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(71) Applicant: **KYMAB LIMITED** [GB/GB]; The Bennet Building (B930), Babraham Research Campus, Cambridge CB22 3AT (GB).

(72) Inventors: **CAMPBELL, Jamie**; c/o The Bennet Building (B930), Babraham Research Campus, Babraham CB22 3AT (GB). **SANDY, Nikole**; c/o The Bennet Building (B930), Babraham Research Campus, Babraham CB22 3AT (GB). **VAN KRINKS, Cassandra**; c/o The Bennet Building (B930), Babraham Research Campus, Babraham CB22 3AT (GB). **ARKINSTALL, Stephen John**; c/o The Bennet Building (B930), Babraham Research Campus, Babraham CB22 3AT (GB). **GERMASCHEWSKI, Volker**; c/o The Bennet Building (B930), Babraham Research Campus, Babraham CB22 3AT (GB). **KIRBY, Ian**; c/o The Bennet Building (B930), Babraham Research Campus, Babraham CB22 3AT (GB). **KOSMAC, Miha**; c/o The Bennet Building (B930), Babraham Research Campus, Babraham CB22 3AT (GB). **GALLAGHER, Thomas**; c/o The Bennet Building (B930), Babraham Research Campus, Babraham CB22 3AT (GB). **DEANTONIO, Cecilia**; c/o The Bennet Building (B930), Babraham Research Campus, Babraham CB22 3AT (GB). **GILLIES, Stephen, Douglas**; 47 Swanson Lane, Carlisle, MA 01741-1044 (US).

(74) Agent: **LEONARD, Thomas**; Kilburn & Strode LLP, 20 Red Lion Street, London, WC1R 4PJ (GB).

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(54) Title: ANTI-PD-L1 ANTIBODIES

(57) Abstract: The present invention relates to anti-PD-L1 antibodies, bispecific antibodies containing one domain with specificity to PD-L1, and to immunocytokines comprising an anti-PD-L1 antibody fused to a cytokine, such as IL-2. The present invention also provides methods of treatment, uses and pharmaceutical compositions comprising the antibodies, bispecific antibodies and immunocytokines.

ANTI-PD-L1 ANTIBODIES

PD-L1 Specific Antibodies

Field of the Invention

Antibodies and methods of using the antibodies are described. In particular, antibodies that specifically bind human PD-L1 antigen and their use in treating various diseases are described.

Introduction

Immunocytokines (antibody-cytokine fusion proteins) were first reported in the literature in the early 1990s and consisted of whole antibody fusions with cytokines such as lymphotoxin (TNF- or interleukin 2 (IL-2). Subsequent studies in GD2-expressing tumour models in mice indicated that the ch14.18 antibody and ch14.18-IL2 immunocytokine both had anti-tumour activity but that the immunocytokine was far more potent than the antibody, even when combined with free IL-2, (see Sabzevari H , Proc. Natl. Acad. Sci. USA, 1994, 91:9626-30; Pancook JD, , Cancer Immunol. Immunother., 1996, 42:88-92; Becker JC, , Proc. Natl. Acad. Sci. USA, 1996, 93:2702-7). In addition, immune-competent mice treated with the immunocytokine, but not the antibody plus IL-2, developed an adaptive immune response dependent on $CD8^+$ T-cells that prevented subsequent tumour challenge (Becker JC, , J. Exp. Med., 1996, 183:2361-6; Becker JC, , Proc. Natl. Acad. Sci. USA, 1996, 93:7826-31). Thus, the targeting of IL-2 to the tumour microenvironment induces an anti-tumour vaccine effect that is not possible with the antibody, either alone or together with the free cytokine. A related humanized immunocytokine, hu 14.18-IL2, achieved clinical proof of concept in relapsed non-bulky neuroblastoma as monotherapy where it induced a significant number of complete responses in patients with no other treatment options (see Shusterman , Journal of Clinical Oncology, 2010, 28(33), 4969–4975). A number of publications describe the ability of this molecule to activate several components of the immune system to kill tumour cells (particularly NK cells and $CD8^+$ T-cells), and develop T-cell memory in order to resist subsequent tumour challenge (Yamane 2009; Expert Opi, Investig. Drugs, 18(7): 991–1000; Neal , 2004, Clin. Cancer Res., 1010, 4839–4847).

As IL-2 based immunocytokines can have significant side effects, recent efforts have focused on the reduction of toxicity whilst maintaining efficacy. One example is Selectikine (EMD 521873), which has a substitution of aspartic acid for threonine at position 20 of IL-2, a key residue in the binding of IL-2R (Gillies , Clinical Cancer Research, 2011, 17(11), 3673–3685). Selectikine, which binds necrotic tissue, has been shown to have good anti-tumour activity, despite its selectivity for the high affinity IL-2R, over the intermediate IL-2R and good tolerability in Phase I studies (Laurent , Journal of Translational Medicine, 2013, 11(1), 5. http://doi.org/10.1186/1479-5876-11-5)

WO2012/178137 (Gillies) and an associated journal article (Gilles, Protein Engineering, Design and Selection, 2013, 26(10), 561-569) describe light chain immunocytokine fusions with tumour targeting antibodies, and modulation of IL-2 activity by the introduction of truncations in the N-terminal part of the cytokine, which decreases signalling through IL-2R . IL-2 fusion proteins that specifically target IL-2R have been shown to have increased toxicity compared with wild-type (Vasquez-Lombardi . Nat Comm, 2017, DOI: 10.1038/ncomms15373), supporting the notion that decreasing IL-2R binding may be beneficial in terms of side effects.

An adaptive immune response involves activation, selection, and clonal proliferation of two major classes of lymphocytes termed T-cells and B-cells. After encountering an antigen, T-cells proliferate and differentiate into antigen-specific effector cells, while B-cells proliferate and differentiate into antibody-secreting cells. T-cell activation is a multi-step process requiring several signalling events between the T-cell and an antigen-presenting cell (APC). For T-cell activation to occur, two types of signals must be delivered to a resting T-cell. The first type is mediated by the antigen-specific T-cell receptor (TcR), and confers specificity to the immune response. The second signal, a costimulatory type signal, regulates the magnitude of the response and is delivered through accessory receptors on the T-cell.

A primary costimulatory signal is delivered through the activating CD28 receptor upon engagement of its ligands B7-1 or B7-2. In contrast, engagement of the inhibitory CTLA-4 receptor by the same B7-1 or B7-2 ligands results in attenuation of a T-cell response. Thus, CTLA-4 signals antagonize costimulation mediated by CD28. At high antigen concentrations, CD28 costimulation overrides the CTLA-4 inhibitory effect. Temporal regulation of the CD28 and CTLA-4 expression maintains a balance between activating and inhibitory signals and ensures the development of an effective immune response, while safeguarding against the development of autoimmunity.

Programmed death-1 (PD-1) is a 50-55 kDa type I transmembrane receptor that is a member of the CD28 family. PD-1 is involved in the regulation of T-cell activation and is expressed on T-cells, B cells, and myeloid cells. Two ligands for PD-1, PD ligand 1 (PD-L1) and ligand 2 (PD-L2) have been identified and have co-stimulatory features.

Programmed cell death 1 ligand 1 (PD-L1), also known as cluster of differentiation (CD274) or B7 homolog 1 (B7-H1), is a member of the B7 family that modulates activation or inhibition of the PD-1 receptor. The open reading frame of PD-L1 encodes a putative type 1 transmembrane protein of 290 amino acids, which includes two extracellular Ig domains (a N-terminal V-like domain and a Ig C-like domain), a hydrophobic transmembrane domain and a cytoplasmic tail of 30 amino acids. The 30 amino acid intracellular (cytoplasmic) domain contains no obvious signalling motifs, but does have a potential site for protein kinase C phosphorylation.

The complete amino acid sequence for PD-L1 can be found in NCBI Reference Sequence: NP_054862.1 (SEQ ID NO: 1), which refers to many journal articles, including, for example, Dong, H., (1999), "PD-L1, a third member of the B7 family, co-stimulates T-cell proliferation and

interleukin-10 secretion," Nat. Med. 5 (12), 1365-1369. The PD-L1 gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, and zebrafish. The murine form of PD-L1 bears 69% amino acid identity with the human form of PD-L1, and also shares a conserved structure.

In humans, PD-L1 is expressed on a number of immune cell types including activated and anergic/exhausted T-cells, on naive and activated B-cells, as well as on myeloid dendritic cells (DC), monocytes and mast cells. It is also expressed on non-immune cells including islets of the pancreas, Kupffer cells of the liver, vascular endothelium and selected epithelia, for example airway epithelia and renal tubule epithelia, where its expression is enhanced during inflammatory episodes. PD-L1 expression is also found at increased levels on a number of tumours including, but not limited to breast (including but not limited to triple negative breast cancer and inflammatory breast cancer), ovarian, cervical, colon, colorectal, lung, including non-small cell lung cancer, renal, including renal cell carcinoma, gastric, oesophageal, bladder, hepatocellular cancer, squamous cell carcinoma of the head and neck (SCCHN) and pancreatic cancer, melanoma and uveal melanoma.

PD-1/PD-L1 signalling is believed to serve a critical non-redundant function within the immune system by negatively regulating T-cell responses. This regulation is involved in T-cell development in the thymus, in regulation of chronic inflammatory responses and in maintenance of both peripheral tolerance and immune privilege. It appears that upregulation of PD-L1 may allow cancers to evade the host immune system and, in many cancers, the expression of PD-L1 is associated with reduced survival and an unfavourable prognosis. Therapeutic monoclonal antibodies that are able to block the PD-1/PD-L1 pathway may enhance anti-tumoural immune responses in patients with cancer. Published clinical data suggest a correlation between clinical responses with tumoural membranous expression of PD-L1 (Brahmer , Journal of Clinical Oncology, 2010, Topalian , NEJM, 2012) and a stronger correlation between lack of clinical responses and a lack of PD-L1 protein localized to the membrane (Brahmer , Journal of Clinical Oncology, 2010, Topalian , NEJM, 2012). Thus, PD-L1 expression in tumours or tumour-infiltrating leukocytes (Herbst RS, , "Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients", Nature, 2014, Nov 27, 515(7528):563-7, doi: 10.1038/nature14011) is a candidate molecular marker for use in selecting patients for immunotherapy, for example, immunotherapy using anti-PD-L1 antibodies. Patient enrichment based on surface expression of PD-L1 may significantly enhance the clinical success of treatment with drugs targeting the PD-1/PD-L1 pathway. There is also evidence of an on-going immune response, such as the tumour infiltrating $CD8^+$ T-cells, or the presence of signature of cytokine activation, such as IFN

Further evidence of PD-L1 expression and correlation to disease will emerge from the numerous ongoing clinical trials. Atezolizumab is the most advanced, and recent data from Phase II trials shows therapeutic effects in metastatic urothelial carcinoma and NSCLC, particularly in patients with PD-$L1^+$ immune cells in the tumour microenvironment (see Fehrenbacher , 2016, The Lancet, http://doi.org/10.1016/S0140-6736(16)00587-0; Rosenberg , 2016, The Lancet,

http://doi.org/10.1016/S0140-6736(16)00561-4). Recent results from a Phase III trial of 1225 patients with NSCLC showed improved survival in patients taking atezolizumab, compared with chemotherapy, regardless of tumour expression of PD-L1 (Rittmeyer ., 2017, The Lancet, 389(10066), 255–265).

Summary of the Invention

Antibodies

Disclosed herein are antibodies and antigen binding fragments thereof that specifically bind to PD-L1. In one embodiment, the antibody or antigen binding fragment thereof specifically binds to surface expressed PD-L1.

In a first configuration, there is provided an antibody or a fragment thereof, that specifically binds to hPD-L1 as defined by Seq ID No:1, and competes for binding to said hPD-L1 with the antibody 1D05, wherein the antibody or fragment comprises a V_H domain which comprises a CDRH3 comprising the motif $X_1GSGX_2YGX_3X_4FD$, wherein X_1, X_2 and X_3 are independently any amino acid, and X_4 is either present or absent, and if present, may be any amino acid.

In a second configuration, there is provided an antibody or a fragment thereof which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 1D05, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:29 or 32, or the CDRH3 sequence of SEQ ID NO:29 or 32 comprising 6 or fewer amino acid substitutions.

In a third configuration, there is provided an antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 1D05 specifically binds.

In a fourth configuration, there is provided an antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 1D05.

In a fifth configuration, there is provided a bispecific antibody or fusion protein comprising an antibody or fragment thereof as defined in any other configuration, embodiment or concept.

In a sixth configuration, there is provided an antibody or fragment as defined in any other configuration, embodiment or concept for use in treating or preventing a hPD-L1-mediated disease or condition.

In a seventh configuration, there is provided the use of an antibody or fragment as defined in any other configuration, embodiment or concept in the manufacture of a medicament for administration to a human for treating or preventing a hPD-L1 mediated disease or condition in the human.

In an eighth configuration, there is provided a method of treating or preventing a hPD-L1 mediated disease or condition in a human, comprising administering to said human a therapeutically

effective amount of an antibody or fragment as defined in any other configuration, embodiment or concept, wherein the hPD-L1 mediated disease or condition is thereby treated or prevented.

In a ninth configuration, there is provided a pharmaceutical composition comprising an antibody of fragment as defined in any other configuration, embodiment or concept and a pharmaceutically acceptable excipient, diluent or carrier.

In a tenth configuration, there is provided a kit comprising a pharmaceutical composition comprising an antibody of fragment as defined in any other configuration, embodiment or concept and a pharmaceutically acceptable excipient, diluent or carrier.

In an eleventh configuration, there is provided a method of modulating PD-1/PD-L1 interaction in a patient, comprising administering an effective amount of an antibody or fragment as defined in any other configuration, embodiment or concept to said patient.

In a twelfth configuration, there is provided a method of inhibiting PD-L1 activity in a patient, comprising administering an effective amount of an antibody or fragment as defined in any other configuration, embodiment or concept to said patient.

