;

(b) SEQ ID NO: 74 and SEQ ID NO: 76;

(c) SEQ ID NO: 78 and SEQ ID NO: 80;

(d) SEQ ID NO: 86 and SEQ ID NO: 88;

(e) SEQ ID NO: 90 and SEQ ID NO: 92;

(f) SEQ ID NO: 94 and SEQ ID NO: 96;

(g) SEQ ID NO: 98 and SEQ ID NO: 100;

or

(h) SEQ ID NO: 106 and SEQ ID NO: 108.

6. The antigen-binding polypeptide of claim 1, wherein the polypeptide has a heavy chain variable domain sequence that is at least 95% identical to SEQ ID NO: 18 and

a light chain variable domain sequence that is at least 95% identical to SEQ ID NO: 20.

7. The antigen-binding polypeptide of any of claims 1-6 wherein the polypeptide is a fully human antibody.
8. The antigen-binding polypeptide of claim 7, wherein the antibody further comprise a human constant region, wherein the human constant region has ADCC and/or CDC activities.
9. A nucleic acid molecule that encodes the antigen-binding polypeptide of any of claims 1-6, wherein the nucleic acid molecule is a DNA molecule or RNA molecule.
10. The nucleic acid molecule of claim 9, wherein the nucleic acid molecule consists essentially of: (a) SEQ ID NO: 17 and SEQ ID NO:19; (b) SEQ ID NO:33 and SEQ ID NO:35; or (c) SEQ ID NO:41 and SEQ ID NO:43.
11. An antibody that binds to a human PD-L1 epitope, comprising a substantially identical pair of a heavy chain variable domain and a light chain variable domain of any of claims 1-6.
12. A pharmaceutical composition comprising the antigen-binding polypeptide of claims 1-8 or the antibody of claims 11, and a pharmaceutically acceptable excipient, carrier or diluent.
13. A method of treating a subject in need thereof for a condition therapeutically, said method comprising administering to said subject a therapeutically effective amount of the pharmaceutical composition of claim 12.
14. A method of treating a subject in need thereof for a condition therapeutically, said method comprising administering to said subject a therapeutically effective amount of the pharmaceutical composition of claim 13 in combination with (a) antibodies targeting other immunosuppressive pathways; (b) chemotherapy or radiation therapy;

(c) other mechanisms of blocking immunosuppressive pathways; or (d) other immunotherapy agents.

15. The method of any of claims 13-14, wherein said condition is mammalian cancer selected from the group consisting of: ovarian cancer, colon cancer, breast cancer, lung cancer, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, mast cell derived tumors, melanoma, bladder cancer, gastric cancer, liver cancer, urothelial carcinoma, cutaneum carcinoma, renal cancer, head and neck cancer, pancreatic cancer, and combinations thereof.
16. The method of claim 15, wherein said mammalian cancer has at least a fraction of the tumor cells expressing detectable amount of PD-L1.
17. A polypeptide that competes for binding to PDL1 against the polypeptide of any of claims 1-5.
18. A mammalian expression system that produces the polypeptide of any of claims 1-8.

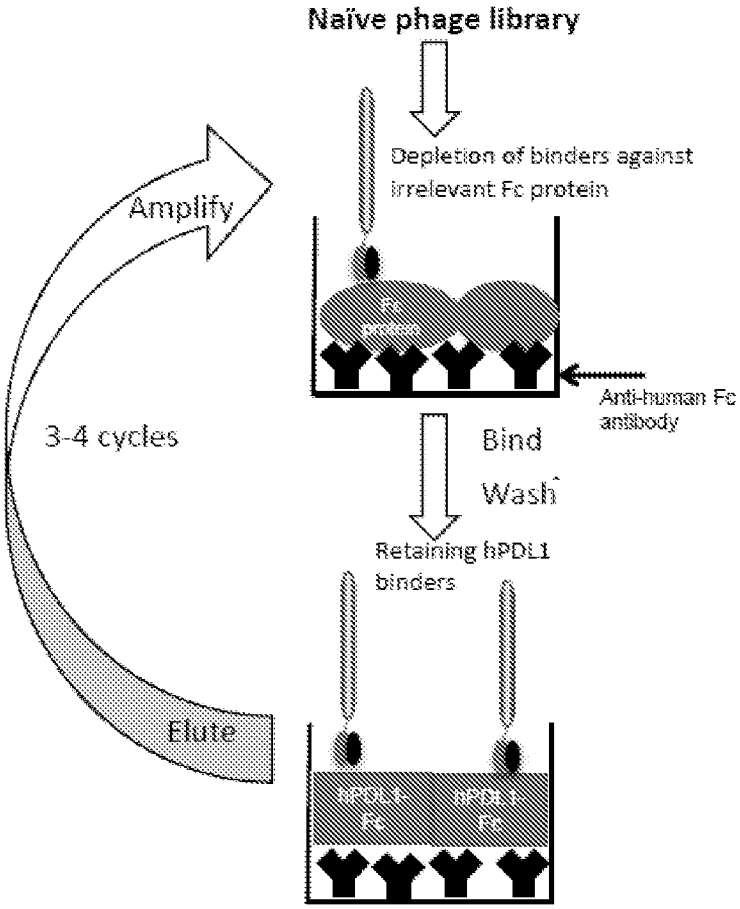

Naïve phage library
Depletion of binders against irrelevant Fc protein
Fc protein
Anti-human Fc antibody
Bind
Wash
Retaining hPDL1 binders
Amplify
3-4 cycles
Elute
hPDL1-Fc
hPDL1-Fc

FIG. 1

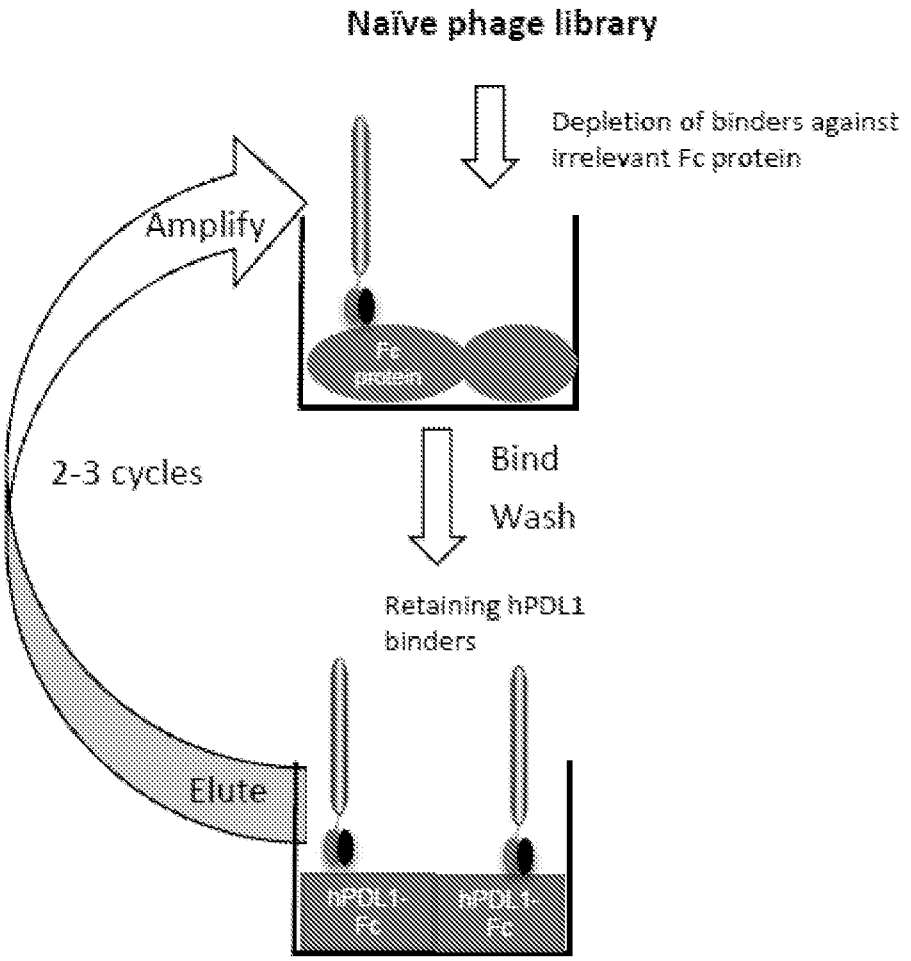

Naïve phage library
Depletion of binders against irrelevant Fc protein
Amplify
Fc protein
2-3 cycles
Bind
Wash
Retaining hPDL1 binders
Elute
hPDL1 Fc
hPDL1 Fc

FIG. 2

Code	Indirect ELISA (hPDL1-Fc)	Indirect ELISA (Fc Protein)	Ratio
	1:10 dilution	1:10 dilution	hPDL1-Fc/Fc protein
3-1D2	0.4806	0.1678	2.9
3-1G2	1.5331	0.1758	8.7
3-1H2	2.6763	0.0907	29.5
3-1E3	1.8786	0.0572	32.8
3-1E4	1.2902	0.1539	8.4
3-1F4	2.356	0.0856	27.5
3-1H4	0.322	0.053	6.1
3-1G6	0.9759	0.0639	15.3
3-1A8	2.6098	0.1629	16.0
3-1D9	2.4438	0.0657	37.2
3-1B11	1.9688	0.0977	20.2
4-1A2	2.6675	0.0615	43.4
4-1B3	1.6244	0.0944	17.2
4-1F3	2.131	0.1901	11.2
4-1H3	1.7804	0.0588	30.3
4-1C4	1.164	0.0618	18.8
4-1G5	1.2259	0.2658	4.6
4-1H6	1.3997	0.0723	19.4
4-1G7	2.0743	0.0952	21.8
4-1E8	2.6676	0.0663	40.2
4-1B9	2.5716	0.0998	25.8
4-1C9	1.3074	0.0834	15.7
4-1H10	2.4456	0.0895	27.3
4-1A11	0.8698	0.0978	8.9
4-1A12	2.6959	0.0664	40.6
4-1B12	2.6846	0.0894	30.0
NC	0.0503	0.0534	

FIG. 3

Code	MFI		Ratio
	hPDL1/293T	293T	hPDL1/293T vs. 293T
3-1D2	89	28	3.2
3-1G2	52	32	1.6
3-1H2	120	32	3.8
3-1E3	157	35	4.5
3-1E4	91	28	3.3
3-1F4	161	35	4.6
3-1H4	95	47	2.0
3-1G6	49	29	1.7
3-1A8	386	26	14.8
3-1D9	86	28	3.1
3-1B11	178	39	4.6
4-1A2	733	39	18.8
4-1B3	185	40	4.6
4-1F3	89	36	2.5
4-1H3	74	35	2.1
4-1C4	101	31	3.3
4-1G5	100	43	2.3
4-1H6	149	40	3.7
4-1G7	193	35	5.5
4-1E8	849	39	21.8
4-1B9	111	39	2.8
4-1C9	151	26	5.8
4-1H10	102	31	3.3
4-1A11	43	28	1.5
4-1A12	683	47	14.5
4-1B12	280	29	9.7
PC	12315		
NC	35		