In a thirteenth configuration, there is provided a method of treating a proliferative disease in an animal (e.g. a human), comprising administering an effective amount of an antibody or fragment as defined in any other configuration, embodiment or concept to said patient.

In a fourteenth configuration, there is provided a method of detecting PD-L1 expression in a sample, comprising contacting the sample with an antibody or fragment as defined in any other configuration, embodiment or concept.

In a fifteenth configuration, there is provided a method comprising contacting a biological sample with an antibody or fragment as defined in any other configuration, embodiment or concept to form a complex with PD-L1 present in the sample and measuring the presence, absence or level of the complex in the biological sample.

In a sixteenth configuration, there is provided a method of detecting PD-L1 expression in a sample, comprising contacting the sample with an antibody or fragment as defined in any other configuration, embodiment or concept.

In a seventeenth configuration, there is provided a method comprising contacting a biological sample with an antibody or fragment as defined in any other configuration, embodiment or concept to form a complex with PD-L1 present in the sample and measuring the presence, absence or level of the complex in the biological sample.

In a eighteenth configuration, there is provided a method for identifying binding partners for PD-L1, the method comprising immunoprecipitating an intact protein complex comprising PD-L1 using an antibody or fragment as defined in any other configuration, embodiment or concept.

In a nineteenth configuration, there is provided a method of diagnosing a disease in a human subject associated with altered PD-L1 expression comprising the steps of contacting a biological sample from the human subject with an antibody as defined in other configuration, embodiment or

concept to form a complex between the antibody and PD-L1 present in the sample; and detecting the amount of the complex.

In a twentieth configuration, there is provided a nucleic acid that encodes the CDRH3 of an antibody or fragment as defined in any other configuration, embodiment or concept.

In a twenty-first configuration, there is provided a nucleic acid that encodes a VH domain and/or a VL domain of an antibody or fragment as defined in any other configuration, embodiment or concept.

In a twenty-second configuration, there is provided a vector comprising the nucleic acid of any other configuration, embodiment or concept; optionally wherein the vector is a CHO or HEK293 vector.

In a twenty-third configuration, there is provided a host comprising the nucleic acid of any other configuration, embodiment or concept or the vector of any other configuration, embodiment or concept.

Immunocytokines

In a first configuration, there is provided an immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and
b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;
d) A light chain constant region, (C_L);
e) Optionally, a linker, (L); and
f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to hPD-L1 as defined by Seq ID No:1, and competes for binding to said hPD-L1 with the antibody 1D05; and

wherein the immunocytokine comprises a V_H domain which comprises a CDRH3 comprising the motif X_1GSGX_2YGX_3X_4FD, wherein X_1, X_2 and X_3 are independently any amino acid, and X_4 is either present or absent, and if present, may be any amino acid.

In a second configuration, there is provided an immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and
b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

d) A light chain constant region, (C_L);

e) Optionally, a linker, (L); and

f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 1D05, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:29 or 32, or the CDRH3 sequence of SEQ ID NO:29 or 32 comprising 6 or fewer amino acid substitutions.

In a third configuration, there is provided an immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

d) A light chain constant region, (C_L);

e) Optionally, a linker, (L); and

f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to hPD-L1; and

wherein the V_H domain comprises a CDRH3 of from 12 to 20 amino acids and which is derived from the recombination of a human V_H gene segment, a human D gene segment and a human J_H gene segment, wherein the human J_H gene segment is IGHJ5 (e.g. IGHJ5*02).

In a fourth configuration, there is provided an immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

d) A light chain constant region, (C_L);

e) Optionally, a linker, (L); and

f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to an epitope that is identical to an epitope to which the antibody 1D05 specifically binds.

In a fifth configuration, there is provided an immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

d) A light chain constant region, (C_L);

e) Optionally, a linker, (L); and

f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site which competes for binding to hPD-L1 with the antibody 1D05.

In a sixth configuration, there is provided an immunocytokine as defined in any other configuration, embodiment or aspect for use in treating or preventing a hPD-L1-mediated disease or condition.

In a seventh configuration, there is provided the use of an immunocytokine as defined in any other configuration, embodiment or aspect in the manufacture of a medicament for administration to a human for treating or preventing a hPD-L1 mediated disease or condition in the human.

In an eighth configuration, there is provided a method of treating or preventing a hPD-L1 mediated disease or condition in a human, comprising administering to said human a therapeutically effective amount of an immunocytokine as defined in any other configuration, embodiment or aspect, wherein the hPD-L1 mediated disease or condition is thereby treated or prevented.

In a ninth configuration, there is provided a pharmaceutical composition comprising an immunocytokine as defined in any other configuration, embodiment or aspect, and a pharmaceutically acceptable excipient, diluent or carrier.

In a tenth configuration, there is provided a kit comprising a pharmaceutical composition comprising an immunocytokine as defined in any other configuration, embodiment or aspect, and a pharmaceutically acceptable excipient, diluent or carrier.

In an eleventh configuration, there is provided a nucleic acid that encodes a heavy chain and/or a light chain of an immunocytokine as defined in any other configuration, embodiment or aspect.

In a twelfth configuration, there is provided a vector comprising the nucleic acid that encodes a heavy chain and/or a light chain of an immunocytokine as defined in any other configuration, embodiment or aspect.

In a thirteenth configuration, there is provided a host comprising the nucleic acid of any other configuration, embodiment or aspect or the vector as defined in any other configuration, embodiment or aspect.

Anti-ICOS Bispecific Antibodies

In a first configuration, there is provided a multispecific antibody (e.g. bispecific antibody or a dual-binding antibody) which binds (and optionally has specificity for) ICOS (e.g. human ICOS) and another target antigen.

In a second configuration, there is provided a composition comprising a multispecific, bispecific or dual-binding antibody as described herein and a pharmaceutically acceptable excipient, diluent or carrier.

In a third configuration, there is provided a multispecific, bispecific or dual-binding antibody as described herein for use in treating or preventing a disease or condition, selected from neurological disease, neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours; such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

In a fourth configuration, there is provided a use of a multispecific, bispecific or dual-binding antibody as described herein in the manufacture of a medicament for administration to a human for treating or preventing a disease or condition in the human selected from neurological disease, neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

In a fifth configuration, there is provided a method of treating or preventing a disease or condition selected from neurological disease, neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous

cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas) in a human, comprising administering to said human a therapeutically effective amount of a multispecific, bispecific or dual-binding antibody as described herein, wherein the disease or condition is thereby treated or prevented.

In a sixth configuration, there is provided a nucleic acid that encodes a heavy chain and/or a light chain of a multispecific antibody as described herein.

In a seventh configuration, there is provided a vector comprising the nucleic acid that encodes a heavy chain and/or a light chain of a multispecific antibody as described herein.

Description of the Figures

Figure 1: Analysis of selected antibodies in a dendritic cell–T-cell mixed lymphocyte reaction. Monocytes were cultured with GM-CSF and IL-4 for seven days, before addition of allogeneic purified $CD3^+$ T-cells and titrations of antibodies. Supernatants were taken at day 5 for analysis of production. Data is shown from one experiment. Note that for 84G09, there is a single point per concentration, as one replicate failed

Figure 2: PD-L1 direct neutralisation ELISA with PD-1 receptor. Neutralisation profiles of 1D05 and 84G09 compared to a benchmark anti-PD-L1 antibody and isotype control. Data representative of three independent experiments

Figure 3: Human PD-L1 CHO-S FACS neutralisation with PD-1 receptor. Neutralisation profiles of 1D05 and 84G09 compared to a benchmark anti-PD-L1 antibody and isotype control. Data representative of three independent experiments

Figure 4: Human PD-L1 CHO FACS neutralisation with CD80 receptor. Neutralisation profiles of the 1D05 and 84G09 compared to the benchmark anti-PD-L1 antibody and isotype control. Data representative of three independent experiments

Figure 5: Binding of lead antibodies to PD-L1 but not PD-L2. Lead antibodies bind to plate bound PD-L1 (Figure 5a) but not PD-L2 (Figure 5b). An anti-PD-L2 antibody was used as a control. Data are expressed as time resolved fluorescence units at 615 nm. Data representative of two independent experiments

Figure 6: Lead antibodies induce IFNγ production in a Dendritic Cell-T-cell mixed lymphocyte reaction. Immature dendritic cells were co-cultured with allogeneic $CD4^+$ T-cells in the presence of antibodies for 5 days. IFNγ was measured in supernatants by ELISA. Data are representative of three independent experiments. B1 refers to a benchmark antibody

Figure 7: Lead antibodies bind to natively expressed PD-L1 on dendritic cells. Dendritic cells were generated from monocyte precursors with GM-CSF and IL-4 and stained with lead antibodies (a) 1D05 and (b) 84G09, and isotype control directly labelled with AlexaFluor647. Data shown is from one blood donor, representative of four donors

Figure 8a: PD-L1 direct neutralisation ELISA with PD-1 receptor. Neutralisation profiles of KM121 hits compared to a benchmark anti-PD-L1 antibody and isotype control. Data representative of three independent experiments

Figure 8b: PD-L1 direct neutralisation ELISA with PD-1 receptor. Neutralisation profiles of KM122 lead candidate molecules compared to the benchmark anti-PD-L1 antibody. Data is from a single experiment

Figure 8c: PD-L1 direct neutralisation ELISA with PD-1 receptor. Neutralisation profile of KM122 lead candidate molecule 416E01 compared to the benchmark anti-PD-L1 antibody. Data is from a single experiment

Figure 9a: PD-L1 direct neutralisation ELISA with CD80 receptor. Neutralisation profiles of KM121 hits compared to a benchmark anti-PD-L1 antibody and isotype control. Data representative of three independent experiments

Figure 9b: PD-L1 direct neutralisation ELISA with CD80 receptor. Neutralisation profiles of KM122 lead candidate molecules compared to the benchmark anti-PD-L1 antibody. Data is from a single experiment

Figure 9c: PD-L1 direct neutralisation ELISA with CD80 receptor. Neutralisation profiles of KM122 lead candidate molecule 416E01 compared to the benchmark anti-PD-L1 antibody. Data is from a single experiment

Figure 10: Bispecific binding as measured by SPR, with PD-L1 as first antigen, and TIGIT as second antigen. A) Bispecific 1, B) Bispecific 2, C) Bispecific 3, D) Bispecific 4. For detailed construction information of each Bispecific construct, see Table 6

Figure 11: Bispecific binding as measured by SPR, with TIGIT as first antigen, and PD-L1 as second antigen. A) Bispecific 1, B) Bispecific 2, C) Bispecific 3, D) Bispecific 4. For detailed construction information of each Bispecific construct, see Table 6

Figure 12(a): Ability of immunocytokine constructs to induce proliferation in IL-expressing TF-1 cells, compared with equimolar concentrations of free IL-2. Data shown is from a single experiment, representative of three experiments

Figure 12(b): Ability of immunocytokine constructs to induce proliferation in IL-expressing TF-1 cells, compared with equimolar concentrations of free IL-2. Data shown is from a single experiment, representative of four experiments

Figure 13(a): Capacity of 1D05 antibody to neutralise the interaction between PD-1 and PD-L1 is unaffected by the fusion of IL-2 to the antibody, as measured in a neutralisation ELISA. Data shown is from a single experiment, representative of three experiments

Figure 13(b): Capacity of 1D05 antibody to neutralise the interaction between CD80 and PD-L1 is unaffected by the fusion of IL-2 to the antibody, as measured in a neutralisation ELISA. Data shown is from a single experiment, representative of three experiments

Figure 14: Mean group and individual animal growth curves for the NOD/SCID: Xenograft efficacy study

Figure 14(a): shows the group mean (n=8/9) tumour growth curve, for this graph when an animal is removed from the study due to tumour size, the last reading is used for the rest of the study. The shaded area shows the area where the last reading is being used

Figures 14(b) to (e): show the individual animal tumour growth curves for each group. (b) A375 tumours alone; (c) A375 tumours co-injected with $CD4^+/8^+$ T-cells at a 6:1 ratio. For panels (d) and (e) A375 tumour cell were co-injected with $CD4^+/8^+$ T-cells at a 6:1 ratio; (d) Isotype Control antibody at 10 mg/kg and (e) anti-PD-L1 antibody 1D05 at 10 mg/kg. Dosing was at 1-hour post tumour/T-cell implantation and on days 3, 6, 8 and 10, shown on the graph by the dotted lines

Figure 15: Kaplan-Meier plot for the NOD/SCID:Xenograft efficacy study showing the number of animals still on study. This plot shows the slight increase in the time on study when $CD4^+/CD8^+$ T-cells are co-injected with the tumour cells (T-cells/A375) (n=9) when compared to the tumour cells alone A375 group (n=9). Treatment with the isotype control (T-cells/A375 – Isotype (n=8)) had no effect on survival when compared to the T-cells co-injected with the tumour cells without antibody. Treatment with 10 mg/kg of the anti-PD-L1 antibody 1D05 (T-cells/A375–anti-PD-L1) (n=8)) significantly increased the time on study when compared to the isotype control group. Dosing was 1-hour post injection of the T-cells/tumour cells and on days 3, 6, 8 and 10, show on the graph by the dotted lines

Figure 16: Expansion of lymphocytes in response to dosing with immunocytokines. Fasting blood samples were taken into EDTA treated tubes pre-treatment (0), and 2, 5 and 7 days post-treatment. Cell counts were measured by the Bayer Advia 120. Results are expressed as fold change in lymphocyte count

Figure 17: Analysis of standard haematological parameters in response to dosing with immunocytokines. Fasting blood samples were taken into EDTA treated tubes pre-treatment and 7 days post-treatment. Analysis of haemoglobin, haematocrit, red blood cell counts and platelet counts were performed using the Bayer Advia 120. Results are expressed as the percentage change in parameter 7 days post-dosing