FIG. 4

Code	1:2 dilution	Inhibition rate(%)
4-1E8	0.1355	94.3
4-1A12	0.1453	93.9
4-1G7	0.166	93.0
4-1A2	0.2382	90.0
4-1B9	0.5471	76.9
4-1B12	0.6111	74.3
4-1H10	0.6749	71.6
3-1B11	0.9586	59.6
3-1E4	1.3562	42.9
3-1A8	1.4935	37.1
3-1H2	1.7556	26.0
4-1G5	1.9666	17.1
3-1F4	2.0946	11.1
4-1A11	2.2841	3.8
4-1C9	2.3192	2.3
3-1E3	2.3195	2.3
4-1H6	2.3718	0.1
4-1B3	2.386	-0.5
4-1F3	2.3923	-0.8
3-1D9	2.4153	-1.8
4-1C4	2.5006	-5.4
4-1H3	2.6041	-9.7
3-1G6	2.7208	-14.6
3-1D2	2.7965	-17.8
3-1G2	2.8253	-19.0
3-1H4	2.8979	-22.1
PC	2.3733	
NC	0.0589	

FIG. 5

Code	1:2 dilution	Inhibition rate(%)
4-1A12	0.099	95.3
4-1G7	0.1222	94.2
4-1E8	0.1795	91.5
4-1H10	0.2274	89.3
4-1B9	0.2373	88.8
4-1A2	0.2495	88.2
4-1B12	0.3233	84.8
3-1B11	0.3494	83.5
3-1E4	0.5115	75.9
3-1H2	0.5519	74.0
4-1G5	0.7667	63.9
3-1A8	0.8139	61.6
4-1F3	0.9102	57.1
4-1C9	0.9241	56.4
3-1F4	1.1417	46.2
4-1B3	1.1561	45.5
4-1H6	1.3543	36.2
3-1G8	1.3567	36.1
4-1C4	1.4423	32.0
3-1D2	1.544	27.2
3-1D9	1.585	25.3
3-1E3	1.7194	19.0
3-1H4	1.8486	12.9
4-1A11	1.9063	10.2
3-1G2	2.0271	4.5
4-1H3	-	-
PC	2.1217	
NC	0.04995	

FIG. 6

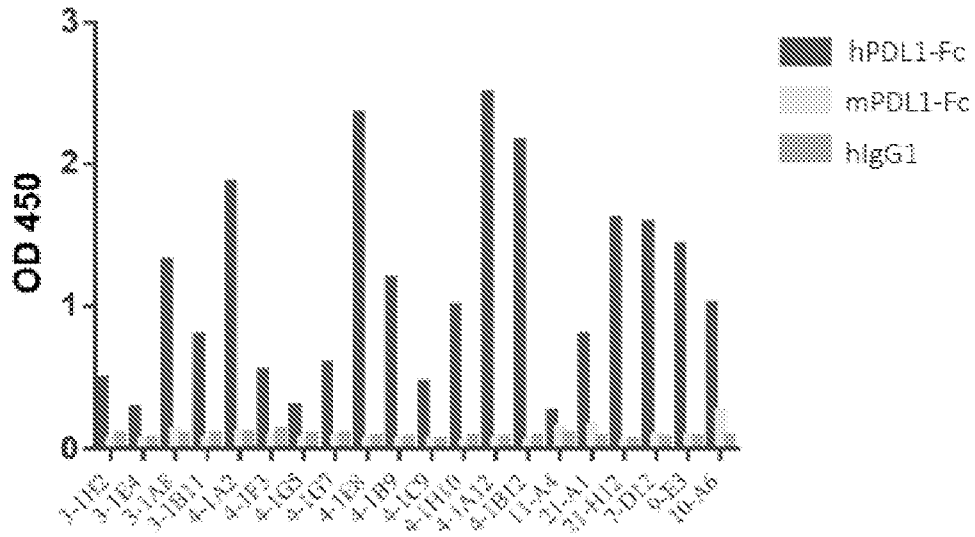
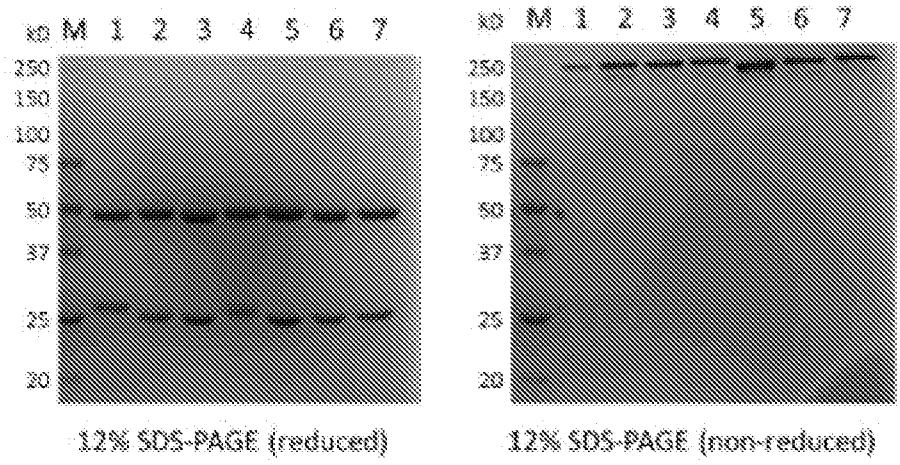


FIG. 7



M: Marker

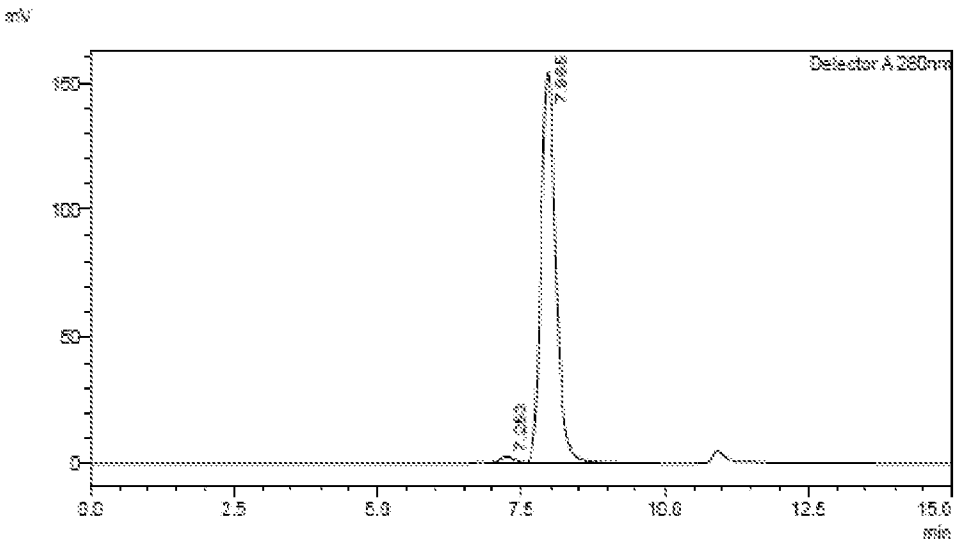
5: 4-1E8 (1ug)

FIG. 8A

<Sample Information>

Sample Name	: 4-1E8 mab		
Sample ID	:		
Data Filename	: 4-1E8 mab.lcd		
Method Filename	: Tsk 3000 15min 20160512.lcm		
Batch Filename	: 20160716.lcb		
Vial #	: 1-40	Sample Type	: Unknown
Injection Volume	: 25 uL		
Date Acquired	: 2016/9/2 12:07:57	Acquired by	: System Administrator
Date Processed	: 2016/9/2 12:22:59	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

Detector A 280nm

Peak#	Ret. Time	Area	Area%	Height	Height%
1	7.253	44142	1.554	2376	1.521
2	7.965	2795890	98.446	153849	98.479
Total		2840032	100.000	156225	100.000

FIG. 8B

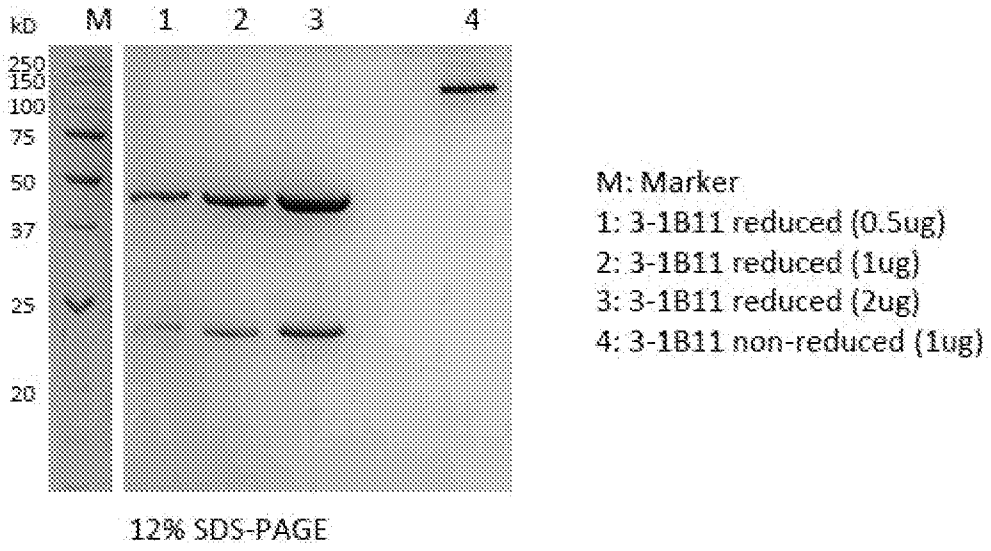
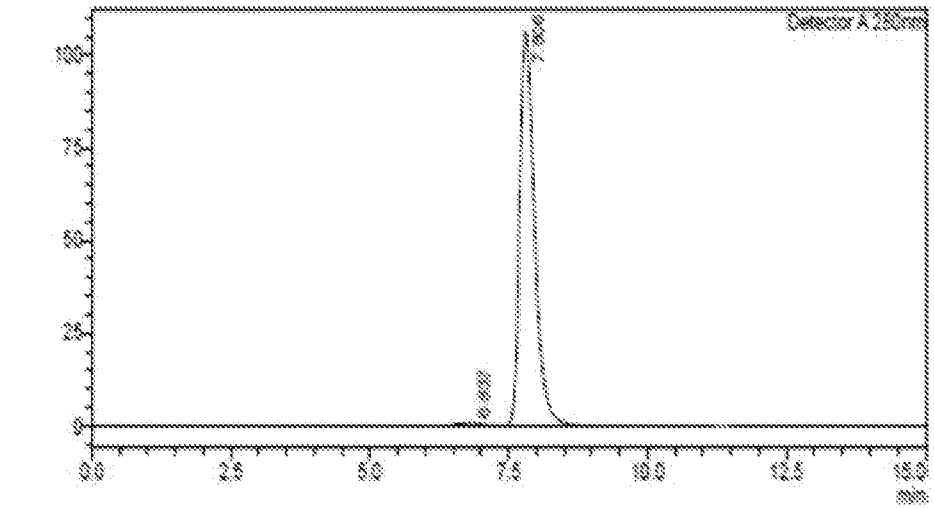


FIG. 9A

Sample Name	: 3-1B11 MAB SML FINAL		
Sample ID	:		
Data Filename	: 3-1B11 MAB SML FINAL.lcd		
Method Filename	: Tsk 3000 15min 20180512.lcm		
Batch Filename	: 20180716.lcb		
Vial #	: 1-5	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 2018/6/29 13:56:21	Acquired by	: System Administrator
Date Processed	: 2018/6/29 14:11:22	Processed by	: System Administrator

<Chromatogram>

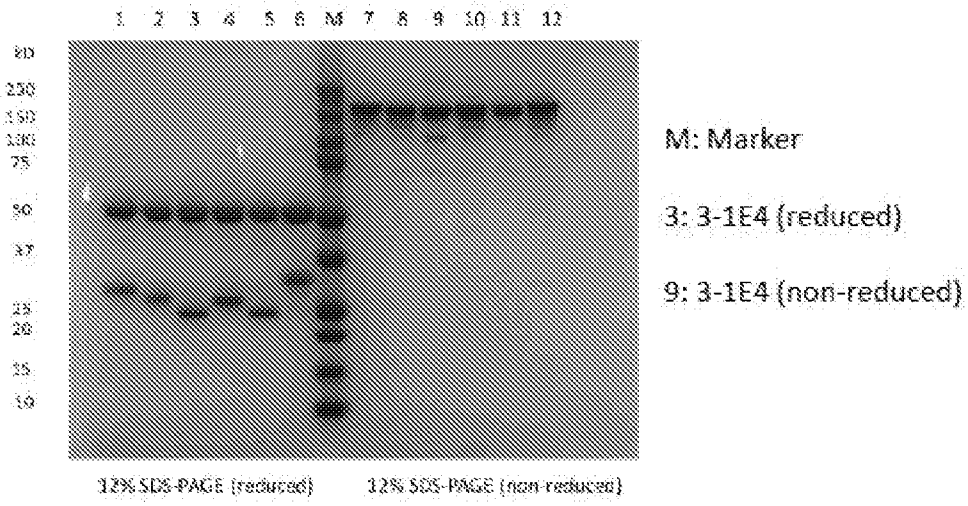


<Peak Table>

Detector A 280nm

Peak#	Ret. Time	Area	Area%	Height	Height%
1	6.837	25619	1.277	882	0.822
2	7.805	1981468	98.723	106498	99.178
Total		2007106	100.000	107380	100.000

FIG. 9B



12% SDS-PAGE

FIG. 10A

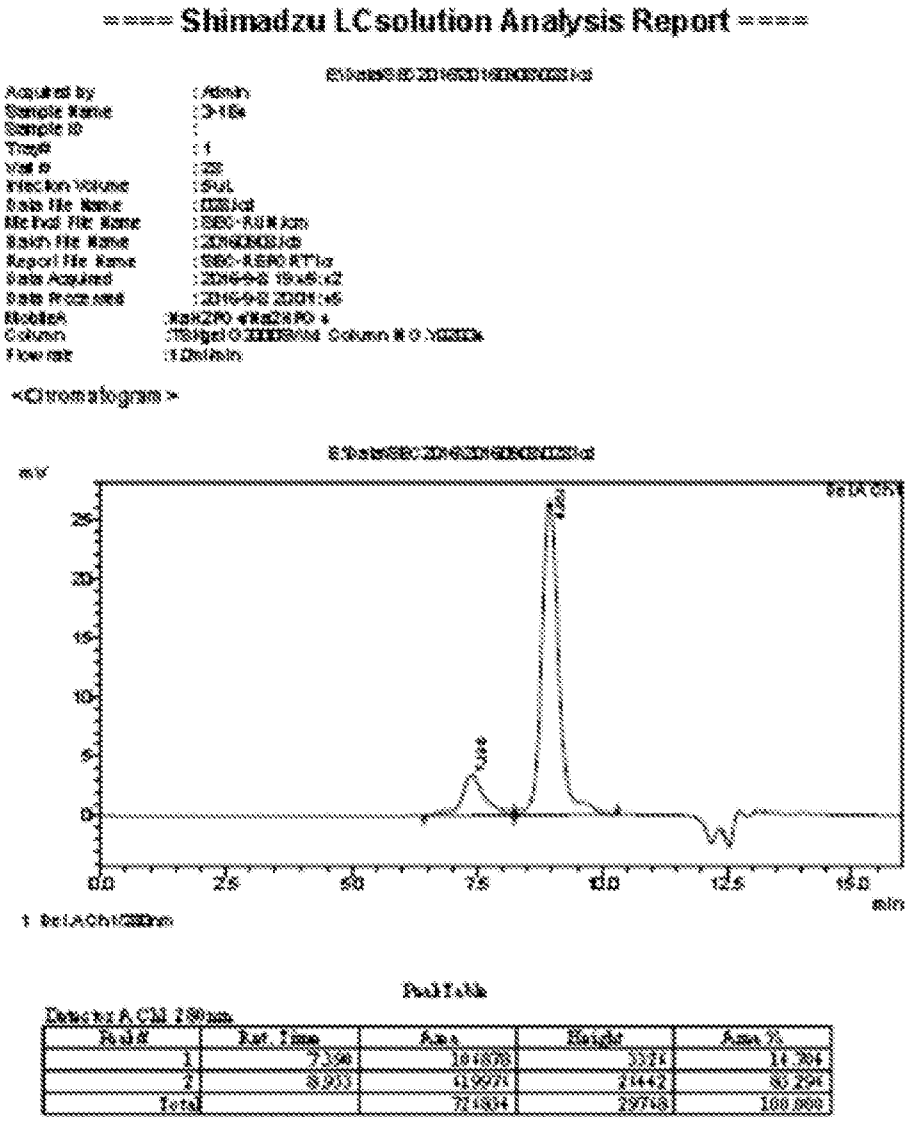


FIG. 10B

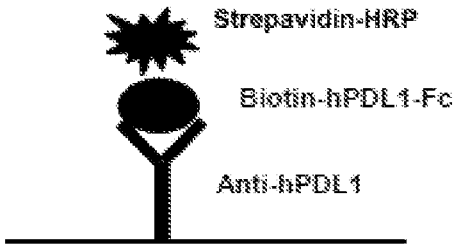
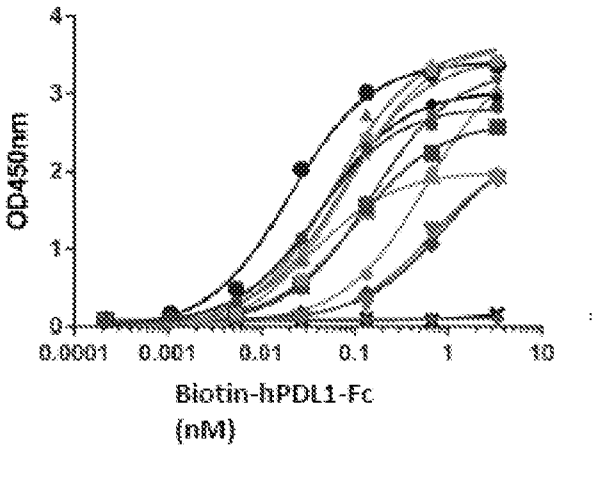
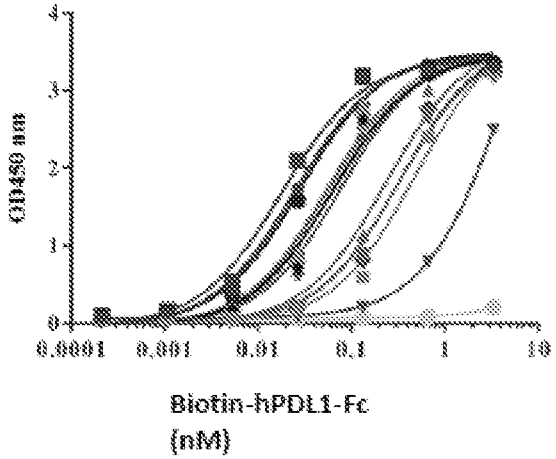


FIG. 11A



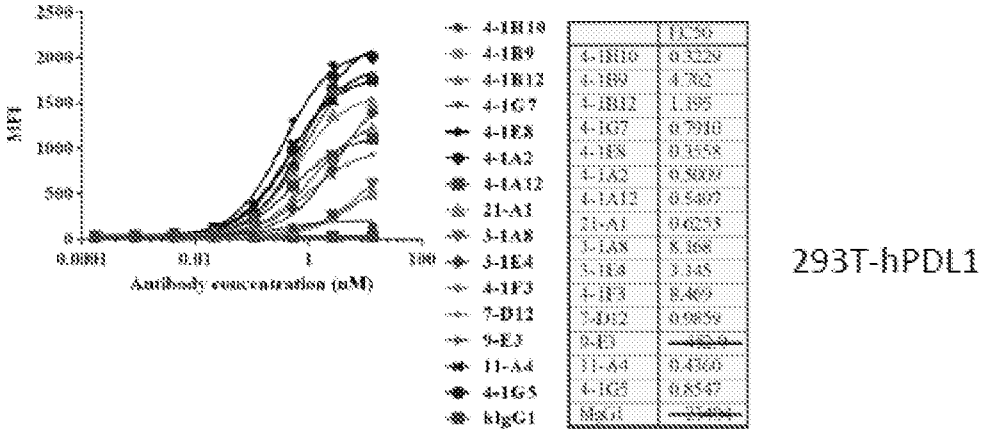
	EC50
4-1E8	0.03913
4-1H10	0.08279
4-1B9	0.06086
4-1B12	0.1511
4-1G7	0.04471
4-1A2	0.02031
4-1A12	0.1080
21-A1	0.03975
3-1A8	0.6715
3-1E4	0.8997
4-1F3	0.5627
7-D12	0.07440
9-E3	4.844
hIgG1	3874

FIG. 11B



	EC50
4-1E8	0.02466
22-A6	0.4816
12-A4	0.2394
35-B1	4.671
3-1F4	0.08354
4-1B3	0.02843
3-1B11	0.01795
3-1H2	0.05385
10-A6	0.3230
14-G10	0.3345
21-G1	0.06416
4-1C9	0.07770
21-H12	0.05603
hIgG1	30.68

FIG. 11C


MFI
2500
2000
1500
1000
500
0
0.0001
0.01
1
100
Antibody concentration (nM)
4-1B10
4-1B9
4-1B12
4-1G7
4-1E8
4-1A2
4-1A12
21-A1
3-1A8
3-1E4
4-1F3
7-D12
9-E3
11-A4
4-1G5
hIgG1
EC50
293T-hPDL1

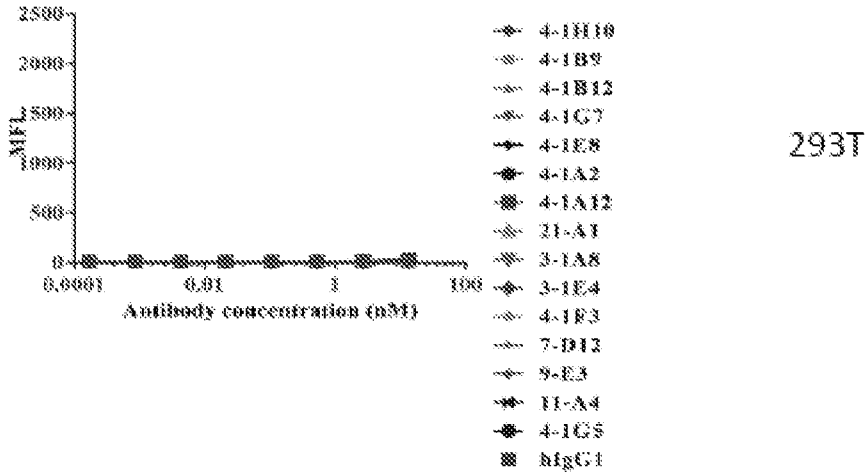

MFI
2500
2000
1500
1000
500
0
0.0001
0.01
1
100
Antibody concentration (nM)
4-1B10
4-1B9
4-1B12
4-1G7
4-1E8
4-1A2
4-1A12
21-A1
3-1A8
3-1E4
4-1F3
7-D12
9-E3
11-A4
4-1G5
hIgG1
293T