Figure 18: Cytokine levels in plasma of cynomolgus monkeys dosed with immunocytokine molecules. Plasma samples were obtained pre-treatment (PT) and 3 days after dosing (D3) and analysed by MSD for levels of a) TNF- ; b) IL-8; c) IL-6; d) IFN ; e) G-CSF and f) IL-2. Where no bar is included, cytokine levels were below the limit of quantification of the assay. IL4, IL-5 and IL- were not detectable in any sample at either timepoint and so are not included in the graphs

Figure 19: Levels of soluble CD25 in plasma of cynomolgus monkeys dosed with immunocytokine molecules. Plasma samples were obtained pre-treatment (PT) and 3 days after dosing (D3) and analysed using a commercial ELISA kit. * indicates levels above limit of quantification (20,000 pg/mL)

Figure 20: Flow cytometric analysis of PBMC subsets. Whole blood was stained for markers of a) T-cells and b) B-cells, NK cells, neutrophils and monocytes, prior to red blood cell lysis and fixation. Data is expressed as the fold change in cell number 5 days after dosing. Data for 1D05 LC D9-7 ICK is missing due to unusable sample

Figure 21: Pharmacokinetic (PK) analysis of immunocytokines. Serum was prepared from blood samples taken at various time points over 96 hours. In panels a) and b), serum was incubated on plates coated with PD-L1 and immunocytokines detected with a biotinylated anti-human Fc detection antibody, and streptavidin-labelled Europium. In panels c) and d), serum was incubated on plates coated with PD-L1 and immunocytokines detected with a biotinylated anti-human IL-2 antibody, and streptavidin-labelled Europium. Results are expressed as ng/mL

Figure 22a: Induction of IFN production in a monocyte–T-cell co-culture assay by anti-PD-L1 antibodies in human IgG1 format. Each data point represents the mean fold induction from at least three independent experiments, ± standard error of the mean

Figure 22b: Induction of IFN production in a monocyte–T-cell co-culture assay by an anti-PD-L1 antibody in human IgG4(PE) format. Each data point represents the mean fold induction from two independent experiments, ± standard deviation

Figure 23(a): Induction of IL-2 in a murine T-cell hybridoma assay. Human PD-L1 transfected LK35.2 cells were loaded with ovalbumin peptide and co-cultured overnight with DO-11-10 T-cell hybridoma cells in the presence of anti-PD-L1 antibodies or controls, prior to collection of supernatants and analysis of IL-2 release. Each data point indicates background-corrected mean IL-2 release from three independent experiments ± standard deviation

Figure 23(b): Induction of IL-2 in a murine T-cell hybridoma assay. Human PD-L1 transfected LK35.2 cells were loaded with ovalbumin peptide and co-cultured overnight with DO-11-10 T-cell hybridoma cells in the presence of ICOS/PD-L1 bi-specific molecules, or individual antibodies, prior to collection of supernatants and analysis of IL-2 release. Each data point indicates background-corrected mean IL-2 release from three independent experiments ± standard deviation

Figure 24(a): Induction of IFN in a DC–T-cell MLR assay. Monocyte derived dendritic cells (DC) were activated with LPS and co-cultured with allogeneic $CD3^+$ T-cells at a 1:1 ratio. IFN was measured by DELFIA assay after 5 days of co-culture. Data is from a single experiment

Figure 24(b): Induction of IL-2 in a DC–T-cell MLR assay. Monocyte derived dendritic cells (DC) were activated with LPS and co-cultured with allogeneic $CD3^+$ T-cells at a 1:1 ratio. IL-2 was measured by DELFIA assay after 3 days of co-culture. Data is from a single experiment

Figure 25: Titration of FIT-Ig molecules, parental monospecific antibodies, and control antibodies in PD-L1/TIGIT AlphaScreen® Binding Assay using method one. Antibodies were incubated with PD-L1 and TIGIT proteins for an hour before the addition of AlphaScreen® acceptor beads for an hour followed by the addition of AlphaScreen® donor beads for another hour prior to the detection of fluorescence. A) Titration of FIT-Ig molecules; B) Titration of monospecific antibodies. Data shown are representative of one unique experiment

Figure 26: Titration of FIT-Ig molecules, parental monospecific antibodies, and control antibodies in PD-L1/TIGIT AlphaScreen® Binding Assay using method two. AlphaScreen® donor and acceptor beads were coated for an hour with PD-L1 and TIGIT proteins respectively before the addition of antibodies for an hour followed by the detection of fluorescence. A) Titration of FIT-Ig molecules; B) Titration of monospecific antibodies. Data shown are representative of one unique experiment

Figure 27: Titration of FIT-Ig molecules, and control antibody in a PD-L1/TIGIT cell recruitment assay by flow cytometry. CHO human PD-L1 and HEK human TIGIT were stained with CellTrace™ Far Red and CellTrace™ Violet respectively and co-cultured in presence of antibodies for an hour prior to the detection of fluorescence and identification of double positive population. Data shown are representative of one unique experiment

Figure 28: Expansion of lymphocytes in response to dosing with immunocytokines. Fasting blood samples were taken into EDTA treated tubes pre-treatment (0), and 2, 5 and 7, 10, 14 and 23 days post-treatment. Cell counts were measured by the Bayer Advia 120. Results are expressed as fold change in lymphocyte count

Figure 29: Levels of soluble CD25 in plasma of cynomolgus monkeys dosed with immunocytokine molecules. Plasma samples were obtained pre-treatment (0) and 3, 7 and 10 days after dosing and analysed using a commercial ELISA kit

Figure 30: Analysis of standard haematological parameters in response to dosing with immunocytokines. Fasting blood samples were taken into EDTA treated tubes pre-treatment (0) and 2, 5, 7, 10, 14 and 23 days post-treatment. Analysis of A) haemoglobin, B) haematocrit, C) red blood cell counts and D) platelet counts were performed using the Bayer Advia 120. Results are expressed as the fold change in parameter at each timepoint

Figure 31: Cytokine levels in plasma of cynomolgus monkeys dosed with immunocytokine molecules. Plasma samples were obtained pre-treatment (0) and 1, 3, 7, 10, 14 and 23 days after dosing and analysed by MSD for levels of a) TNF- ; b) IL-8; c) IL-6; d) IFN ; e) G-CSF, f) IL-2, g) IL-4 and h) IL-5. Where no bar is included, cytokine levels were below the limit of quantification of the assay. IL- as not detectable in any samples and so is not included in the graphs

Figure 32: Pharmacokinetic (PK) analysis of immunocytokines. Serum was prepared from blood samples taken at various time points over 96 hours. Serum was incubated on plates coated with PD-L1 and immunocytokines detected with a biotinylated anti-human Fc detection antibody, and streptavidin-labelled Europium. Results are expressed as % peak concentration

Figure 33: Expansion of specific T-cell subsets by ICK molecules. Whole blood was incubated with antibodies for staining, before red blood cell lysis, fixation and analysis by flow cytometry. Results are expressed as fold change in absolute (a) $CD4^+$ T-cell and (b) $CD8^+$ T-cell numbers at each timepoint.

Figure 34: Effector function of lead antibodies in a reporter cell assay. PD-L1 expressing target cells (ES2) were co-cultured overnight with Jurkat cells, engineered to express NFAT-induced luciferase and Fc RIIIa, in the presence of PD-L1 antibodies. Each data point indicates mean fold induction of relative light units ± standard deviation. Data is from one representative experiment, of three independent experiments

Figure 35: Binding of lead antibodies to cell-expressed cynomolgus PD-L1. Antibodies were titrated on CHO cells expressing cynomolgus PD-L1, and bound antibody detected with an anti-human IgG AlexaFluor 647. Data is from a single experiment

Figure 36(a): Human PD-L1 CHO-S FACS neutralisation with PD-1 receptor. Neutralisation profiles of lead antibodies compared to a benchmark anti-PD-L1 antibody and isotype control. Data representative of two independent experiments

Figure 36(b): Human PD-L1 CHO-S FACS neutralisation with CD80 receptor. Neutralisation profiles of lead antibodies compared to a benchmark anti-PD-L1 antibody and isotype control. Data representative of two independent experiments

Figure 37: Induction of IFN production in a monocyte–T-cell co-culture assay by anti-PD-L1 antibodies in human IgG1 format. Each data point represents the mean fold induction of IFN from at least three independent experiments, ± standard error of the mean

Detailed Description

1. Definitions

Unless otherwise defined herein, scientific and technical terms shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of this disclosure, suitable methods and materials are described below. The abbreviation, "e.g." is derived from the Latin exempli gratia, and is used herein to indicate a non-limiting example. Thus, the abbreviation "e.g." is synonymous with the term "for example."

In the specification and claims, the term "about" is used to modify, for example, the quantity of an ingredient in a composition, concentration, volume, process temperature, process time, yield, flow rate, pressure, and like values, and ranges thereof, employed in describing the embodiments of the disclosure. The term "about" refers to variation in the numerical quantity that can occur, for

example, through typical measuring and handling procedures used for making compounds, compositions, concentrates or use formulations; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of starting materials or ingredients used to carry out the methods, and like proximate considerations. The term "about" also encompasses amounts that differ due to aging of a formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a formulation with a particular initial concentration or mixture. Where modified by the term "about" the claims appended hereto include equivalents to these quantities.

As used herein, "administer" or "administration" refers to the act of injecting or otherwise physically delivering a substance as it exists outside the body (e.g., an anti-hPD-L1 antibody provided herein) into a patient, such as by mucosal, intradermal, intravenous, intramuscular delivery and/or any other method of physical delivery described herein or known in the art. When a disease, or a symptom thereof, is being treated, administration of the substance typically occurs after the onset of the disease or symptoms thereof. When a disease, or symptoms thereof, are being prevented, administration of the substance typically occurs before the onset of the disease or symptoms thereof.

The term "antibody", "immunoglobulin" or "Ig" may be used interchangeably herein and means an immunoglobulin molecule that recognizes and specifically binds to a target, such as a protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, or combinations of the foregoing through at least one antigen recognition site within the variable region of the immunoglobulin molecule. As used herein, the term "antibody" encompasses intact polyclonal antibodies, intact monoclonal antibodies, antibody fragments (such as Fab, Fab', $F(ab')_2$, and Fv fragments), single chain Fv (scFv) mutants, multispecific antibodies such as bispecific antibodies (including dual binding antibodies), chimeric antibodies, humanized antibodies, human antibodies, fusion proteins comprising an antigen determination portion of an antibody, and any other modified immunoglobulin molecule comprising an antigen recognition site so long as the antibodies exhibit the desired biological activity. The term "antibody" can also refer to a Y-shaped glycoprotein with a molecular weight of approximately 150 kDa that is made up of four polypeptide chains: two light (L) chains and two heavy (H) chains. There are five types of mammalian Ig heavy chain isotypes denoted by the Greek letters), delta (δ), epsilon (ε), gamma (γ), and mu type of heavy chain defines the class of antibody, i.e., IgA, IgD, IgE, IgG, and IgM, respectively. The γ and classes are further divided into subclasses on the basis of differences in the constant domain sequence and function, e.g., IgG1, hIgG2, mIgG2A, mIgG2B, IgG3, IgG4, IgA1 and IgA2. In mammals, there are two types of immunoglobulin light chains, λ and κ. The "variable region" or "variable domain" of an antibody refers to the amino-terminal domains of the heavy or light chain of the antibody. The variable domains of the heavy chain and light chain may be referred to as "V_H" and "V_L", respectively. These domains are generally the most variable parts of the antibody (relative to other antibodies of the same class) and contain the antigen binding sites.

The antibodies described herein may be oligoclonal, polyclonal, monoclonal (including full-length monoclonal antibodies), camelised, chimeric, CDR-grafted, multi-specific, bi-specific (including dual-binding antibodies), catalytic, chimeric, humanized, fully human, anti-idiotypic, including antibodies that can be labelled in soluble or bound form as well as fragments, variants or derivatives thereof, either alone or in combination with other amino acid sequences provided by known techniques. An antibody may be from any species. Antibodies described herein can be naked or conjugated to other molecules such as toxins, radioisotopes, etc.

The term "antigen binding domain," "antigen binding region," "antigen binding fragment," and similar terms refer to that portion of an antibody which comprises the amino acid residues that interact with an antigen and confer on the binding agent its specificity and affinity for the antigen (e.g. the complementarity determining regions (CDRs)). The antigen binding region can be derived from any animal species, such as rodents (e.g. rabbit, rat or hamster) and humans. Preferably, the antigen binding region will be of human origin.

Antigen binding fragments described herein can include single-chain Fvs (scFv), single- chain antibodies, single domain antibodies, domain antibodies, Fv fragments, Fab fragments, F(ab') fragments, $F(ab')_2$ fragments, antibody fragments that exhibit the desired biological activity, disulfide-stabilised variable region (dsFv), dimeric variable region (diabody), anti-idiotypic (anti-Id) antibodies (including, e.g. anti-Id antibodies to antibodies), intrabodies, linear antibodies, single-chain antibody molecules and multispecific antibodies formed from antibody fragments and epitope-binding fragments of any of the above. In particular, antibodies and antibody fragments described herein can include immunoglobulin molecules and immunologically active fragments of immunoglobulin molecules, i.e., molecules that contain an antigen-binding site. Digestion of antibodies with the enzyme, papain, results in two identical antigen-binding fragments, known also as "Fab" fragments, and a "Fc" fragment, having no antigen-binding activity but having the ability to crystallize. "Fab" when used herein refers to a fragment of an antibody that includes one constant and one variable domain of each of the heavy and light chains. The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native- sequence Fc regions and variant Fc regions. The "Fc fragment" refers to the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, the region which is also recognized by Fc receptors (FcR) found on certain types of cells. Digestion of antibodies with the enzyme, pepsin, results in a $F(ab')_2$ fragment in which the two arms of the antibody molecule remain linked and comprise two-antigen binding sites. The $F(ab')_2$ fragment has the ability to crosslink antigen.