FIG. 12A

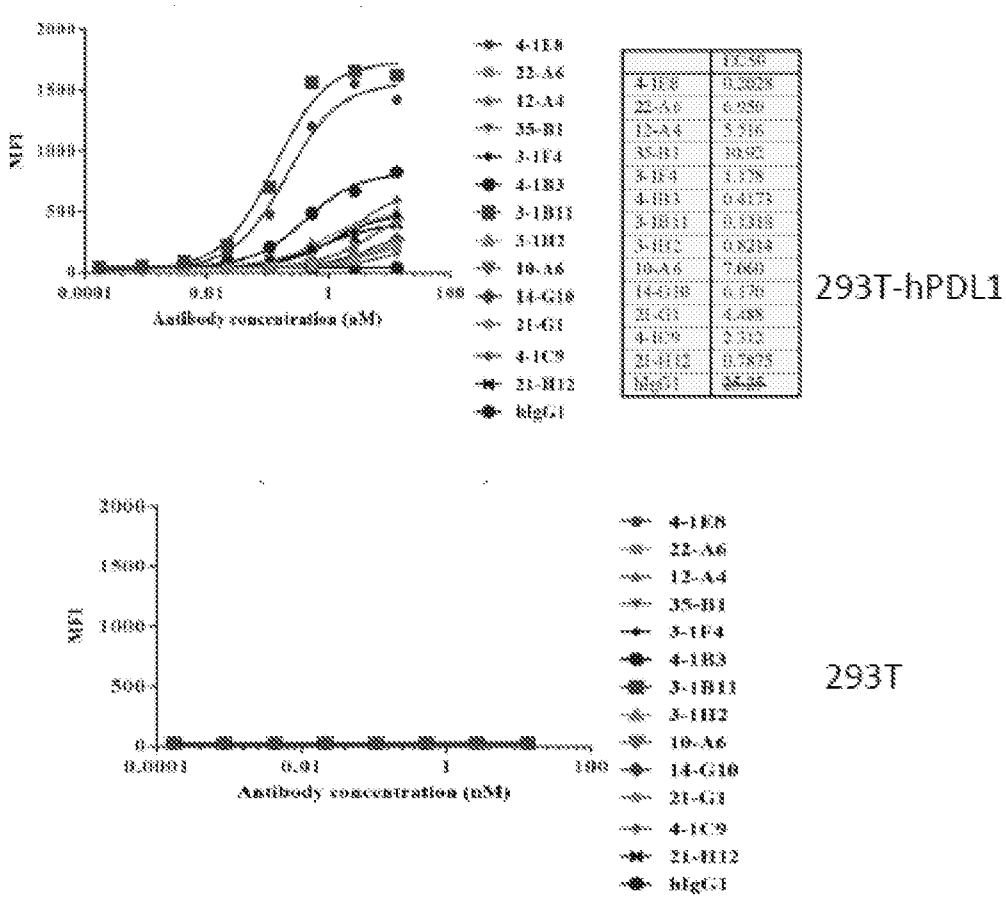


FIG. 12B

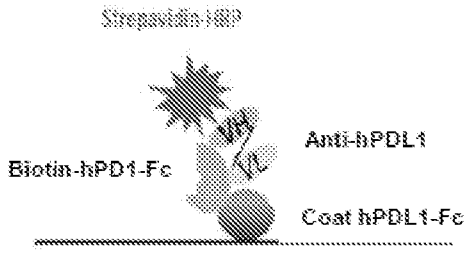
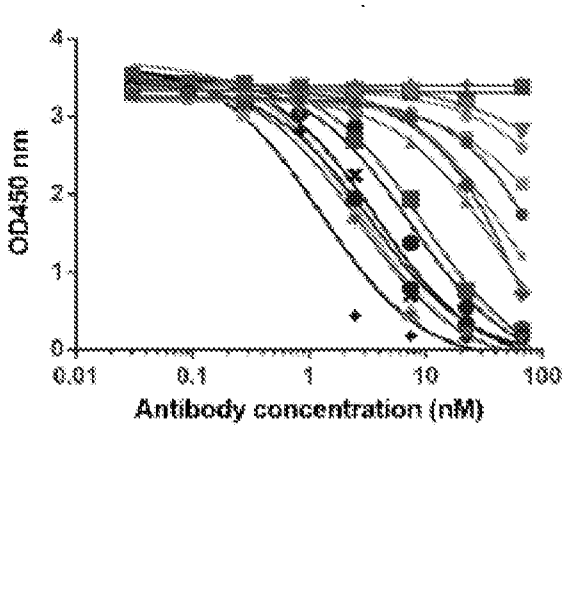


FIG. 13A



	IC50
4-1H10	212.0
4-1B9	98.79
4-1B12	43.91
4-1G7	2.672
4-1E8	1.257
4-1A2	3.305
4-1A12	9.499
21-A1	2.714
3-1A8	100.7
3-1E4	92.74
4-1F3	196.7
7-D12	52.36
9-E3	~~5.600e-008~~
11-A4	3.820
4-1G5	7.372
hIgG1	~~2.606~~

FIG. 13B

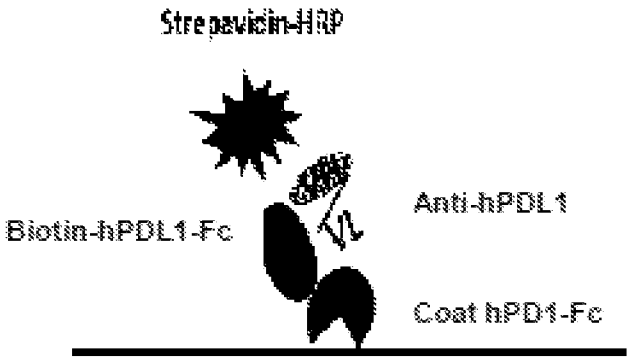
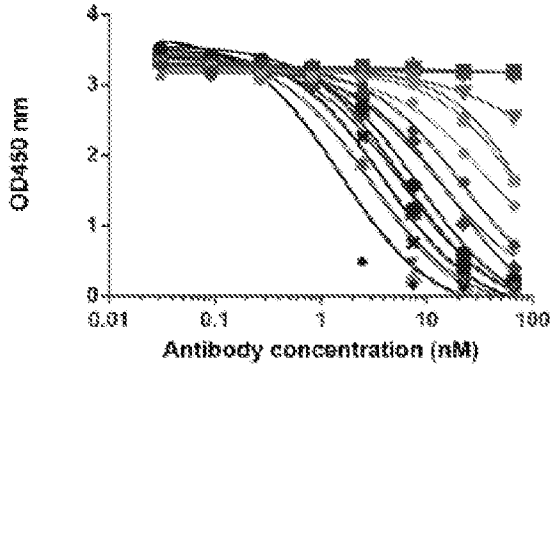


FIG. 14A



	IC50
4-1H10	20.91
4-1B9	112.4
4-1B12	337.6
4-1G7	2.948
4-1E8	1.531
4-1A2	5.910
4-1A12	5.921
21-A1	2.943
3-1A8	82.29
3-1E4	16.57
4-1F3	36.13
7-D12	12.20
9-E3	0.1367
11-A4	3.988
4-1G5	8.564
hIgG1	42.62

FIG. 14B

	RBA(IC50, nM)		ELISA	FACS
Antibody Code	PD1 coated	PDL1 coated	(EC50, nM)	(EC50, nM)
4-1E8	1.257	1.531	0.0391	0.3558
3-1B11	1.389	0.7955	0.018	0.1318
4-1G7	2.672	2.948	0.04471	0.791
21-A1	2.714	2.943	0.0398	0.6253
4-1A2	3.305	5.91	0.0203	0.5009
11-A4	3.82	3.988	0.0163	0.436
4-1G5	7.372	8.564	0.0147	0.8547
4-1A12	9.499	5.921	0.105	0.5497
4-1B3	17.46	9.866	0.0284	0.4173
14-G10	26.75	11.88	0.3345	6.17
3-1H2	29.96	5.826	0.0539	0.8214
4-1B12	43.91	337.6	0.1511	1.185
7-D12	52.36	12.2	0.0744	0.9859
10-A6	57.14	25.11	0.323	7.08
4-1C9	59.97	19.67	0.0777	2.312
21-G1	70.45	10.33	0.0642	4.488
3-1E4	92.74	16.57	0.8997	3.145
4-1B9	98.79	112.4	0.0609	4.702
3-1A8	100.7	82.29	0.6715	8.168
21-H12	145.4	23.71	0.056	0.7875
4-1F3	198.7	36.13	0.5627	8.469
4-1H10	212	20.91	0.0828	0.3229
35-B1	-	-	4.671	10.92
12-A4	-	344.3	0.2394	5.516
22-A6	-	-	0.4816	6.95
9-E3	-	-	-	-
3-1F4	~974967	~511744	0.0635	1.178

FIG. 15

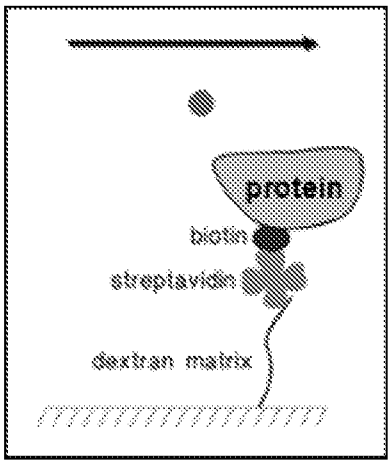


FIG. 16A

Antibody Code	ka (1/Ms)	kd (1/s)	KD (M)
4-1E8	5.56E+05	2.48E-03	4.46E-09
4-1G7	8.26E+04	3.63E-03	4.39E-08
4-1A2	5.24E+05	2.55E-03	4.88E-09
21-A1	5.02E+05	2.19E-03	4.36E-09
7-D12	1.28E+06	1.00E-02	7.82E-09
11-A4	4.03E+05	2.89E-03	7.16E-09
4-1G5	5.01E+04	6.63E-03	1.32E-07
4-1B3	4.20E+05	4.47E-03	1.06E-08
3-1B11	4.11E+05	9.54E-04	2.32E-09
3-1H2	5.45E+05	5.97E-03	1.10E-08