"Fv" when used herein refers to the minimum fragment of an antibody that retains both antigen-recognition and antigen-binding sites. This region consists of a dimer of one heavy and one light chain variable domain in tight, non-covalent or covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface

of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e. the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (e.g. isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, and are directed against a single antigentic determinant or epitope. In contrast, polyclonal antibody preparations typically include different antibodies directed against different antigenic determinants (or epitopes). The term "monoclonal antibody" as used herein encompasses both intact and full-length monoclonal antibodies as well as antibody fragments (such as Fab, Fab', $F(ab')_2$, Fv), single chain (scFv) mutants, fusion proteins comprising an antibody portion, and any other modified immunoglobulin molecule comprising an antigen recognition site. Furthermore, "monoclonal antibody" refers to such antibodies made in any number of ways including, but not limited to, hybridoma, phage selection, recombinant expression, and transgenic animals.

The monoclonal antibodies herein can include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is(are) identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies that exhibit the desired biological activity.

The term "humanized antibody" refers to a subset of chimeric antibodies in which a "hypervariable region" from a non-human immunoglobulin (the donor antibody) replaces residues from a hypervariable region in a human immunoglobulin (recipient antibody). In general, a humanized antibody will include substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin sequence, and all or substantially all of the framework regions are those of a human immunoglobulin sequence, although the framework regions may include one or more substitutions that improve antibody performance, such as binding affinity, isomerization, immunogenicity, etc.

The term "bispecific antibody" means an antibody which comprises specificity for two target molecules, and includes, but is not limited to, formats such as DVD-Ig (see DiGiammarino , "Design and generation of DVD-Ig™ molecules for dual-specific targeting", Meth. Mo. Biol., 2012, 889, 145-156), mAb^2 (see WO2008/003103, the description of the mAb^2 format is incorporated herein by reference), FIT-Ig (see WO2015/103072, the description of the FIT-Ig scaffold is incorporated herein by reference), mAb-dAb, dock and lock, Fab-arm exchange, SEEDbody, Triomab, LUZ- - body, orthogonal Fab, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody,

BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH3, Diabody-CH3, Triple body, Miniantibody, minibody, TriBi minibody, scFv-CH3 KIH, scFv-CH-CL-scFv, F(ab')2-scFv, scFv-KIH, Fab-scFv-Fc, tetravalent HCab, ImmTAC, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, DT-IgG, DutaMab, IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv, scFv4-Ig and zybody. For a review of bispecific formats, see Spiess, C., , Mol. Immunol. (2015). In another embodiment, the bispecific molecule comprises an antibody which is fused to another non-Ig format, for example a T-cell receptor binding domain; an immunoglobulin superfamily domain; an agnathan variable lymphocyte receptor; a fibronectin domain (e.g. an Adnectin™); an antibody constant domain (e.g. a CH_3 domain, e.g., a CH_2 and/or CH_3 of an Fcab™) wherein the constant domain is not a functional CH_1 domain; an scFv; an $(scFv)_2$; an sc-diabody; an scFab; a centyrin and an epitope binding domain derived from a scaffold selected from CTLA-4 (Evibody™); a lipocalin domain; Protein A such as Z-domain of Protein A (e.g. an Affibody™ or SpA); an A-domain (e.g. an Avimer™ or Maxibody™); a heat shock protein (such as and epitope binding domain derived from GroEI and GroES); a transferrin domain (e.g. a trans-body); ankyrin repeat protein (e.g. a DARPin™); peptide aptamer; C-type lectin domain (e.g. Tetranectin™); - crystallin or human ubiquitin (an affilin); a PDZ domain; scorpion toxin; and a kunitz type domain of a human protease inhibitor.

In one embodiment, the bispecific antibody is a mAb^2. A mAb^2 comprises a V_H and V_L domain from an intact antibody, fused to a modified constant region, which has been engineered to form an antigen-binding site, known as an "Fcab". The technology behind the Fcab/mAb^2 format is described in more detail in WO2008/003103, and the description of the mAb^2 format is incorporated herein by reference.

In one embodiment, a "bispecific antibody" does not include a FIT-Ig format. In one embodiment, a "bispecific antibody" does not include a mAb^2 format. In one embodiment, a "bispecific antibody" does not include either a FIT-Ig format or a mAb^2 format.

In another embodiment, the bispecific antibody is a "dual binding antibody". As used herein, the term "dual binding antibody" is a bispecific antibody wherein both antigen-binding domains are formed by a V_H/V_L pair, and includes FIT-Ig (see WO2015/103072, incorporated herein by reference), mAb-dAb, dock and lock, Fab-arm exchange, SEEDbody, Triomab, LUZ- -body, orthogonal Fab, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH3, Diabody-CH3, Triple body, Miniantibody, minibody, scFv-CH_3 KIH, scFv-CH-CL-scFv, $F(ab')_2$-scFv, scFv-KIH, Fab-scFv-Fc, tetravalent HCab, ImmTAC, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, DT-IgG, DutaMab, IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv and scFv4-Ig.

The term "hypervariable region", "CDR region" or "CDR" refers to the regions of an antibody variable domain which are hypervariable in sequence and/or form structurally defined loops. Generally, antigen binding sites of an antibody include six hypervariable regions: three in the V_H (CDRH1, CDRH2, CDRH3), and three in the V_L (CDRL1, CDRL2, CDRL3). These regions of the heavy and light chains of an antibody confer antigen-binding specificity to the antibody. CDRs may be defined according to the Kabat system (see Kabat, E. A. , 1991, "Sequences of Proteins of Immunological Interest", 5th edit., NIH Publication no. 91-3242, U.S. Department of Health and Human Services). Other systems may be used to define CDRs, which as the system devised by Chothia (see Chothia, C. & Lesk, A. M., 1987, "Canonical structures for the hypervariable regions of immunoglobulins", J. Mol. Biol., 196, 901-917) and the IMGT system (see Lefranc, M. P., 1997, "Unique database numbering system for immunogenetic analysis", Immunol. Today, 18, 50). An antibody typically contains 3 heavy chain CDRs and 3 light chain CDRs. The term CDR or CDRs is used here to indicate one or several of these regions. A person skilled in the art is able to readily compare the different systems of nomenclature and determine whether a particular sequence may be defined as a CDR.

A "human antibody" is an antibody that possesses an amino-acid sequence corresponding to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies and specifically excludes a humanized antibody comprising non- human antigen-binding residues. The term "specifically binds to" refers to measurable and reproducible interactions such as binding between a target and an antibody, which is determinative of the presence of the target in the presence of a heterogeneous population of molecules including biological molecules. For example, an antibody that specifically binds to a target (which can be an epitope) is an antibody that binds this target with greater affinity, avidity, more readily, and/or with greater duration than it binds to other targets. In one embodiment, the extent of binding of an antibody to an unrelated target is less than about 10% of the binding of the antibody to the target as measured, e.g. by a radioimmunoassay (RIA).

An antibody or a fragment thereof that specifically binds to a hPD-L1 antigen may be cross-reactive with related antigens. Preferably, an antibody or a fragment thereof that specifically binds to a hPD-L1 antigen does not cross-react with other antigens (but may optionally cross-react with PD-L1 of a different species, e.g. rhesus, or murine). An antibody or a fragment thereof that specifically binds to a hPD-L1 antigen can be identified, for example, by immunoassays, BIAcore™, or other techniques known to those of skill in the art. An antibody or a fragment thereof binds specifically to a PD-L1 antigen when it binds to a hPD-L1 antigen with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as radioimmunoassays (RIA) and enzyme-linked immunosorbent assays (ELISAs). Typically, a specific or selective reaction will be at least twice background signal or noise and more typically more than 10 times (such as more than 15 times, more than 20 times, more than 50 times or more than 100 times) background. See, e.g. Paul, ed., 1989,

Fundamental Immunology Second Edition, Raven Press, New York at pages 332-336 for a discussion regarding antibody specificity.

The term "aliphatic amino acid" means that the amino acid R groups are nonpolar and hydrophobic. Hydrophobicity increases with increasing number of C atoms in the hydrocarbon chain. Glycine, Alanine, Valine, Leucine and Isoleucine are aliphatic amino acids.

The term "aromatic amino acid" means that the amino acid R groups contain an aromatic ring system. Phenylalanine, Tyrosine and Tryptophan are aromatic amino acids.

The term "hydroxyl-containing amino acid" means that the amino acid R groups contain a hydroxyl group, and are hydrophilic. Serine, Cysteine, Threonine and Methionine are hydroxyl-containing amino acids.

The term "basic amino acid" means that the amino acid R groups are nitrogen containing and are basic at neutral pH. Histidine, Lysine and Arginine are basic amino acids.

The term "cyclic amino acid" means that the amino acid R groups have an aliphatic cyclic structure. Proline is the only cyclic aliphatic amino acid.

The term "acidic amino acid" means that the amino acid R groups are polar and are negatively charged at physiological pH. Aspartate and Glutamate are acidic amino acids.

The term "amide amino acid" means that the amino acid R groups contain an amide group. Asparagine and Glutamine are amide amino acids.

As used herein, "authorization number" or "marketing authorization number" refers to a number issued by a regulatory agency upon that agency determining that a particular medical product and/or composition may be marketed and/or offered for sale in the area under the agency's jurisdiction. As used herein "regulatory agency" refers to one of the agencies responsible for evaluating, e.g. the safety and efficacy of a medical product and/or composition and controlling the sales/marketing of such products and/or compositions in a given area. The Food and Drug Administration (FDA) in the US and the European Medicines Agency (EPA) in Europe are but two examples of such regulatory agencies. Other non-limiting examples can include SDA, MPA, MHPRA, IMA, ANMAT, Hong Kong Department of Health-Drug Office, CDSCO, Medsafe, and KFDA.

As used herein, the term "biomarker" refers to a gene that is differentially expressed in individuals having a disease of interest, for example, a gene that is differentially expressed in individuals having cancer. In one embodiment, PD-L1 is a biomarker whose expression in tumours may be indicative as to whether or not a patient would respond to a particular type of treatment, in particular, whether a patient would response to treatment targeting PD-L1, for example, immunotherapy using anti-PD-L1 antibodies. In one embodiment, PD-L1 is a biomarker whose expression in tumours may be indicative as to whether or not a patient would respond to a particular type of treatment, in particular, whether a patient would response to treatment targeting PD-1, for example, immunotherapy using anti-PD-1 antibodies. In another embodiment, PD-L1 may be free or membrane bound. In another embodiment, PD-L1 may be fixed or unfixed.

As used herein, a "buffer" refers to a chemical agent that is able to absorb a certain quantity of acid or base without undergoing a strong variation in pH.

As used herein, the term "carrier" refers to a diluent, adjuvant (e.g., Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions.

The term "chemotherapeutic agent" or "chemotherapy" refers to a therapeutic agent whose primary purpose is to destroy cancer cells, typically by interfering with the tumour cell's ability to grow or multiply. There are many different types of chemotherapeutic agents, with more than 50 approved chemotherapy drugs available. Chemotherapeutic drugs can be classified based on how they work. Alkylating drugs kill cancer cells by directly attacking DNA, the genetic material of the genes. Cyclophosphamide is an alkylating drug. Antimetabolites interfere with the production of DNA and keep cells from growing and multiplying. An example of an antimetabolite is 5-fluorouracil (5-FU). Anti-tumour antibiotics are made from natural substances such as fungi in the soil. They interfere with important cell functions, including production of DNA and cell proteins. Doxorubicin and bleomycin belong to this group of chemotherapy drugs. Plant alkaloids prevent cells from dividing normally. Vinblastine and vincristine are plant alkaloids obtained from the periwinkle plant. Steroid hormones slow the growth of some cancers that depend on hormones. For example, tamoxifen is used to treat breast cancers that depend on the hormone estrogen for growth. DNA damage response (DDR) inhibitors, such as PARP inhibitors, block DNA repair mechanisms following single or double stranded breaks.

Examples of chemotherapeutic agents include Adriamycin, Doxorubicin, 5-Fluorouracil, Cytosine arabinoside (Ara-C), Cyclophosphamide, Thiotepa, Taxotere (docetaxel), Busulfan, Cytoxin, Taxol, Methotrexate, Cisplatin, Melphalan, Vinblastine, Bleomycin, Etoposide, Ifosfamide, Mitomycin C, Mitoxantrone, Vincreistine, Vinorelbine, Carboplatin, Teniposide, Daunomycin, Carminomycin, Aminopterin, Dactinomycin, Mitomycins, Esperamicins (see, U.S. Patent No. 4,675,187), Melphalan, and other related nitrogen mustards. Suitable toxins and chemotherapeutic agents are described in Remington's Pharmaceutical Sciences, 19th Ed. (Mack Publishing Co. 1995), and in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th Ed. (MacMillan Publishing Co. 1985). Another example of chemotherapeutic agents is the class of antibody-conjugated toxins, including, but not limited to pyrrolobenzodiazepiness, maytansanoids, calicheamicin, etc. Other suitable toxins and/or chemotherapeutic agents are known to those of skill in the art.

As used herein, the term "composition" is intended to encompass a product containing the specified ingredients (e.g. an antibody of the invention) in, optionally, the specified amounts, as well

as any product which results, directly or indirectly, from combination of the specified ingredients in, optionally, the specified amounts.

As used herein the term "comprising" or "comprises" is used with reference to antibodies, fragments, uses, compositions, methods, and respective component(s) thereof, that are essential to the method or composition, yet open to the inclusion of unspecified elements, whether essential or not.

The term "consisting of" refers to antibodies, fragments, uses, compositions, methods, and respective components thereof as described herein, which are exclusive of any element not recited in that description of the embodiment.

As used herein the term "consisting essentially of" refers to those elements required for a given embodiment. The term permits the presence of elements that do not materially affect the basic and novel or functional characteristic(s) of that embodiment.

In the context of a polypeptide, the term "derivative" as used herein refers to a polypeptide that comprises an amino acid sequence of a hPD-L1 polypeptide, a fragment of a hPD-L1 polypeptide, or an antibody that specifically binds to a hPD-L1 polypeptide which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a hPD-L1 polypeptide, a fragment of a hPD-L1 polypeptide, or an antibody that specifically binds to a hPD-L1 polypeptide which has been chemically modified, e.g. by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a hPD-L1 polypeptide, a fragment of a hPD-L1 polypeptide, or a hPD-L1 antibody may be chemically modified, e.g. by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. The derivatives are modified in a manner that is different from naturally occurring or starting peptide or polypeptides, either in the type or location of the molecules attached. Derivatives further include deletion of one or more chemical groups which are naturally present on the peptide or polypeptide. A derivative of a hPD-L1 polypeptide, a fragment of a hPD-L1 polypeptide, or a hPD-L1 antibody may be chemically modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a hPD-L1 polypeptide, a fragment of a hPD-L1 polypeptide, or a hPD-L1 antibody may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a hPD-L1 polypeptide, a fragment of a hPD-L1 polypeptide, or a hPD-L1 antibody described herein.

The term "effector function" as used herein is meant to refer to one or more of antibody dependant cell mediated cytotoxic activity (ADCC), complement-dependant cytotoxic activity (CDC) mediated responses, Fc-mediated phagocytosis or antibody dependant cellular phagocytosis (ADCP) and antibody recycling via the FcRn receptor.

An "effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired effect, including a therapeutic or prophylactic result. A "therapeutically effective amount" refers to the minimum concentration required to effect a measurable improvement or prevention of a particular disorder. A therapeutically effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the antibody to elicit a desired response in the individual. A therapeutically effective amount is also one in which toxic or detrimental effects of the antibody are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at the dosages and for periods of time necessary, to achieve the desired prophylactic result. In some embodiments, the effective amount of an antibody of the invention is from about 0.1 mg/kg (mg of antibody per kg weight of the subject) to about 100 mg/kg. In certain embodiments, an effective amount of an antibody provided therein is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg (or a range therein). In some embodiments, "effective amount" as used herein also refers to the amount of an antibody of the invention to achieve a specified result (e.g. inhibition of a hPD-L1 biological activity of a cell).

The term "epitope" as used herein refers to a localized region on the surface of an antigen, such as hPD-L1 polypeptide or hPD-L1 polypeptide fragment, that is capable of being bound to one or more antigen binding regions of an antibody, and that has antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human, that is capable of eliciting an immune response. An epitope having immunogenic activity is a portion of a polypeptide that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of a polypeptide to which an antibody specifically binds as determined by any method well known in the art, for example, by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics. A region of a polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide. The epitope may or may not be a three-dimensional surface feature of the antigen. In certain embodiments, a hPD-L1 epitope is a three-dimensional surface feature of a hPD-L1 polypeptide (e.g. in a trimeric form of a hPD-L1 polypeptide). In other embodiments, a hPD-L1 epitope is linear feature of a hPD-L1 polypeptide (e.g. in a trimeric form or monomeric form of the hPD-L1 polypeptide). Antibodies provided herein may specifically bind to an epitope of the monomeric (denatured) form of hPD-L1, an epitope of the trimeric (native) form of hPD-L1, or both the monomeric (denatured) form and the trimeric (native) form of hPD-L1. In specific embodiments, the antibodies provided herein specifically bind to an epitope of the trimeric form of hPD-L1 but do not specifically bind the monomeric form of hPD-L1.

The term "excipients" as used herein refers to inert substances which are commonly used as a diluent, vehicle, preservatives, binders, or stabilizing agent for drugs and includes, but not limited to, proteins (e.g. serum albumin, etc.), amino acids (e.g. aspartic acid, glutamic acid, lysine, arginine, glycine, histidine, etc.), fatty acids and phospholipids (e.g. alkyl sulfonates, caprylate, etc.), surfactants (e.g. SDS, polysorbate, nonionic surfactant, etc.), saccharides (e.g. sucrose, maltose, trehalose, etc.) and polyols (e.g. mannitol, sorbitol, etc.). See, also, Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, Pa., which is hereby incorporated by reference in its entirety.

As used herein, the term "fixed" or "fixation" refers to a chemical process by which biological tissues are preserved from decay, to prevent autolysis or putrefaction. In general, fixation involves exposing the tissue to chemical compounds such as alcohols or aldehydes such as formaldehyde to terminate ongoing biochemical reactions. In some instances, fixation may also increase the mechanical strength or stability of the treated tissues. The term "unfixed" refers to a tissue that has not been subjected to a chemical process to prevent tissue decay. As used herein, the term "surface expressed" means that the protein is embedded in or spans a cell membrane or is associated with a protein that is embedded in or spans a cell membrane (i.e. a membrane associated protein). In one embodiment, a surface expressed protein includes one or more transmembrane domains. In another embodiment, the protein is associated with the exterior or interior surface of a cell membrane indirectly via association with another membrane spanning protein (i.e. the surface expressed protein is not spanning the cell membrane itself). In general, surface expressed proteins that are integrated into a cell membrane or expressed endogenously within a cell are more likely to fold in the correct conformation than recombinantly produced free forms of the same protein.

In the context of a peptide or polypeptide, the term "fragment" as used herein refers to a peptide or polypeptide that comprises less than the full length amino acid sequence. Such a fragment may arise, for example, from a truncation at the amino terminus, a truncation at the carboxy terminus, and/or an internal deletion of a residue(s) from the amino acid sequence. Fragments may, for example, result from alternative RNA splicing or from in vivo protease activity. In certain embodiments, PD-L1 fragments include polypeptides comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino residues, at least 70 contiguous amino acid residues, at least 80 contiguous amino acid residues, at least 90 contiguous amino acid residues, at least contiguous 100 amino acid residues, at least 125 contiguous amino acid residues, at least 150 contiguous amino acid residues, at least 175 contiguous amino acid residues, at least 200 contiguous amino acid residues, or at least 250 contiguous amino acid residues of the amino acid sequence of a hPD-L1 polypeptide or an antibody that specifically binds to a hPD-L1 polypeptide. In a specific embodiment, a fragment of a hPD-L1

polypeptide or an antibody that specifically binds to a hPD-L1 antigen retains at least 1, at least 2, or at least 3 functions of the polypeptide or antibody.

The term "free" refers to a polypeptide, for example, PD-L1 or fragments and variants thereof, that is combined with a buffer, wherein the polypeptide is not associated with a cell surface or cell membrane. As such, the term "free" can refer to a polypeptide that is capable of surface expression (i.e. includes one or more transmembrane domains or membrane association domains), but that is not, in its present state, expressed on the surface of a cell or bound to a protein that is expressed on the surface of a cell. A free polypeptide can also refer to a free recombinant or native or unbound polypeptide. In the context of phage display, a free antigen can be selected in solution (referred to herein as a "soluble selection") or adsorbed to a surface, for example, adsorbed to the surface of a 96-well plate (referred to herein as "biopanning selection").

The term "fusion protein" as used herein refers to a polypeptide that comprises an amino acid sequence of an antibody and an amino acid sequence of a heterologous polypeptide or protein (i.e. a polypeptide or protein not normally a part of the antibody (e.g. a non-anti-hPD-L1 antigen antibody)). The term "fusion" when used in relation to hPD-L1 or to an anti-hPD-L1 antibody refers to the joining of a peptide or polypeptide, or fragment, variant and/or derivative thereof, with a heterologous peptide or polypeptide. Preferably, the fusion protein retains the biological activity of the hPD-L1 or anti-hPD-L1 antibody. In certain embodiments, the fusion protein comprises a hPD-L1 antibody VH domain, VL domain, VH CDR (one, two or three VH CDRs), and/or VL CDR (one, two or three VL CDRs), wherein the fusion protein specifically binds to a hPD-L1 epitope.

The term "heavy chain" when used with reference to an antibody refers to five distinct types, called alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), based on the amino acid sequence of the heavy chain constant domain. These distinct types of heavy chains are well known and give rise to five classes of antibodies, IgA, IgD, IgE, IgG and IgM, respectively, including four subclasses of IgG, namely IgG1, IgG2, IgG3 and IgG4. Preferably the heavy chain is a human heavy chain. In the human population, multiple heavy chain constant region alleles, of each immunoglobulin or immunoglobulin subclass, exist. The nucleotide and amino acid sequences of these allelic variants are accessible on publicly available databases such as IMGT, ENSEMBL Swiss-Prot and Uniprot. Allelic variants may also be identified in various genome sequencing projects. In one embodiment, the antibodies and antibody fragments disclosed herein comprise a heavy chain encoded by a IgG1 constant region allele, which includes, but is not limited to, human IGHG1*01 (Seq ID Nos:340, 341 & 537), IGHG1*02 (Seq ID Nos:340, 341 &537), IGHG1*03 (Seq ID Nos:523 & 524), IGHG1*04 (Seq ID Nos:525 & 526) and IGHG1*05 (Seq ID Nos:340, 341 & 537). In one embodiment, the antibodies and antibody fragments disclosed herein comprise a protein encoded by a IgG2 constant region allele, which includes, but is not limited to, human IGHG2*01 (Seq ID Nos:527 & 528), IGHG2*02 (Seq ID Nos:529 & 530), IGHG2*03 (Seq ID Nos:527 & 528), IGHG2*04 (Seq ID Nos:531 & 532), IGHG2*05 (Seq ID Nos:527 & 528) and IGHG2*06 (Seq ID Nos:533 & 534). In one embodiment, the antibodies

or antibody fragments disclosed herein comprise a protein encoded by a IgG3 constant region allele, which includes but is not limited to human IGHG3*01, IGHG3*02, IGHG3*03, IGHG3*04, IGHG3*05, IGHG3*06, IGHG3*07, IGHG3*08, IGHG3*09, IGHG3*10, IGHG3*11, IGHG3*12, IGHG3*13, IGHG3*14, IGHG3*15, IGHG3*16, IGHG3*17, IGHG3*18 and IGHG3*19. In one embodiment, the antibodies or antibody fragments disclosed herein comprise a protein encoded by a IgG4 constant region allele, which includes but is not limited to human IGHG4*01 (Seq ID Nos:192 & 193), IGHG4*02 (Seq ID Nos:194 & 195), IGHG4*03 (Seq ID Nos:196 & 197) and IGHG4*04 (Seq ID Nos:192 & 193). In another example, the heavy chain is a disabled IgG isotype, e.g. a disabled IgG4. In certain embodiments, the antibodies of the invention comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-
Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE (SEQ ID No:199. In another embodiment, the antibodies and antibody fragments disclosed herein comprise a heavy chain constant region encoded by a murine IgG1 constant region allele, which includes but is not limited to mouse IGHG1*01 or IGHG1*02. In one embodiment, the antibodies and antibody fragments disclosed herein comprise a heavy chain constant region encoded by a murine IgG2 constant region allele, which includes, but is not limited to, mouse IGHG2A*01, IGHG2A*02, IGHG2B*01, IGHG2B*02, IGHG2C*01, IGHG2C*02 or IGHG2C*03. In one embodiment, the antibodies or antibody fragments disclosed herein comprise a protein encoded by a murine IgG3 constant region allele, which includes but is not limited to mouse IGHG3*01.

The term "host" as used herein refers to an animal, preferably a mammal, and most preferably a human.

The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

The term "an IL-2 cytokine" as used herein refers to a cytokine-like molecule which has a similar activity to a wild-type IL-2. It may have activity at the high ( ) affinity IL-2 receptor and/or the intermediate affinity (-2 receptor. The cytokine may be a variant IL-2 cytokine having one or more amino acid deletions, substitutions or additions. Variant cytokines are described in more detail hereinbelow.

The term "immunomodulatory agent" and variations thereof including, but not limited to, immunomodulatory agents, as used herein refer to an agent that modulates a host's immune system. In certain embodiments, an immunomodulatory agent is an immunosuppressant agent. In certain other embodiments, an immunomodulatory agent is an immunostimulatory agent. In accordance with the invention, an immunomodulatory agent used in the combination therapies of the invention does

not include an anti-hPD-L1 antibody or antigen-binding fragment. Immunomodulatory agents include, but are not limited to, small molecules, peptides, polypeptides, proteins, fusion proteins, antibodies, inorganic molecules, mimetic agents, and organic molecules.

The term "in combination" in the context of the administration of other therapies refers to the use of more than one therapy. The use of the term "in combination" does not restrict the order in which therapies are administered to a subject with a disease. A first therapy can be administered before (e.g. 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks), concurrently, or after (e.g. 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks) the administration of a second therapy to a subject which had, has, or is susceptible to a hPD-L1-mediated disease. Any additional therapy can be administered in any order with the other additional therapies. In certain embodiments, the antibodies of the invention can be administered in combination with one or more therapies (e.g. therapies that are not the antibodies of the invention that are currently administered to prevent, treat, manage, and/or ameliorate a hPD-L1-mediated disease. Non-limiting examples of therapies that can be administered in combination with an antibody of the invention include analgesic agents, anaesthetic agents, antibiotics, or immunomodulatory agents or any other agent listed in the U.S. Pharmacopoeia and/or Physician's Desk Reference.

The term "immunocytokine", as used herein refers to an antibody format which is fused to a cytokine molecule. The antibody format may be any of those described herein, and the cytokine may be fused directly, or by means of a linker or chemical conjugation to either the N- or C-terminus of the heavy or the light chain of the antibody format.

As used herein, "injection device" refers to a device that is designed for carrying out injections, an injection including the steps of temporarily fluidically coupling the injection device to a person's tissue, typically the subcutaneous tissue. An injection further includes administering an amount of liquid drug into the tissue and decoupling or removing the injection device from the tissue. In some embodiments, an injection device can be an intravenous device or IV device, which is a type of injection device used when the target tissue is the blood within the circulatory system, e.g. the blood in a vein. A common, but non-limiting example of an injection device is a needle and syringe.