FIG. 16B

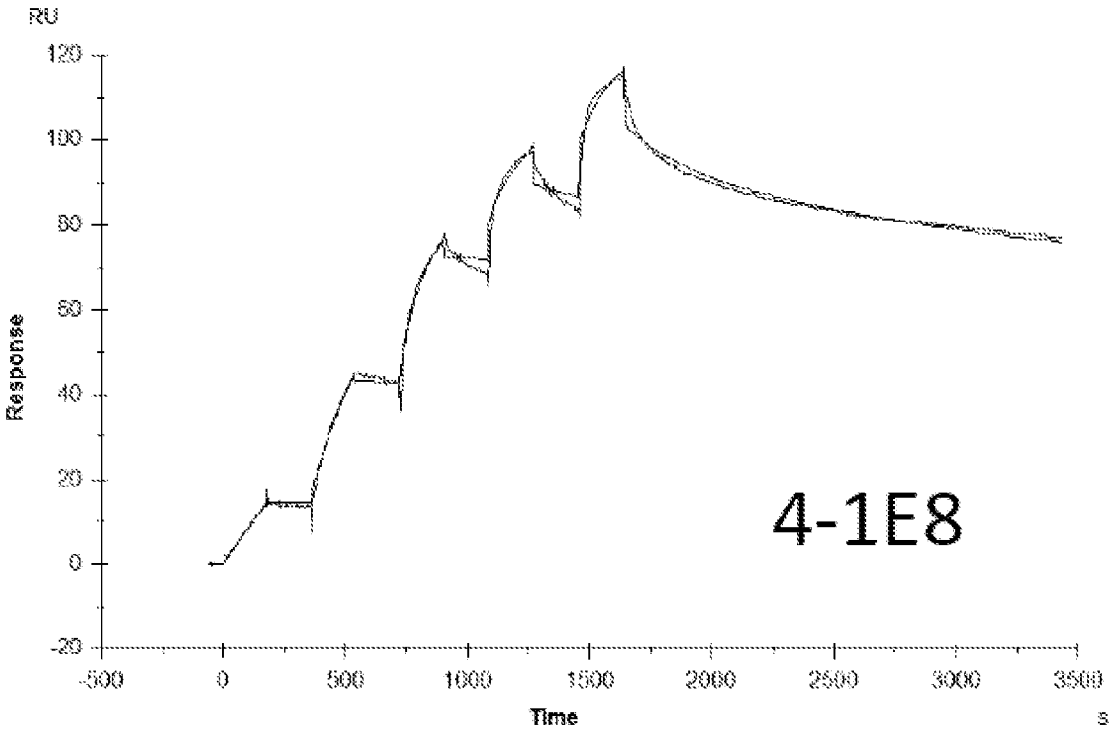


FIG. 16C

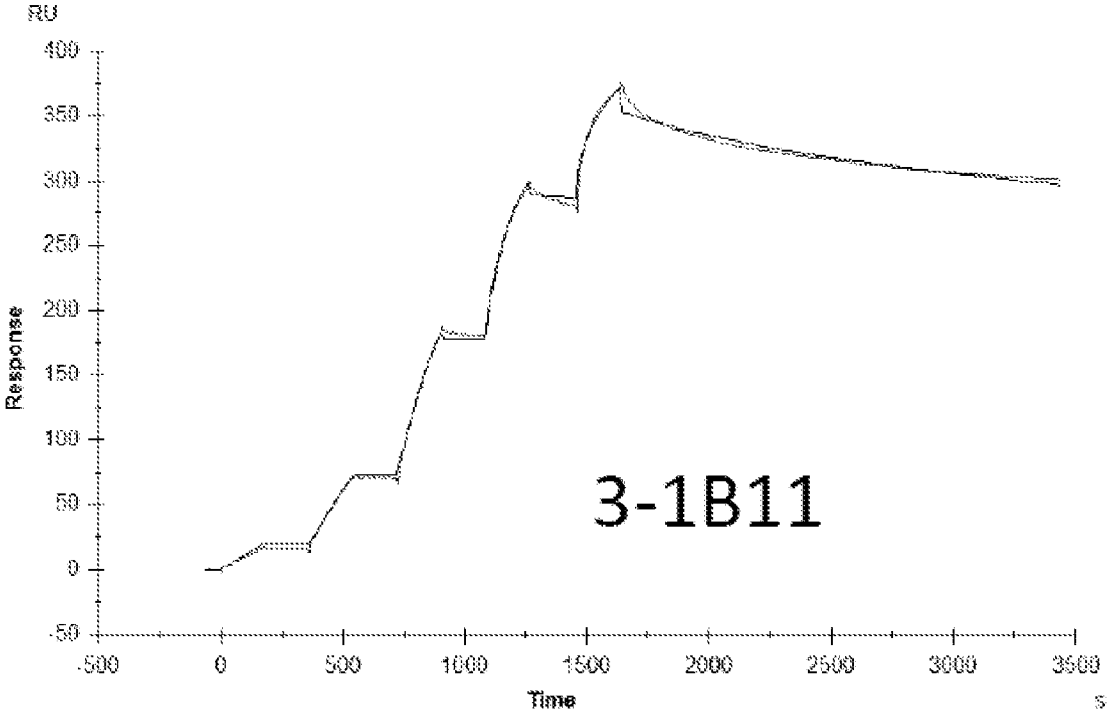


FIG. 16D

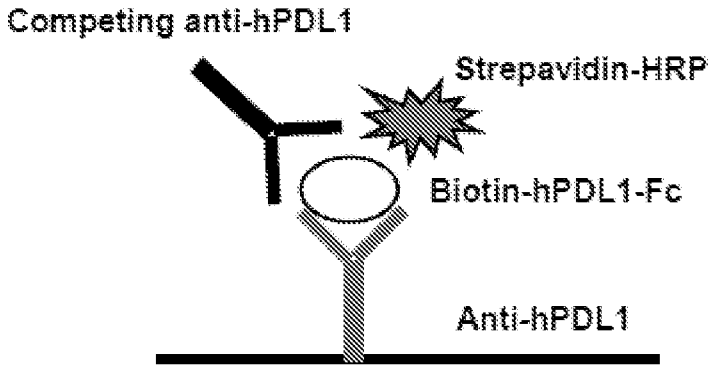


FIG. 17A

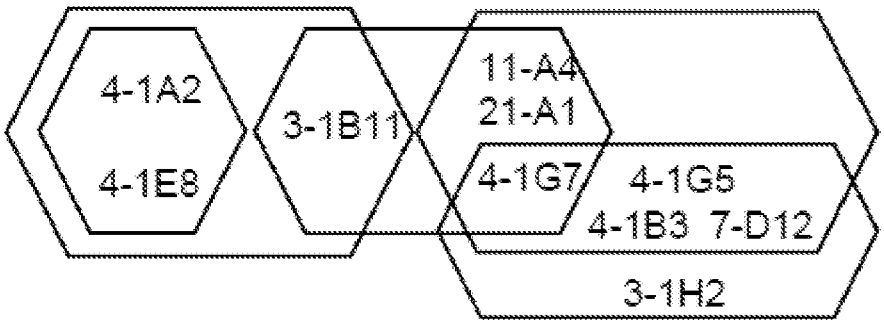


FIG. 17B

Percent Inhibition of Binding

	Coating Ab									
Competitive Ab	4-1E8	4-1A2	3-1B11	11-A4	21-A1	4-1G7	4-1G5	4-1B3	7-D12	3-1H2
4-1E8	94%	94%	94%	95%	94%	93%	96%	96%	96%	96%
4-1A2	77%	74%	67%	88%	89%	85%	91%	92%	93%	92%
3-1B11	89%	89%	89%	94%	93%	93%	95%	95%	95%	95%
11-A4	80%	78%	79%	92%	91%	90%	95%	93%	95%	94%
21-A1	91%	88%	91%	94%	95%	94%	95%	95%	96%	95%
4-1G7	88%	85%	87%	93%	94%	93%	95%	94%	96%	94%
4-1G5	71%	66%	65%	82%	87%	79%	90%	89%	91%	90%
4-1B3	52%	49%	45%	76%	83%	76%	87%	87%	90%	89%
7-D12	47%	36%	45%	70%	78%	74%	86%	80%	87%	85%
3-1H2	55%	44%	38%	63%	67%	70%	80%	71%	77%	86%

FIG. 17C

FIG. 18A Unstained

FIG. 18B 4-1E8

FIG. 18C 3-1E4

FIG. 18D 3-1B11

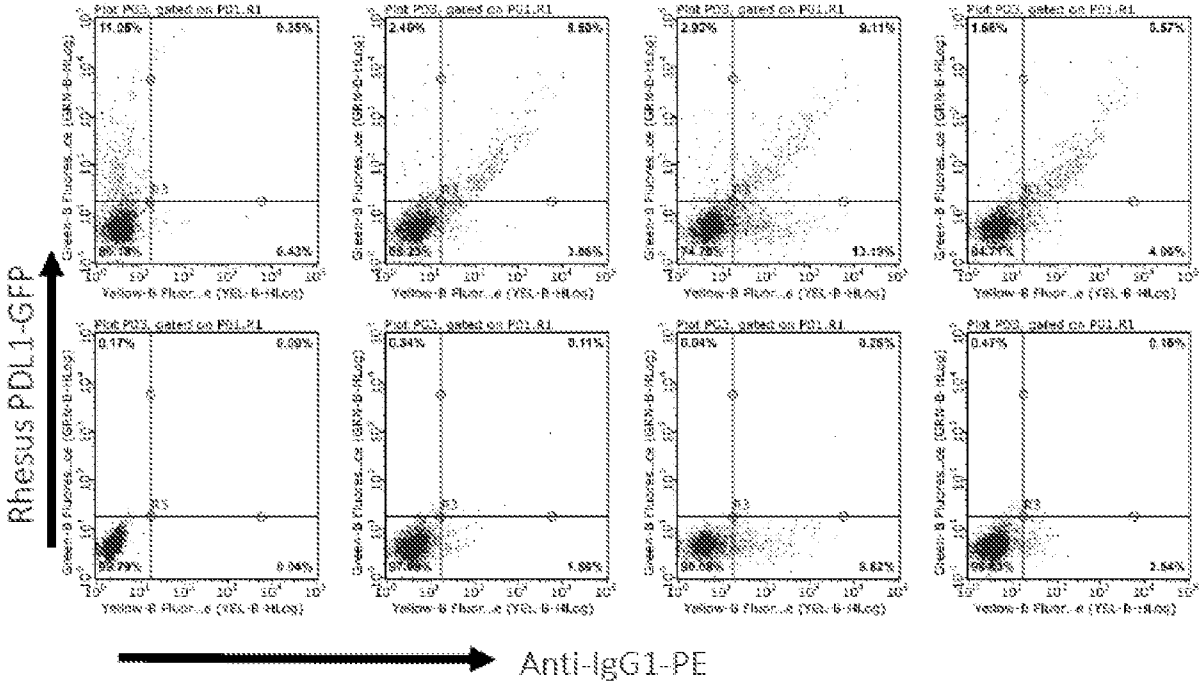
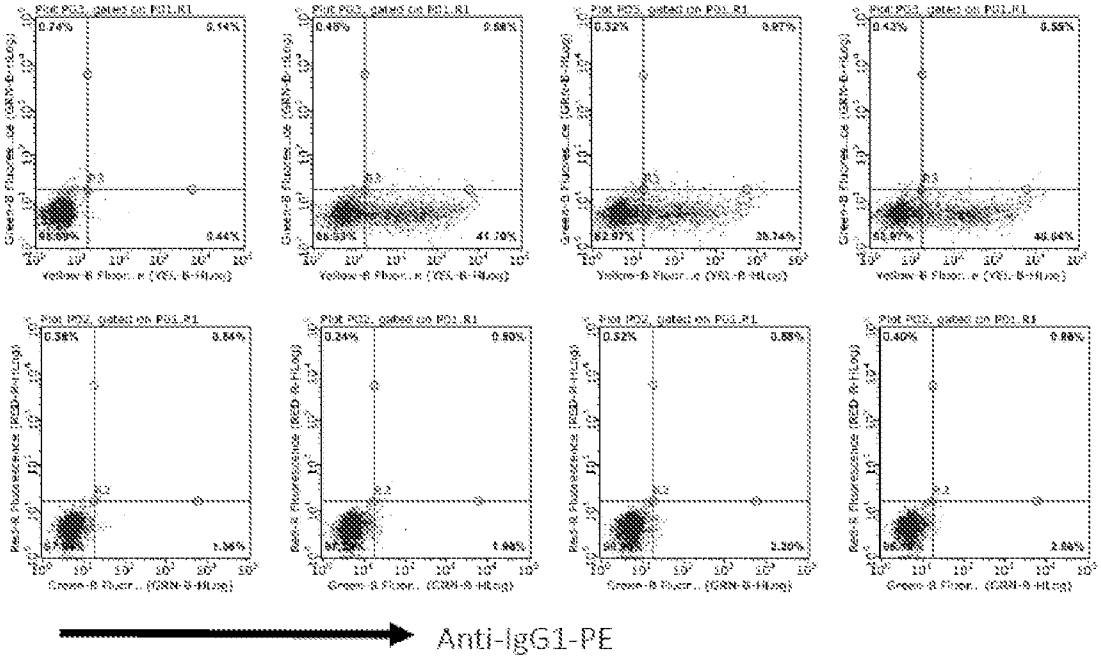