As used herein, "instructions" refers to a display of written, printed or graphic matter on the immediate container of an article, for example the written material displayed on a vial containing a pharmaceutically active agent, or details on the composition and use of a product of interest included in a kit containing a composition of interest. Instructions set forth the method of the treatment as contemplated to be administered or performed.

An "isolated" or "purified" antibody or protein is one that has been identified, separated and/or recovered from a component of its production environment (e.g. natural or recombinant). For

example, the antibody or protein is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the antibody is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of an antibody in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of antibody having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the antibody is recombinantly produced, it is also preferably substantially free of culture medium, i.e. culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the antibody is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly, such preparations of the antibody have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the antibody of interest. In a preferred embodiment, antibodies of the invention are isolated or purified.

The terms "Kabat numbering," and like terms are recognized in the art and refer to a system of numbering amino acid residues which are more variable (i.e. hypervariable) than other amino acid residues in the heavy chain variable regions of an antibody, or an antigen binding portion thereof (Kabat (1971) Ann. NY Acad. Sci., 190:382-391 and, Kabat (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For the heavy chain variable region, the hypervariable region typically ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 102 for CDR3.

"Label" or "labelled" as used herein refers to the addition of a detectable moiety to a polypeptide, for example, a radiolabel, fluorescent label, enzymatic label, chemiluminescent label or a biotinyl group or gold. Radioisotopes or radionuclides may include ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{115}In, ^{125}I, ^{131}I, fluorescent labels may include rhodamine, lanthanide phosphors or FITC and enzymatic labels may include horserad -galactosidase, luciferase, alkaline phosphatase. Additional labels include, by way of illustration and not limitation: enzymes, such as glucose-6-phosphate dehydrogenase ("G6PDH"), alpha-D-galactosidase, glucose oxydase, glucose amylase, carbonic anhydrase, acetylcholinesterase, lysozyme, malate dehydrogenase and peroxidase; dyes (e.g. cyanine dyes, e.g. Cy5™, Cy5.5™. or Cy7™); additional fluorescent labels or fluorescers include, such as fluorescein and its derivatives, fluorochrome, GFP (GFP for "Green Fluorescent Protein"), other fluorescent proteins (e.g. mCherry, mTomato), dansyl, umbelliferone, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde, and fiuorescamine; fluorophores such as lanthanide cryptates and chelates e.g. Europium etc (Perkin Elmer and Cisbio Assays); chemoluminescent labels or chemiluminescers, such as isoluminol, luminol and the dioxetanes; sensitisers; coenzymes; enzyme substrates; particles, such as latex or carbon particles; metal sol; crystallite; liposomes; cells, etc.,

which may be further labelled with a dye, catalyst or other detectable group; molecules such as biotin, digoxygenin or 5-bromodeoxyuridine; toxin moieties, such as for example a toxin moiety selected from a group of Pseudomonas exotoxin (PE or a cytotoxic fragment or mutant thereof), Diptheria toxin or a cytotoxic fragment or mutant thereof, a botulinum toxin A, B, C, D, E or F, ricin or a cytotoxic fragment thereof e.g. ricin A, abrin or a cytotoxic fragment thereof, saporin or a cytotoxic fragment thereof, pokeweed antiviral toxin or a cytotoxic fragment thereof and bryodin 1 or a cytotoxic fragment thereof.

The term "light chain" when used in reference to an antibody refers to the immunoglobulin light chains, of which there are two types in mammals, lambda (λ) and kappa (κ). Preferably, the light chain is a human light chain. Preferably the light chain constant region is a human constant region. In the human population, multiple light chain constant region alleles exist. The nucleotide and amino acid sequences of these allelic variants are accessible on publicly available databases such as IMGT, ENSEMBL, Swiss-Prot and Uniprot. In one embodiment, the antibodies or antibody fragments disclosed herein comprise a protein encoded by a human κ constant region allele, which includes, but is not limited to, IGKC*01 (Seq ID Nos:206 & 207), IGKC*02 (Seq ID Nos:208 & 209), IGKC*03 (Seq ID Nos:210 & 211), IGKC*04 (Seq ID Nos:212 & 213) and IGKC*05 (Seq ID Nos:214 & 215). In one embodiment, the antibodies or antibody fragments disclosed herein comprise a protein encoded by a human λ constant region allele, which includes but is not limited to IGLC1*01 (Seq ID Nos:216 & 217), IGLC1*02 (Seq ID Nos:218, 219 & 220), IGLC2*01 (Seq ID Nos:221, 222 & 538), IGLC2*02 (Seq ID Nos:224 & 225), IGLC2*03 (Seq ID Nos:224 & 225), IGLC3*01 (Seq ID Nos:226 & 227), IGLC3*02 (Seq ID Nos:228 & 229), IGLC3*03 (Seq ID Nos:230 & 231), IGLC3*04 (Seq ID Nos:232 & 233), IGLC6*01 (Seq ID Nos:234 & 235), IGLC7*01 (Seq ID Nos:236 & 237), IGLC7*02 (Seq ID Nos:236 & 237), IGLC7*03 (Seq ID Nos:535 & 536). In another embodiment, the antibodies and antibody fragments disclosed herein comprise a light chain constant region region allele, which includes, but is not limited to, IGKC*01, IGKC*03 or IGKC*03. In another embodiment, the antibodies and antibody fragments disclosed herein comprise a light chain constant region encoded by a mouse λ constant region allele, which includes, but is not limited to, IGLC1*01, IGLC2*01 or IGLC3*01.

"Percent (%) amino acid sequence identity" and "homology" with respect to a peptide, polypeptide or antibody sequence are defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or MEG ALIGN™ (DNASTAR) software. In one embodiment, the % homology is about 70%. In one embodiment, the % homology is about 75%. In one

embodiment, the % homology is about 80%. In one embodiment, the % homology is about 85%. In one embodiment, the % homology is about 90%. In one embodiment, the % homology is about 92%. In one embodiment, the % homology is about 95%. In one embodiment, the % homology is about 97%. In one embodiment, the % homology is about 98%. In one embodiment, the % homology is about 99%. In one embodiment, the % homology is 100%.

The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to those which are found in nature and not manipulated by a human being.

As used herein, "packaging" refers to how the components are organized and/or restrained into a unit fit for distribution and/or use. Packaging can include, e.g. boxes, bags, syringes, ampoules, vials, tubes, clamshell packaging, barriers and/or containers to maintain sterility, labelling, etc.

The term "pharmaceutically acceptable" as used herein means being approved by a regulatory agency of the Federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia or other generally recognized Pharmacopeia for use in animals, and more particularly in humans.

As used herein, the term "polynucleotide," "nucleotide," nucleic acid" "nucleic acid molecule" and other similar terms are used interchangeable and include DNA, RNA, mRNA and the like.

As used herein, the terms "prevent", "preventing", and "prevention" refer to the total or partial inhibition of the development, recurrence, onset or spread of a hPD-L1-mediated disease and/or symptom related thereto, resulting from the administration of a therapy or combination of therapies provided herein (e.g. a combination of prophylactic or therapeutic agents, such as an antibody of the invention).

The term "soluble" refers to a polypeptide, such as PD-L1 and variants or fragments thereof, that is lacking one or more transmembrane or cytoplasmic domains found in the native or membrane-associated form. In one embodiment, the "soluble" form of PD-L1 lacks both the transmembrane domain and the cytoplasmic domain.

The term "subject" or "patient" refers to any animal, including, but not limited to, mammals. As used herein, the term "mammal" refers to any vertebrate animal that suckle their young and either give birth to living young (eutharian or placental mammals) or are egg-laying (metatharian or nonplacental mammals). Examples of mammalian species include, but are not limited to, humans and other primates, including non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats (including cotton rats) and guinea pigs; birds, including domestic, wild and game birds such as chickens, turkeys and other gallinaceous birds, ducks, geese, and the like.

As used herein "substantially all" refers to refers to at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or about 100%.

The term "substantially free of surfactant" as used herein refers to a formulation of an antibody that specifically binds to a hPD-L1 antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants and/or less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants.

The term "substantially free of salt" as used herein refers to a formulation of an antibody that specifically binds to a hPD-L1 antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of inorganic salts.

The term "surfactant" as used herein refers to organic substances having amphipathic structures; namely, they are composed of groups of opposing solubility tendencies, typically an oil-soluble hydrocarbon chain and a water-soluble ionic group. Surfactants can be classified, depending on the charge of the surface-active moiety, into anionic, cationic, and non-ionic surfactants. Surfactants are often used as wetting, emulsifying, solubilizing, and dispersing agents for various pharmaceutical compositions and preparations of biological materials.

As used herein, the term "tag" refers to any type of moiety that is attached to, e.g. a polypeptide and/or a polynucleotide that encodes a hPD-L1 or hPD-L1 antibody or antigen binding fragment thereof. For example, a polynucleotide that encodes a hPD-L1, hPD-L1 antibody or antigen binding fragment thereof can contain one or more additional tag-encoding nucleotide sequences that encode e.g. a detectable moiety or a moiety that aids in affinity purification. When translated, the tag and the antibody can be in the form of a fusion protein. The term "detectable" or "detection" with reference to a tag refers to any tag that is capable of being visualized or wherein the presence of the tag is otherwise able to be determined and/or measured (e.g. by quantitation). A non-limiting example of a detectable tag is a fluorescent tag.

As used herein, the term "therapeutic agent" refers to any agent that can be used in the treatment, management or amelioration of a hPD-L1-mediated disease and/or a symptom related thereto. In certain embodiments, the term "therapeutic agent" refers to an antibody of the invention. In certain other embodiments, the term "therapeutic agent" refers to an agent other than an antibody of the invention. Preferably, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment, management or amelioration of a hPD-L1-mediated disease or one or more symptoms related thereto. In specific embodiments, the therapeutic agent is a fully human anti-hPD-L1 antibody, such as a fully human anti-hPD-L1 monoclonal antibody.

As used herein, the term "therapy" refers to any protocol, method and/or agent that can be used in the prevention, management, treatment and/or amelioration of a hPD-L1-mediated disease (e.g. cancer). In certain embodiments, the terms "therapies" and "therapy" refer to a biological therapy, supportive therapy, and/or other therapies useful in the prevention, management, treatment

and/or amelioration of a hPD-L1-mediated disease known to one of skill in the art such as medical personnel.

The terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity, and/or duration of a hPD-L1-mediated disease (e.g. cancer) resulting from the administration of one or more therapies (including, but not limited to, the administration of one or more prophylactic or therapeutic agents, such as an antibody of the invention). In specific embodiments, such terms refer to the reduction or inhibition of the binding of hPD-L1 to PD-1, the reduction or inhibition of the binding of hPD-L1 to CD80, and/or the inhibition or reduction of one or more symptoms associated with a hPD-L1-mediated disease, such as cancer. In specific embodiments, such terms refer to the reduction or inhibition of the binding of hPD-L1 to PD-1 and/or CD80, and/or the inhibition or reduction of one or more symptoms associated with a hPD-L1-mediated disease, such as cancer. In an example, the cell is a human cell. In specific embodiments, a prophylactic agent is a fully human anti-hPD-L1 antibody, such as a fully human anti-hPD-L1 monoclonal antibody.

The term "variable region" or "variable domain" refers to a portion of the light and heavy chains, typically about the amino-terminal 120 to 130 amino acids in the heavy chain and about 100 to 110 amino acids in the light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complimentarily determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). The CDRs of the PD-L1 and heavy chains are primarily responsible for the interaction of the antibody with antigen. Numbering of amino acid positions used herein is according to the EU Index, as in Kabat (1991) Sequences of proteins of immunological interest. (U.S. Department of Health and Human Services, Washington, D.C.) 5th ed. ("Kabat "). In preferred embodiments, the variable region is a human variable region.

Definitions of common terms in cell biology and molecular biology can be found in "The Merck Manual of Diagnosis and Therapy", 19th Edition, published by Merck Research Laboratories, 2006 (ISBN 0-911910-19-0); Robert S. Porter (eds.), The Encyclopedia of Molecular Biology, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); Benjamin Lewin, Genes X, published by Jones & Bartlett Publishing, 2009 (ISBN-10: 0763766321); Kendrew (Eds.), Molecular Biology and Biotechnology: a Comprehensive Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8) and Current Protocols in Protein Sciences 2009, Wiley Intersciences, Coligan , eds.

Unless otherwise stated, the present invention was performed using standard procedures, as described, for example in Sambrook , Molecular Cloning: A Laboratory Manual (4 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., USA (2012); Davis , Basic Methods in Molecular Biology, Elsevier Science Publishing, Inc., New York, USA (1995); or Methods in Enzymology: Guide to Molecular Cloning Techniques Vol.152, S. L. Berger and A. R. Kimmel Eds., Academic Press Inc., San Diego, USA (1987); Current Protocols in Protein Science (CPPS) (John E.

Coligan, , ed., John Wiley and Sons, Inc.), Current Protocols in Cell Biology (CPCB) (Juan S. Bonifacino ed., John Wiley and Sons, Inc.), and Culture of Animal Cells: A Manual of Basic Technique by R. Ian Freshney, Publisher: Wiley-Liss; 5th edition (2005), Animal Cell Culture Methods (Methods in Cell Biology, Vol. 57, Jennie P. Mather and David Barnes editors, Academic Press, 1st edition, 1998) which are all incorporated by reference herein in their entireties.

Other terms are defined herein within the description of the various aspects of the invention.