FIG. 19A Unstained

FIG. 19B 4-1E8

FIG. 19C 3-1E4

FIG. 19D 3-1B11



Antibody	Median	SD	Replicates
Nivo	0.10	0.07	6
4-1E8	0.17	0.18	6
3-1B11	2.21	1.14	5
3-1E4	1.18	0.55	4

FIG. 20

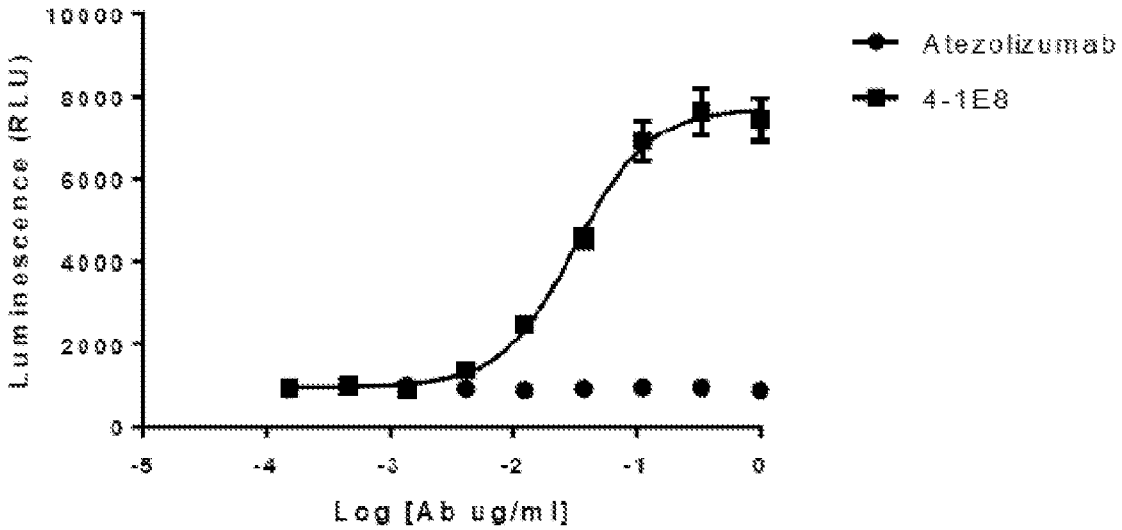


FIG. 21

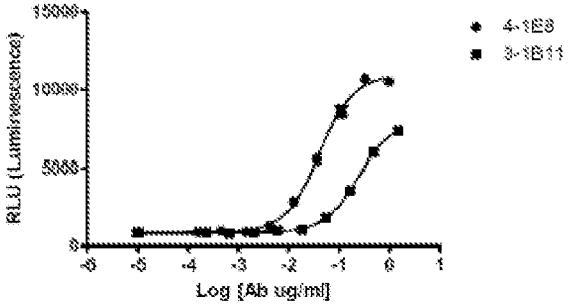


FIG. 22A

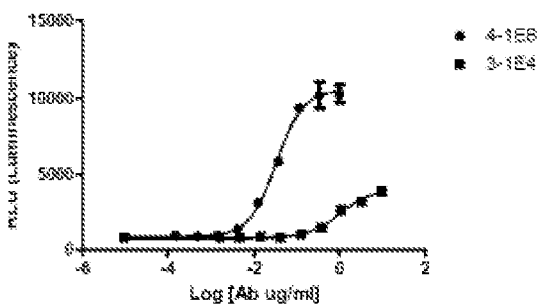


FIG. 22B

Antibody	EC50 (ug/mL)	SD	Replicates
4-1E8	0.034	0.005	7
3-1B11	0.210	0.048	2
3-1E4	0.801	0.325	2