2. PD-L1 antibodies

Many tumour cells express surface molecules that are specific to cancer that can serve as diagnostic and/or therapeutic antibody targets. Examples of cell surface proteins expressed by tumour molecules that can be useful as biomarkers include, for example, members of the B7 family of proteins, major histocompatibility complex molecules (MHC), cytokine and growth factor receptors such as the receptor for eipdermal growth factor (EGFR). The B7 family is a group of proteins that are members of the immunoglobulin (Ig) superfamily of cell-surface proteins that bind to receptors on lymphocytes to regulate immune responses. The family includes transmembrane or glycosylphosphatidylinositol (GPI)-linked proteins characterized by extracellular Ig-like domains (IgV and IgC domains related to the variable and constant domains of immunoglobulins). All members have short cytoplasmic domains. There are seven known members of the B7 family: B7-1, B7-2, PD-L1 (B7-H1), PD-L2, B7-H2, B7-H3, and B7-H4.

The complete amino acid sequence for PD-L1 can be found in NCBI Reference Sequence: NP_054862.1 (SEQ ID No:1), which refers to many journal articles, including, for example, Dong, H., (1999), "PD-L1, a third member of the B7 family, co-stimulates T- cell proliferation and interleukin-10 secretion," Nat. Med. 5 (12), 1365-1369, the disclosure of which is hereby incorporated by reference herein in its entirety. The amino acid sequence of PD-L1 includes a 30 amino acid long cytoplasmic domain that is unique to PD-L1, which shows little homology to other molecules, including other B7 family members.

In one embodiment, the antibody is a polyclonal antibody. Methods for generating polyclonal antibodies are known, and include, for example, inoculating a suitable mammal with an antigen to induce the immune system of the animal to produce immunoglobulins (IgGs) that specifically bind the injected antigen. Examples of suitable mammals include, for example, mouse, guinea pig, hamster, rat, rabbit sheep or goat. The polyclonal IgG is then typically purified from the mammal's serum. In one embodiment, the antibody is a polyclonal antibody that binds to a surface expressed protein. In another embodiment, the antibody is a polyclonal antibody that specifically binds to a member of the B7 family of proteins. In a more specific embodiment, the antibody is a polyclonal antibody that specifically binds PD-L1. In another embodiment, the antibody is a polyclonal antibody that specifically binds surface expressed PD-LI. In a more particular embodiment, the polyclonal antibody or antigen binding fragment thereof specifically binds human PD-L1. In another embodiment, the antibody is a

polyclonal antibody that specifically binds soluble PD-L1. The term "soluble" also refers to a protein, such as PD-L1 that is lacking one or more transmembrane domain or cytoplasmic domains. In one embodiment, the "soluble" form of PD-L1 lacks both the transmembrane domain and the cytoplasmic domain. In one embodiment, the antibody is a polyclonal antibody that binds "free" PD-L1 (i.e. PD-L1 that is not associated with a cell membrane or surface, either directly or indirectly).

In another embodiment, the antibody can be a monoclonal antibody. Methods of making monoclonal antibodies are known and include, for example, fusing myeloma cells with the cells from an animal that was immunized with the desired antigen. In other embodiments, the monoclonal antibodies may be generated using recombinant DNA technology. In one embodiment, the antibody is a monoclonal antibody that specifically binds a surface expressed protein. In one embodiment, the antibody is a fully human monoclonal antibody. In another embodiment, the antibody is a monoclonal antibody that specifically binds to a member of the B7 family of proteins. In a more specific embodiment, the antibody is a monoclonal antibody that specifically binds PD-L1. In another embodiment, the antibody is a monoclonal antibody that specifically binds surface expressed PD-L1. In a more particular embodiment, the monoclonal antibody or antigen binding fragment thereof specifically binds human PD-L1. In another embodiment, the antibody is a monoclonal antibody that specifically binds soluble PD-L1. In one embodiment, the antibody is a monoclonal antibody that specifically binds soluble PD-L1 that is lacking one or more transmembrane domain or cytoplasmic domains. In one embodiment, the antibody is a monoclonal antibody that specifically binds soluble PD-L1 that is lacking both the transmembrane domain and the cytoplasmic domain. In one embodiment, the antibody is a monoclonal antibody that binds "free" PD-L1 (i.e. PD-L1 that is not associated with a cell membrane or surface, either directly or indirectly).

In an example the binding site(s) of the antibody or fragment are selected from a plurality (e.g. library) of binding sites. For example, the plurality of binding sites comprises or consists of a plurality of 4-chain antibodies or fragments thereof, e.g. dAbs, Fabs or scFvs. Suitable methods for producing pluralities of binding sites for screening include phage display (producing a phage display library of antibody binding sites), ribosome display (producing a ribosome display library of antibody binding sites), yeast display (producing a yeast display library of antibody binding sites), or immunisation of a non-human vertebrate (e.g. a rodent, e.g. a mouse or rat, e.g. a Velocimouse™, Kymouse™, Xenomouse™, Aliva Mouse™, HuMab Mouse™, Omnimouse™, Omnirat™ or MeMo Mouse™) with hPD-L1 or a hPD-L1 epitope and isolation of a repertoire of antibody-producing cells (e.g. a B-cell, plasma cell or plasmablast repertoire) and/or a repertoire of isolated antibodies, fragments or binding sites.

PD-L1 binding ability, specificity and affinity (Kd, K_{off} and/or K_{on}) can be determined by any routine method in the art, e.g. by surface plasmon resonance (SPR). The term "Kd" or "K_D", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction. Such binding measurements can be made using a variety of binding assays known in the

art, e.g. using surface plasmon resonance (SPR), such as by Biacore™ or using the ProteOn XPR36™ (Bio-Rad®), using KinExA® (Sapidyne Instruments, Inc), or using ForteBio Octet (Pall ForteBio Corp.).

In one embodiment, the surface plasmon resonance (SPR) is carried out at 25 °C. In another embodiment, the SPR is carried out at 37 °C.

In one embodiment, the SPR is carried out at physiological pH, such as about pH7 or at pH7.6 (e.g. using Hepes buffered saline at pH 7.6 (also referred to as HBS-EP)).

In one embodiment, the SPR is carried out at a physiological salt level, e.g. 150 mM NaCl.

In one embodiment, the SPR is carried out at a detergent level of no greater than 0.05% by volume, e.g. in the presence of P20 (polysorbate 20; e.g. Tween 20™) at 0.05% and EDTA at 3 mM.

In one example, the SPR is carried out at 25 °C or 37 °C in a buffer at pH 7.6, 150 mM NaCl, 0.05% detergent (e.g. P20) and 3mM EDTA. The buffer can contain 10 mM Hepes. In one example, the SPR is carried out at 25 °C or 37 °C in HBS-EP. HBS-EP is available from Teknova Inc. (California; catalogue number H8022).

In an example, the affinity of the antibody or fragment is determined using SPR by:

1. Coupling anti-mouse (or other relevant human, rat or non-human vertebrate antibody constant region species-matched) IgG (e.g. Biacore™ BR-1008-38) to a biosensor chip (e.g. GLM chip) such as by primary amine coupling;
2. Exposing the anti-mouse IgG (or other matched species antibody) to a test IgG antibody to capture test antibody on the chip;
3. Passing the test antigen over the chip's capture surface at 1024 nM, 256 nM, 64 nM, 16 nM, 4 nM with a 0 nM (i.e. buffer alone); and
4. And determining the affinity of binding of test antibody to test antigen using surface plasmon resonance, e.g. under an SPR condition discussed above (e.g. at 25 °C in physiological buffer). SPR can be carried out using any standard SPR apparatus, such as by Biacore™ or using the ProteOn XPR36™ (Bio-Rad®).

Regeneration of the capture surface can be carried out with 10 mM glycine at pH 1.7. This removes the captured antibody and allows the surface to be used for another interaction. The binding data can be fitted to 1:1 model inherent using standard techniques, e.g. using a model inherent to the ProteOn XPR36™ analysis software.

The present inventors have identified a number of antibodies having specificity for hPD-L1, which have a number of potential utilities and benefits over existing antibodies. For example, the antibodies described herein may have one or more of the following properties:

a. Specificity for blocking only one of the ligands of PD-L1 (e.g. blocks CD80/PD-L1 interaction, but not PD-1/PD-L1 interaction)
b. Immunogenicity/lack of side effects
c. Solubility

d. Stability
e. Ease of formulation
f. Frequency of dosing and/or route of administration, for example due to improved half-life over existing anti-PDL1 antibodies
g. Manufacturability (e.g. expression, ease of purification, isoforms)

1D05 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:33, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:34. 1D05 has a light chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:35 (heavy chain nucleic acid sequence Seq ID No:36). A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

84G09 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:13, comprising the CDRH1 amino acid sequence of Seq ID No:7 (IMGT) or Seq ID No:10 (Kabat), the CDRH2 amino acid sequence of Seq ID No:8 (IMGT) or Seq ID No:11 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:9 (IMGT) or Seq ID No:12 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:14. 84G09 has a light chain variable region (V_L) amino acid sequence of Seq ID No:23, comprising the CDRL1 amino acid sequence of Seq ID No:17 (IMGT) or Seq ID No:20 (Kabat), the CDRL2 amino acid sequence of Seq ID No:18 (IMGT) or Seq ID No:21 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:19 (IMGT) or Seq ID No:22 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:24. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and

538. A full length heavy chain amino acid sequence is Seq ID No:15 (heavy chain nucleic acid sequence Seq ID No:16). A full length light chain amino acid sequence is Seq ID No:25 (light chain nucleic acid sequence Seq ID No:26).

1D05 HC mutant 1 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:47, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). 1D05 HC mutant 1 has a light chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

1D05 HC mutant 2 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:48, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). 1D05 HC mutant 2 has a light chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

1D05 HC mutant 3 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:49, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). 1D05 HC mutant 3 has a light

chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

1D05 HC mutant 4 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:342, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). 1D05 HC mutant 4 has a light chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

1D05 LC mutant 1 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:33, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:34. 1D05 LC mutant 1has a light chain variable region (V_L) amino acid sequence of Seq ID No:50, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The CDRL2 sequence of 1D05 LC Mutant 1 is as defined by the Kabat or IMGT systems from the V_L sequence of Seq ID No:50. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID

No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:35 (heavy chain nucleic acid sequence Seq ID No:36).

1D05 LC mutant 2 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:33, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:34. 1D05 LC mutant 2 has a light chain variable region (V_L) amino acid sequence of Seq ID No:51, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:35 (heavy chain nucleic acid sequence Seq ID No:36).

1D05 LC mutant 3 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:33, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:34. 1D05 LC mutant 3 has a light chain variable region (V_L) amino acid sequence of Seq ID No:298, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The CDRL2 sequence of 1D05 LC Mutant 3 is as defined by the Kabat or IMGT systems from the V_L sequence of Seq ID No:298. The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:35 (heavy chain nucleic acid sequence Seq ID No:36). A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

411B08 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:58, comprising the CDRH1 amino acid sequence of Seq ID No:52 (IMGT) or Seq ID No:55 (Kabat), the CDRH2 amino acid sequence of Seq ID No:53 (IMGT) or Seq ID No:56 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:54 (IMGT) or Seq ID No:57 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:59. 411B08 has a light chain variable region (V_L) amino acid sequence of Seq ID No:68, comprising the CDRL1 amino acid sequence of Seq ID No:62 (IMGT) or Seq ID No:65 (Kabat), the CDRL2 amino acid sequence of Seq ID No:63 (IMGT) or Seq ID No:66 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:64 (IMGT) or Seq ID No:67 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:69. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:60 (heavy chain nucleic acid sequence Seq ID No:61). A full length light chain amino acid sequence is Seq ID No:70 (light chain nucleic acid sequence Seq ID No:71).

411C04 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:78, comprising the CDRH1 amino acid sequence of Seq ID No:72 (IMGT) or Seq ID No:75 (Kabat), the CDRH2 amino acid sequence of Seq ID No:73 (IMGT) or Seq ID No:76 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:74 (IMGT) or Seq ID No:77 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:79. 411C04 has a light chain variable region (V_L) amino acid sequence of Seq ID No:88, comprising the CDRL1 amino acid sequence of Seq ID No:82 (IMGT) or Seq ID No:85 (Kabat), the CDRL2 amino acid sequence of Seq ID No:83 (IMGT) or Seq ID No:86 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:84 (IMGT) or Seq ID No:87 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:89. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:80 (heavy chain nucleic acid sequence Seq ID No:81). A full length light chain amino acid sequence is Seq ID No:90 (light chain nucleic acid sequence Seq ID No:91).

411D07 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:98, comprising the CDRH1 amino acid sequence of Seq ID No:92 (IMGT) or Seq ID No:95 (Kabat), the CDRH2 amino acid sequence of Seq ID No:93 (IMGT) or Seq ID No:96 (Kabat), and the CDRH3 amino

acid sequence of Seq ID No:94 (IMGT) or Seq ID No:97 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:99. 411D07 has a light chain variable region (V_L) amino acid sequence of Seq ID No:108, comprising the CDRL1 amino acid sequence of Seq ID No:102 (IMGT) or Seq ID No:105 (Kabat), the CDRL2 amino acid sequence of Seq ID No:103 (IMGT) or Seq ID No:106 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:104 (IMGT) or Seq ID No:107 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:109. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:100 (heavy chain nucleic acid sequence Seq ID No:101). A full length light chain amino acid sequence is Seq ID No:110 (light chain nucleic acid sequence Seq ID No:111).

385F01 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:118, comprising the CDRH1 amino acid sequence of Seq ID No:112 (IMGT) or Seq ID No:115 (Kabat), the CDRH2 amino acid sequence of Seq ID No:113 (IMGT) or Seq ID No:116 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:114 (IMGT) or Seq ID No:117 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:119. 385F01 has a light chain variable region (V_L) amino acid sequence of Seq ID No:128, comprising the CDRL1 amino acid sequence of Seq ID No:122 (IMGT) or Seq ID No:125 (Kabat), the CDRL2 amino acid sequence of Seq ID No:123 (IMGT) or Seq ID No:126 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:124 (IMGT) or Seq ID No:127 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:129. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:120 (heavy chain nucleic acid sequence Seq ID No:121). A full length light chain amino acid sequence is Seq ID No:130 (light chain nucleic acid sequence Seq ID No:131).