FIG. 22C

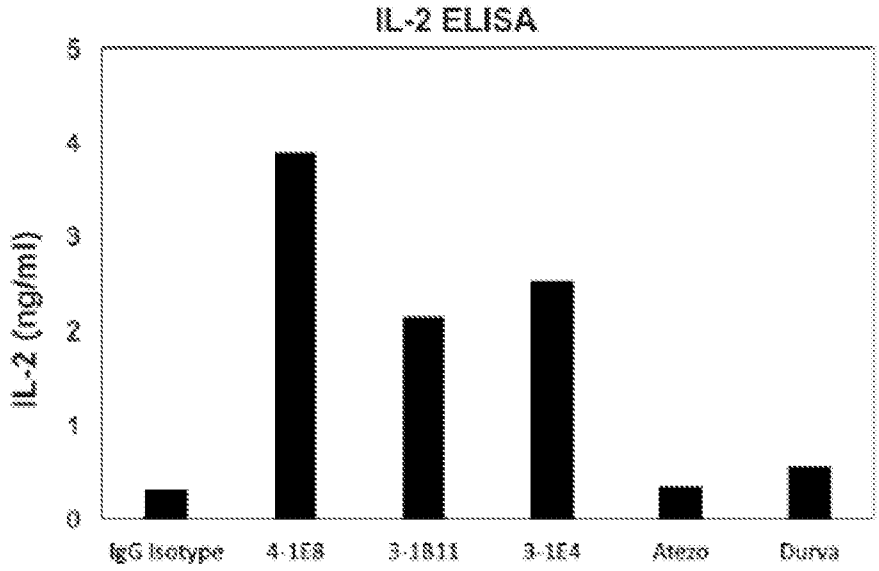


FIG. 23A

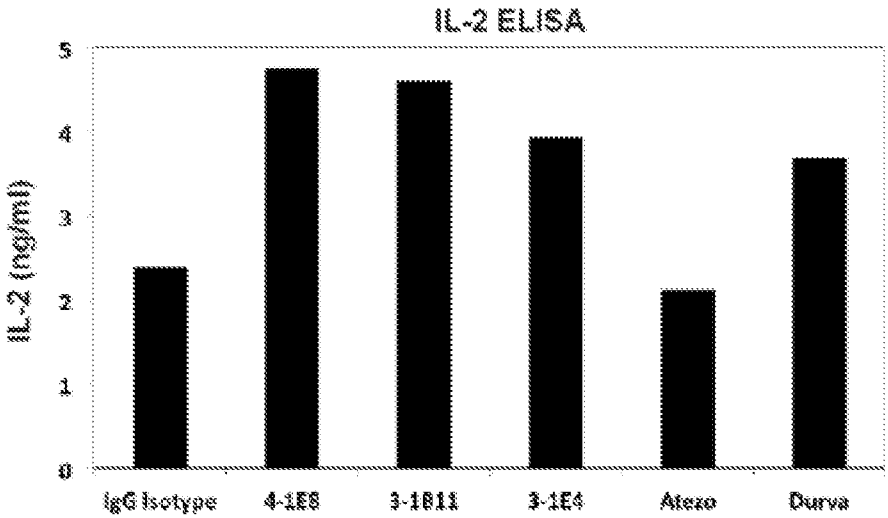


FIG. 23B

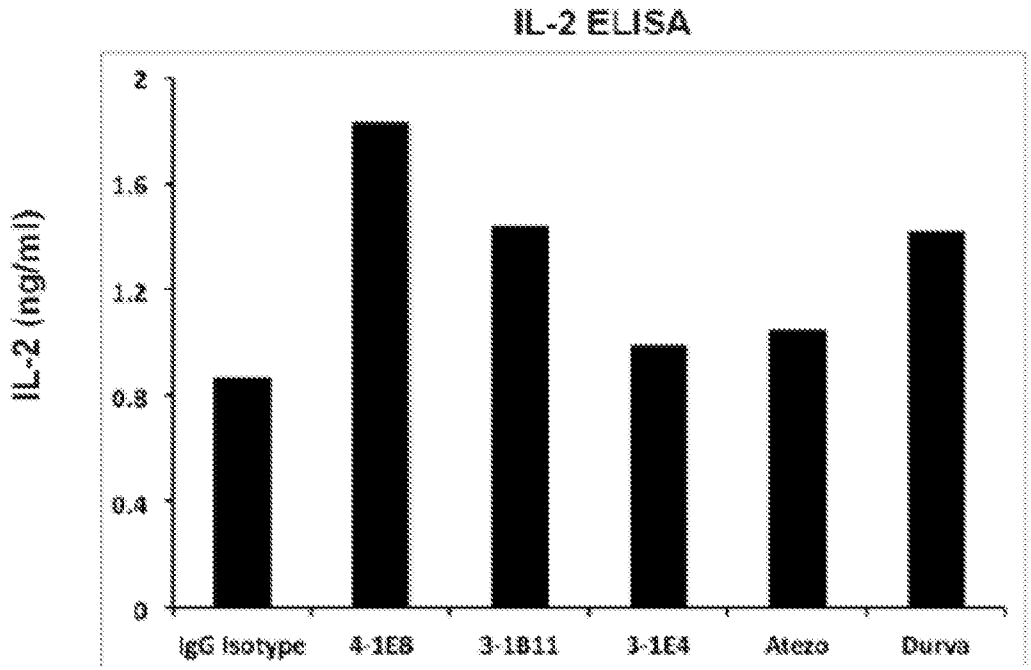


FIG. 23C

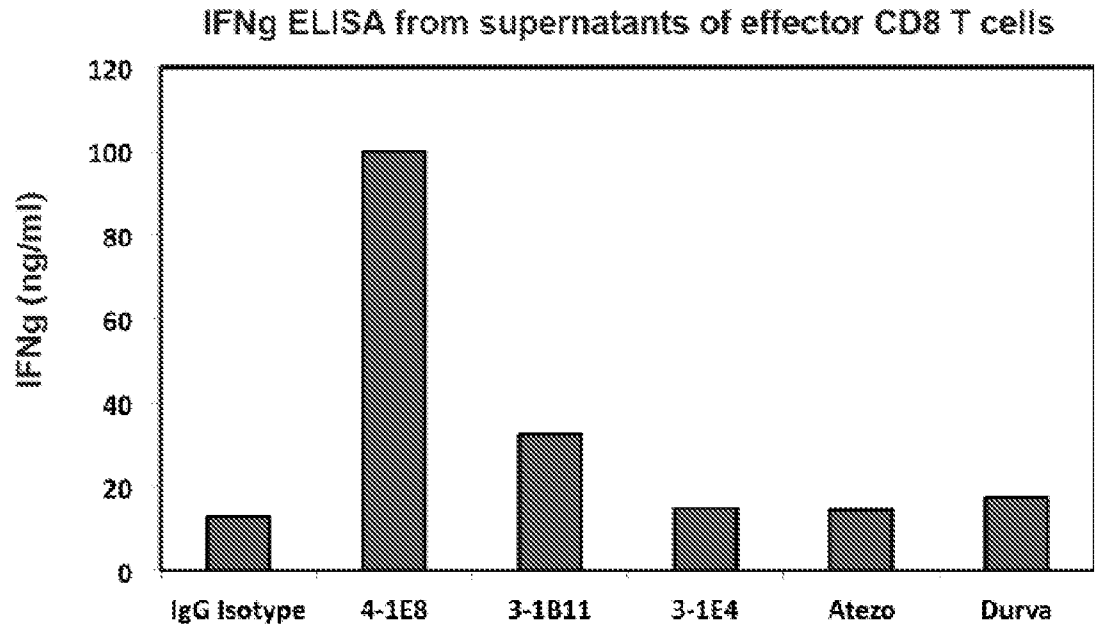


FIG. 24

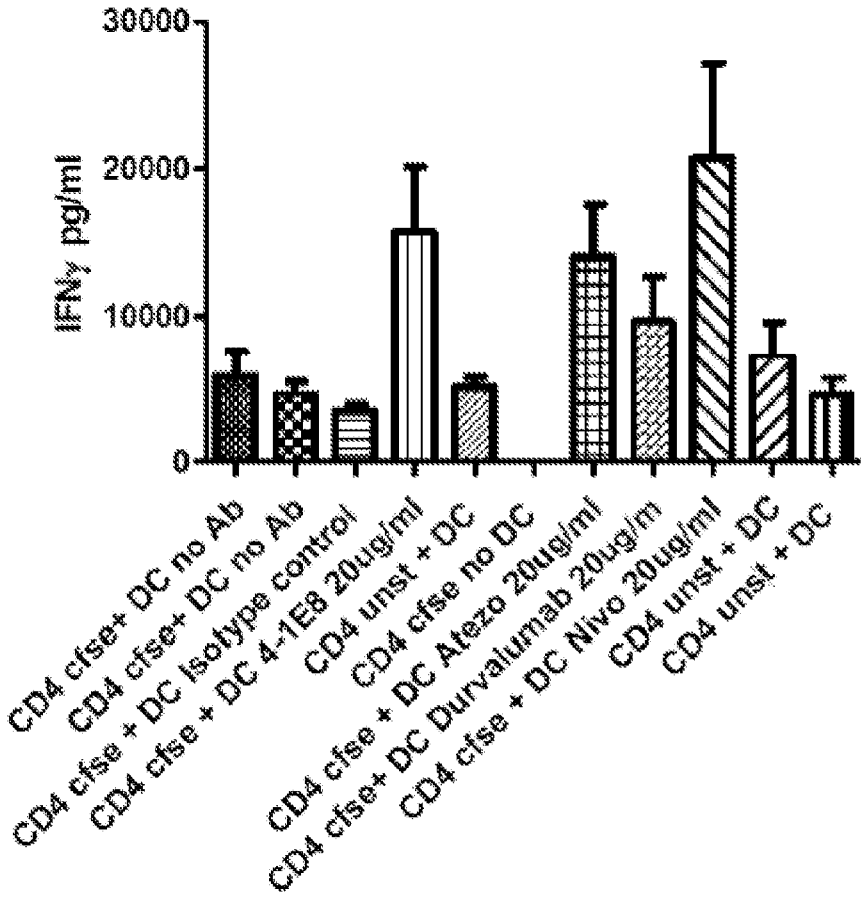

30000
20000
10000
0
IFNγ pg/ml
CD4 cfse+ DC no Ab
CD4 cfse+ DC no Ab
CD4 cfse + DC isotype control
CD4 cfse + DC 4-1E8 20ug/ml
CD4 unst + DC
CD4 cfse no DC
CD4 cfse + DC Atezo 20ug/ml
CD4 cfse+ DC Durvalumab 20ug/m
CD4 cfse + DC Nivo 20ug/ml
CD4 unst + DC
CD4 unst + DC

FIG. 25A

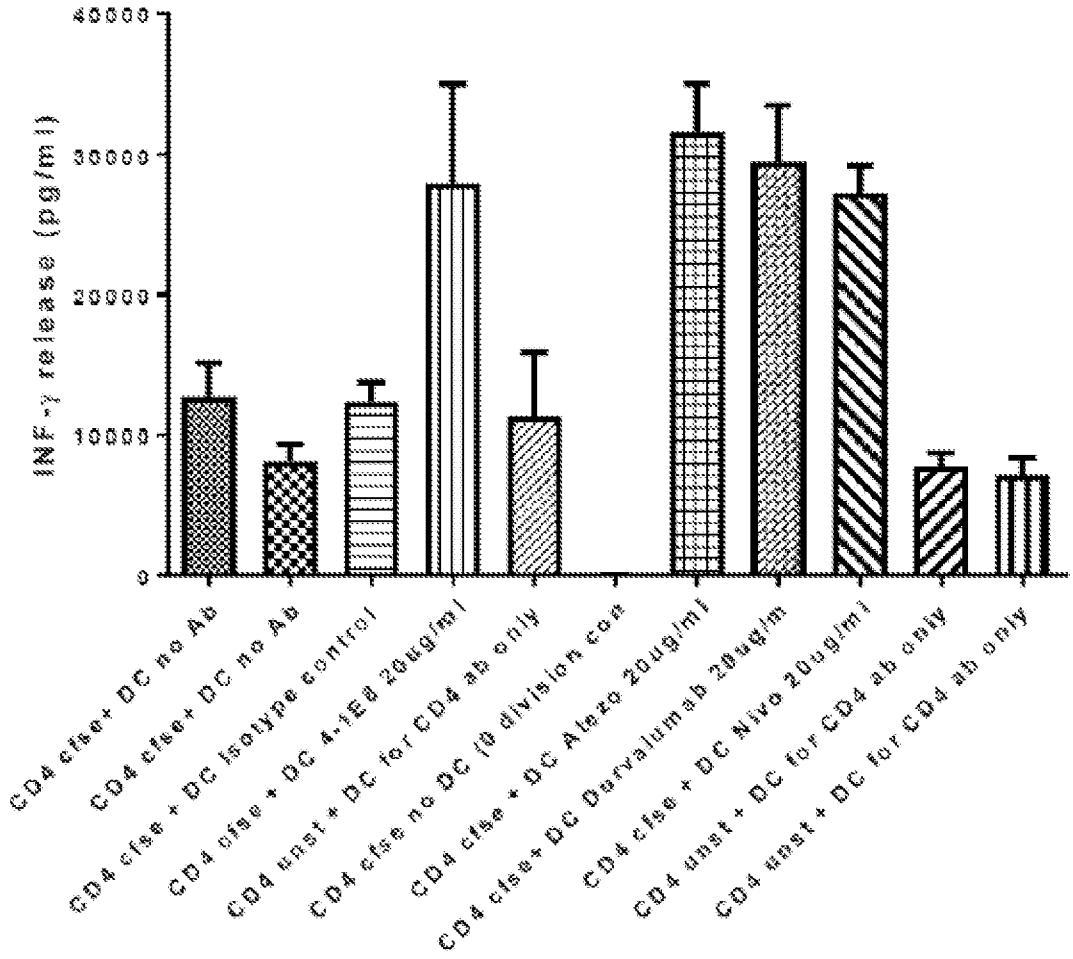


FIG. 25B

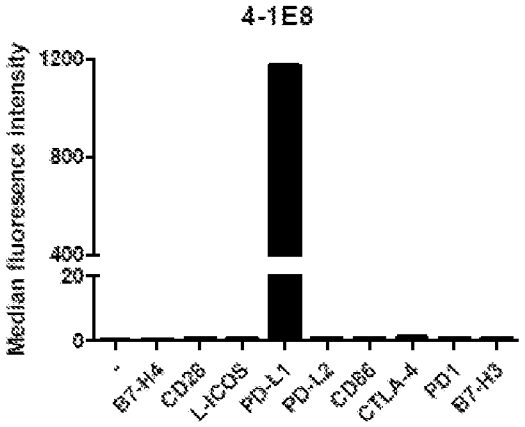


FIG. 26A

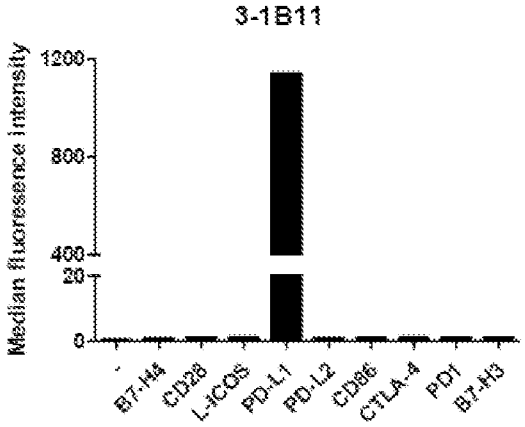


FIG. 26B

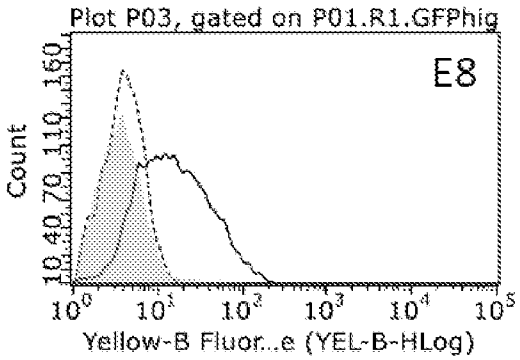


FIG. 27A

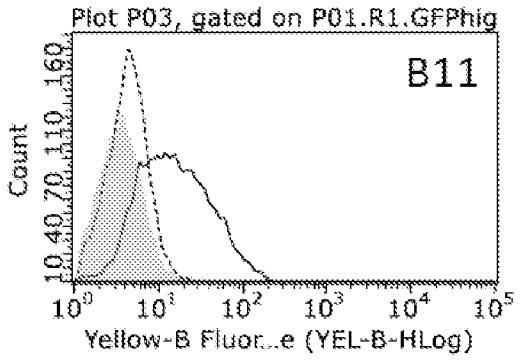


FIG. 27B

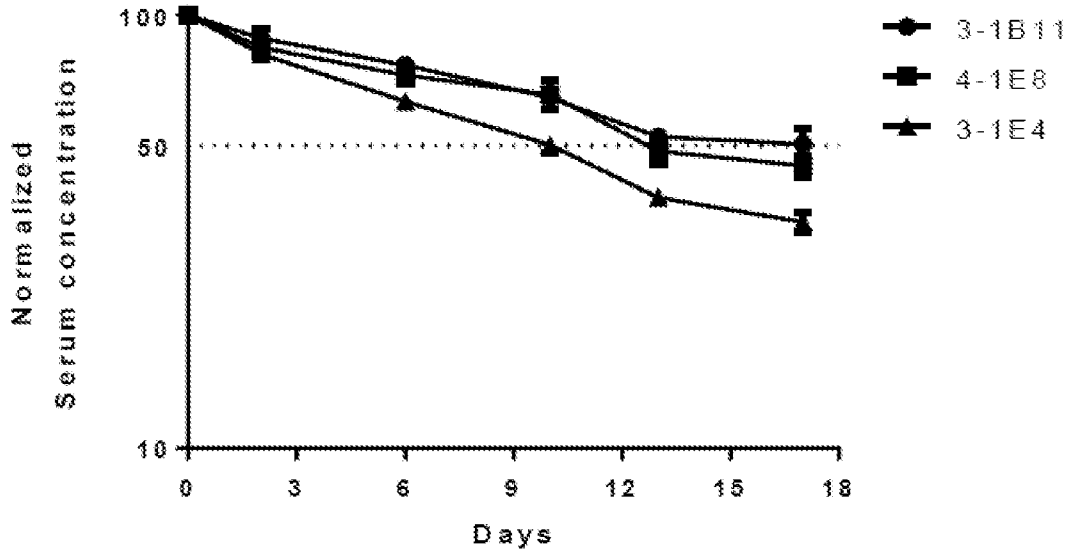


FIG. 28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/101659

A. CLASSIFICATION OF SUBJECT MATTER

C07K 16/30(2006.01)i; A61K 39/395(2006.01)i; A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, DWPI, CNTXT, WOTXT, USTXT, EPTXT, JPTXT, CNKI, Web of Science, Google Scholar, Patentics, incoPat, Bio-Sequence Database of Chinese Patent, NCBI, EBI, STN: Applicator/Inventors, PD-L1, B7-H1, CD274, Programmed Death Ligand 1, antibody, heavy chain, light chain, variable region, VH, VL, SEQ ID NOs:1-108

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 106432501 A (SHANGHAI YAOMING BIOTECHNOLOGY CO., LTD.) 22 February 2017 (2017-02-22) Claims 1-11, 14-25, 27-28, 30-35	17
X	CN 104736168 A (SORRENTO THERAPEUTICS INC.) 24 June 2015 (2015-06-24) Claims 1-13	17
X	CN 102264762 A (DANA-FARBER CANCER INSTITUTE ET AL.) 30 November 2011 (2011-11-30) Claims 7-12, 19-26, 28, 30-35, 44-47	17
X	CN 108350082 A (I-MAB) 31 July 2018 (2018-07-31) Claims 1-25, 27-32	17
X	CN 105579471 A (MERCK SHARP & DOHME CORP.) 11 May 2016 (2016-05-11) Claims 1-6, 10-20	17
X	CN 101248089 A (MEDAREX, INC.) 20 August 2008 (2008-08-20) Claims 6-9, 21-22, 27-28, 31-37, 40-42, 45-52, 55-56, 59-63	17

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2019	**19 November 2019**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **FENG,Xiaoliang** Telephone No. **86-(10)-53961927**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 105777906 A (SUZHOU DINGFU TARGETS BIOTECHNOLOGY CO., LTD.) 20 July 2016 (2016-07-20) the whole document	1-18
A	CN 106496327 A (KUNSHAN BAIERTAI BIOLOGICAL TECHNOLOGY CO., LTD.) 15 March 2017 (2017-03-15) the whole document	1-18
A	CN 107973854 A (SUZHOU GALAXY BIOPHARMA CO., LTD.) 01 May 2018 (2018-05-01) the whole document	1-18
A	CN 108239149 A (NANJING CHUANQI BIOTECHNOLOGY CO., LTD.) 03 July 2018 (2018-07-03) the whole document	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/101659

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **13-16**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] The subject-matter of claims 13-16 relates to a method of treating a subject in need, therefore does not warrant an international search according to the criteria set out in Rule 39.1(iv). However, the search has also been carried out based on the use of the pharmaceutical composition for manufacturing of a medicament for treating a subject in need thereof for a condition therapeutically.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/101659

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	106432501	A	22 February 2017	None			
CN	104736168	A	24 June 2015	AU	2018202465	A1	26 April 2018
				KR	20150042751	A	21 April 2015
				CN	104736168	B	21 September 2018
				AU	2013267161	A1	20 November 2014
				BR	112014029883	A2	27 June 2017
				EP	2854843	A2	08 April 2015
				CN	109467601	A	15 March 2019
				JP	2015519375	A	09 July 2015
				US	2013323249	A1	05 December 2013
				US	10058609	B2	28 August 2018
				EP	2854843	A4	01 June 2016
				CA	2872030	A1	05 December 2013
				US	2017281765	A1	05 October 2017
				JP	2017197586	A	02 November 2017
				WO	2013181634	A3	13 March 2014
				CO	7160115	A2	15 January 2015
				US	9175082	B2	03 November 2015
				WO	2013181634	A2	05 December 2013
				US	2019060451	A1	28 February 2019
				HK	1204557	A1	27 November 2015
				US	2017182161	A1	29 June 2017
CN	102264762	A	30 November 2011	JP	2015214549	A	03 December 2015
				AU	2009296392	B2	02 June 2016
				US	10011656	B2	03 July 2018
				US	2013291136	A1	31 October 2013
				HU	E030807	T2	29 May 2017
				DK	2342226	T3	26 September 2016
				KR	20180004288	A	10 January 2018
				BR	PI0919377	A2	27 September 2016
				SI	2342226	T1	30 November 2016
				IL	211830	D0	30 June 2011
				IL	265397	D0	30 May 2019
				WO	2010036959	A3	23 September 2010
				JP	2018113969	A	26 July 2018
				KR	20180129984	A	05 December 2018
				EP	3133086	B1	01 August 2018
				AU	2009296392	A1	01 April 2010
				ES	2592216	T3	28 November 2016
				WO	2010036959	A2	01 April 2010
				CA	2738252	C	01 May 2018
				CN	102264762	B	27 March 2018
				EP	2342226	A2	13 July 2011
				IL	211830	A	31 January 2017
				KR	20110079673	A	07 July 2011
				MX	2011003195	A	12 August 2011
				US	2011271358	A1	03 November 2011
				US	2018371084	A1	27 December 2018
				US	2016137731	A1	19 May 2016
				CA	2998281	A1	01 April 2010

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/101659

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
				EP	2342226	A4	28 November 2012
				AU	2018202800	A1	10 May 2018
				US	9102727	B2	11 August 2015
				US	8552154	B2	08 October 2013
				KR	101924874	B1	04 December 2018
				CN	108484767	A	04 September 2018
				JP	6087503	B2	08 March 2017
				AU	2016222431	A1	22 September 2016
				SI	EP2342226	T1	30 November 2016
				PL	2342226	T3	31 January 2017
				MX	349463	B	31 July 2017
				EP	3530672	A1	28 August 2019
				AU	2018202800	B2	11 July 2019
				EP	3133086	A1	22 February 2017
				JP	2012503984	A	16 February 2012
				KR	101814408	B1	04 January 2018
				CA	2738252	A1	01 April 2010
				EP	2342226	B1	22 June 2016
CN	108350082	A	31 July 2018	KR	101996019	B1	03 July 2019
				US	2018346574	A1	06 December 2018
				KR	20180039182	A	17 April 2018
				US	2018346573	A1	06 December 2018
				US	2018208659	A1	26 July 2018
				IL	263509	D0	31 January 2019
				SG	11201811003P	A	30 January 2019
				CL	2018003583	A1	17 May 2019
				BR	112018075737	A2	26 March 2019
				KR	20190079713	A	05 July 2019
				AU	2017284632	A1	03 January 2019
				CA	3027209	A1	21 December 2017
				EP	3325513	A1	30 May 2018
				WO	2017215590	A1	21 December 2017
				US	10059769	B2	28 August 2018
				US	10208119	B2	19 February 2019
				EP	3325513	A4	19 December 2018
				CO	2018013500	A2	19 February 2019
				PE	20190510	A1	10 April 2019
CN	105579471	A	11 May 2016	TW	201429990	A	01 August 2014
				BR	112015014833	A2	12 January 2016
				JP	2016504336	A	12 February 2016
				EP	2935329	A1	28 October 2015
				AU	2013361617	A1	02 July 2015
				US	2015355184	A1	10 December 2015
				CA	2895191	A1	26 June 2014
				KR	20150097670	A	26 August 2015
				WO	2014100079	A1	26 June 2014
				US	9709568	B2	18 July 2017
				KR	101780877	B1	21 September 2017
				AR	093984	A1	01 July 2015
				TW	I655209	B	01 April 2019

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/101659

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
		RU 2689953 C2	29 May 2019
		MX 361502 B	06 December 2018
		RU 2015129813 A	27 January 2017
		AU 2013361617 B2	05 January 2017
		HK 1210785 A1	06 May 2016
		MX 2015008045 A	29 October 2015
CN 101248089 A	20 August 2008	JP 2016006123 A	14 January 2016
		US 8383796 B2	26 February 2013
		AU 2006265108 A1	11 January 2007
		US 2016075782 A1	17 March 2016
		NO 20080590 L	31 March 2008
		EP 1907424 A2	09 April 2008
		HR P20080053 A2	31 August 2009
		ES 2546333 T3	22 September 2015
		EA 200800229 A1	30 June 2008
		KR 101704734 B1	09 February 2017
		HR P20151102 T1	20 November 2015
		IL 241092 D0	30 November 2015
		SI EP1907424 T1	31 December 2015
		NO 20080590 A	31 March 2008
		KR 20170018085 A	15 February 2017
		EA 019344 B1	31 March 2014
		CN 105330741 A	17 February 2016
		SG 163554 A1	30 August 2010
		US 2009055944 A1	26 February 2009
		BR PI0613361 A2	04 January 2011
		KR 101607288 B1	05 April 2016
		IL 188124 D0	20 March 2008
		RS 54271 B1	29 February 2016
		JP 2008544755 A	11 December 2008
		ZA 200710919 A	29 October 2008
		US 2011209230 A1	25 August 2011
		AU 2006265108 B2	17 May 2012
		CA 2612241 A1	11 January 2007
		ME 02260 B	29 February 2016
		JP 5252635 B2	31 July 2013
		KR 20080045674 A	23 May 2008
		KR 101888321 B1	13 August 2018
		ZA 200710919 B	29 October 2008
		UA 99701 C2	25 September 2012
		EP 2982379 A1	10 February 2016
		JP 2013150606 A	08 August 2013
		US 7943743 B2	17 May 2011
		DK 1907424 T3	09 November 2015
		US 2015337038 A1	26 November 2015
		WO 2007005874 A2	11 January 2007
		MX 2007015942 A	07 March 2008
		KR 20140002041 A	07 January 2014
		SI 1907424 T1	31 December 2015
		PT 1907424 E	09 October 2015

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/101659

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
				NZ	564592	A	25 November 2011
				JP	2018027952	A	22 February 2018
				WO	2007005874	A3	19 July 2007
				CA	2612241	C	06 November 2018
				EP	1907424	B1	29 July 2015
				US	9580505	B2	28 February 2017
CN	105777906	A	20 July 2016	CN	105777906	B	23 April 2019
CN	106496327	A	15 March 2017	CN	106496327	B	15 January 2019
CN	107973854	A	01 May 2018	WO	2019114235	A1	20 June 2019
CN	108239149	A	03 July 2018		None		