386H03 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:158, comprising the CDRH1 amino acid sequence of Seq ID No:152 (IMGT) or Seq ID No:155 (Kabat), the CDRH2 amino acid sequence of Seq ID No:153 (IMGT) or Seq ID No:156 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:154 (IMGT) or Seq ID No:157 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:159. 386H03 has a light chain variable region (V_L) amino acid sequence of Seq ID No:168, comprising the CDRL1 amino acid sequence of Seq ID No:162 (IMGT)

or Seq ID No:165 (Kabat), the CDRL2 amino acid sequence of Seq ID No:163 (IMGT) or Seq ID No:166 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:164 (IMGT) or Seq ID No:167 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:169. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:160 (heavy chain nucleic acid sequence Seq ID No:161). A full length light chain amino acid sequence is Seq ID No:170 (light chain nucleic acid sequence Seq ID No:171).

389A03 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:178, comprising the CDRH1 amino acid sequence of Seq ID No:172 (IMGT) or Seq ID No:175 (Kabat), the CDRH2 amino acid sequence of Seq ID No:173 (IMGT) or Seq ID No:176 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:174 (IMGT) or Seq ID No:177 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:179. 389A03 has a light chain variable region (V_L) amino acid sequence of Seq ID No:188, comprising the CDRL1 amino acid sequence of Seq ID No:182 (IMGT) or Seq ID No:185 (Kabat), the CDRL2 amino acid sequence of Seq ID No:183 (IMGT) or Seq ID No:186 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:184 (IMGT) or Seq ID No:187 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:189. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:180 (heavy chain nucleic acid sequence Seq ID No:181). A full length light chain amino acid sequence is Seq ID No:190 (light chain nucleic acid sequence Seq ID No:191).

413D08 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:138, comprising the CDRH1 amino acid sequence of Seq ID No:132 (IMGT) or Seq ID No:135 (Kabat), the CDRH2 amino acid sequence of Seq ID No:133 (IMGT) or Seq ID No:136 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:134 (IMGT) or Seq ID No:137 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:139. 413D08 has a light chain variable region (V_L) amino acid sequence of Seq ID No:148, comprising the CDRL1 amino acid sequence of Seq ID No:142 (IMGT) or Seq ID No:145 (Kabat), the CDRL2 amino acid sequence of Seq ID No:143 (IMGT) or Seq ID No:146 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:144 (IMGT) or Seq ID No:147 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:149. The V_H domain may be

combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No: 140 (heavy chain nucleic acid sequence Seq ID No:141). A full length light chain amino acid sequence is Seq ID No:150 (light chain nucleic acid sequence Seq ID No:151).

413G05 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:244, comprising the CDRH1 amino acid sequence of Seq ID No:238 (IMGT) or Seq ID No:241 (Kabat), the CDRH2 amino acid sequence of Seq ID No:239 (IMGT) or Seq ID No:242 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:240 (IMGT) or Seq ID No:243 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:245. 413G05 has a light chain variable region (V_L) amino acid sequence of Seq ID No:254, comprising the CDRL1 amino acid sequence of Seq ID No:248 (IMGT) or Seq ID No:251 (Kabat), the CDRL2 amino acid sequence of Seq ID No:249 (IMGT) or Seq ID No:252 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:250 (IMGT) or Seq ID No:253 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:255. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:246 (heavy chain nucleic acid sequence Seq ID No:247). A full length light chain amino acid sequence is Seq ID No:256 (light chain nucleic acid sequence Seq ID No:257).

413F09 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:264, comprising the CDRH1 amino acid sequence of Seq ID No:258 (IMGT) or Seq ID No:261 (Kabat), the CDRH2 amino acid sequence of Seq ID No:259 (IMGT) or Seq ID No:262 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:260 (IMGT) or Seq ID No:263 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:265. 413F09 has a light chain variable region (V_L) amino acid sequence of Seq ID No:274, comprising the CDRL1 amino acid sequence of Seq ID No:268 (IMGT) or Seq ID No:271 (Kabat), the CDRL2 amino acid sequence of Seq ID No:269 (IMGT) or Seq ID No:272 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:270 (IMGT) or Seq ID No:273 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:275. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID

No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:266 (heavy chain nucleic acid sequence Seq ID No:267). A full length light chain amino acid sequence is Seq ID No:276 (light chain nucleic acid sequence Seq ID No:277).

414B06 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:284, comprising the CDRH1 amino acid sequence of Seq ID No:278 (IMGT) or Seq ID No:281 (Kabat), the CDRH2 amino acid sequence of Seq ID No:279 (IMGT) or Seq ID No:282 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:280 (IMGT) or Seq ID No:283 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:285. 414B06 has a light chain variable region (V_L) amino acid sequence of Seq ID No:294, comprising the CDRL1 amino acid sequence of Seq ID No:288 (IMGT) or Seq ID No:291(Kabat), the CDRL2 amino acid sequence of Seq ID No:289 (IMGT) or Seq ID No:292 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:290 (IMGT) or Seq ID No:293 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:295. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:286 (heavy chain nucleic acid sequence Seq ID No:287). A full length light chain amino acid sequence is Seq ID No:296 (light chain nucleic acid sequence Seq ID No:297).

416E01 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:349, comprising the CDRH1 amino acid sequence of Seq ID No:343 (IMGT) or Seq ID No:346 (Kabat), the CDRH2 amino acid sequence of Seq ID No:344 (IMGT) or Seq ID No:347 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:345 (IMGT) or Seq ID No:348 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:350. 416E01 has a light chain variable region (V_L) amino acid sequence of Seq ID No:359, comprising the CDRL1 amino acid sequence of Seq ID No:353 (IMGT) or Seq ID No:356 (Kabat), the CDRL2 amino acid sequence of Seq ID No:354 (IMGT) or Seq ID No:357 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:355 (IMGT) or Seq ID No:358 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:360. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:351

(heavy chain nucleic acid sequence Seq ID No:352). A full length light chain amino acid sequence is Seq ID No:361 (light chain nucleic acid sequence Seq ID No:362).

The antibodies of the invention are described with respect to the following concepts, aspects, sentences, arrangements and embodiments. Unless otherwise stated, all concepts, embodiments, sentences, arrangements and aspects are to be read as being able to be combined with any other concept, aspect, sentence, arrangement or embodiment, unless such combination would not make technical sense or is explicitly stated otherwise.

Concept 1. An antibody or a fragment thereof, which specifically binds to hPD-L1 as defined by Seq ID No:1, and competes for binding to said hPD-L1 with the antibody 1D05, wherein the antibody or fragment comprises a V_H domain which comprises a CDRH3 comprising the motif $X_1GSGX_2YGX_3X_4FD$, wherein X_1, X_2 and X_3 are independently any amino acid, and X_4 is either present or absent, and if present, may be any amino acid.

In these concepts, antibodies or fragments may include or may not include bispecific antibodies. In one embodiment, in these concepts, antibodies or fragments includes bispecific antibodies. In one embodiment, a bispecific antibody does not include a FIT-Ig format. In one embodiment, a bispecific antibody does not include a mAb^2 format. In one embodiment, a bispecific antibody does not include either a FIT-Ig format or a mAb^2 format. In one embodiment, the antibody or fragment in these concepts includes a bispecific antibody, but does not include a bispecific antibody having a FIT-Ig format. In one embodiment, the antibody or fragment in these concepts includes a bispecific antibody, but does not include a bispecific antibody having a mAb^2 format. In one embodiment, the antibody or fragment in these concepts includes a bispecific antibody, but does not include a bispecific antibody having a FIT-Ig format or a mAb^2 format. In another embodiment, in these concepts, antibodies or fragments include dual binding antibodies.

Preferably, an antibody or a fragment thereof that specifically binds to a hPD-L1 antigen does not cross-react with other antigens (but may optionally cross-react with PD-L1 of a different species, e.g., rhesus, cynomolgus, or murine). An antibody or a fragment thereof that specifically binds to a hPD-L1 antigen can be identified, for example, by immunoassays, BIAcore™, or other techniques known to those of skill in the art. An antibody or a fragment thereof binds specifically to a hPD-L1 antigen when it binds to a hPD-L1 antigen with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as radioimmunoassays (RIA) and enzyme-linked immunosorbent assays (ELISAs). Typically, a specific or selective reaction will be at least twice background signal or noise and more typically more than 10 times background. See, e.g. Paul, ed., 1989, Fundamental Immunology Second Edition, Raven Press, New York at pages 332-336 for a discussion regarding antibody specificity.

In one embodiment, the antibody or fragment is a human antibody. In one embodiment, the antibody or fragment is a human antibody or fragment. In one embodiment, the antibody or fragment

is a fully human antibody or fragment. In one embodiment, the antibody or fragment is a fully human monoclonal antibody or fragment.

There is also provided concept 1a: An antibody or a fragment thereof, that specifically binds to hPD-L1 as defined by Seq ID No:1, and competes for binding to said hPD-L1 with the antibody 411B08, wherein the antibody or fragment comprises a V_H domain which comprises a CDRH3 comprising the motif $ARX_1RX_2X_3SDX_4X_5D$, wherein X_1, X_2, X_3, X_4 and X_5 are independently any amino acid.

There is also provided concept 1b: An antibody or a fragment thereof, that specifically binds to hPD-L1 as defined by Seq ID No:1, and competes for binding to said hPD-L1 with the antibody 411B08, wherein the antibody or fragment comprises a V_H domain which comprises a CDRH3 comprising the motif $X_1RDGSGSY$, wherein X_1 is any amino acid.

As provided in the concepts or aspects herein, an anti-PD-L1 antibody or immunocytokine may bind to PD-L1, e.g. human PD-L1 with a K_D of less than 50 nM, less than 40 nM, less than 30 nM as determined by surface plasmon resonance. Another embodiment, anti-PD-L1 antibody or immunocytokine may bind to PD-L1, e.g. human PD-L1 with a K_D of less than 20 nM, less than 15 nM, less than 10 nM as determined by surface plasmon resonance. anti-PD-L1 antibody or immunocytokine may bind to PD-L1, e.g. human PD-L1 with a K_D of less than 8 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM or less than 1 nM as determined by surface plasmon resonance. The K_D may be 0.9 nM or less, 0.8 nM or less, 0.7 nM or less, 0.6 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, or 0.1 nM or less.

In another embodiment, the K_D is within a range of 0.01 to 1 nM, or a range of 0.05 to 2 nM, or a range of 0.05 to 1nM. The K_D may be with regard to hPD-L1, cynoPD-L1 and/or mouse PD-L1.

In another embodiment, the anti-PD-L1 antibodies described herein have a K_{ON} rate (e.g. as measured by SPR, e.g. at 25 °C or at 37 °C) of approximately 0.5 to 10 µM, for example approximately 1 to 8 µM or approximately 1 to 7 µM. In another embodiment, the K_{ON} rate is approximately 1 to 5 µM, e.g. approximately 1 µM, approximately 1.5 µM, approximately 2 µM, approximately 2.5µM or approximately 3 µM. In another embodiment, the K_{ON} rate is approximately 3.5 µM, approximately 4 µM, approximately 4.5 µM, approximately 5 µM or approximately 5.5 µM.

In another embodiment, the anti-PD-L1 antibodies described herein have a K_{OFF} rate (e.g. as measured by SPR, e.g. at 25 °C or at 37 °C) of approximately 0.01 to 100 mM, for example approximately 0.1 to 50 mM or approximately 0.5 to 50 mM. In another embodiment, the K_{OFF} rate is approximately 0.5 to 10 mM, or approximately 0.5 to 10 mM, e.g. approximately 1 mM, approximately 2 mM, approximately 3 mM, approximately 4 mM or approximately 5 mM. In another embodiment, the K_{OFF} rate is approximately 0.6 mM, approximately 0.7 mM, approximately 0.8 mM or approximately 0.9 mM.

In another embodiment, the anti-PD-L1 antibodies (and immunocytokines) described in the concepts and aspects herein provide improved transient expression levels over other anti-PD-L1

antibodies and immunocytokines. Thus, in one embodiment, the anti-PD-L1 antibody (or immunocytokine) is expressed in a HEK293 cell, e.g. a HEK293T cell, at an expression level of approximately 100 µg/mL, or in a range of approximately 100 to 350 µg/mL. In another embodiment, the expression level is above approximately 350 µg/mL.

In another embodiment, the anti-PD-L1 antibody (or immunocytokine) is expressed in a CHO cell, e.g. an Expi-CHO cell, at an expression level of approximately 100 µg/mL, or in a range of approximately 100 to 350 µg/mL. In another embodiment, the expression level is above approximately 350 µg/mL.

In another embodiment, the anti-PD-L1 antibody (or immunocytokine) is expressed in a CHO cell, e.g. an Expi-CHO cell or a CHO-E7 EBNA cell, at an expression level of approximately 100 µg/mL, or in a range of approximately 100 to 350 µg/mL. In another embodiment, the expression level is above approximately 350 µg/mL. The antibody described herein as 1D05, formatted as a human IgG1 (Seq ID No:340, at 2L volume in CHO-E7 EBNA cells has an expression level of approximately 115 µg/mL. The antibody described herein as 416E01, formatted as a human IgG1 (Seq ID No:340), at 2L volume in CHO-E7 EBNA cells has an expression level of approximately 160 µg/mL. The antibody described herein as 1414B06, formatted as a human IgG1 (Seq ID No:340), at 2L volume in CHO-E7 EBNA cells has an expression level of approximately 783 µg/mL. The antibody described herein as 413G05, formatted as a human IgG1 (Seq ID No:340), at 2L volume in CHO-E7 EBNA cells has an expression level of approximately 383 µg/mL.

In any of these expression systems, the expression is carried out of a scale of between approximately 0.5 mL and 3 mL, for example between approximately 0.5 mL and 2 mL. In any of these expression systems, the anti-PD-L1 antibody (or immunocytokine) may be expressed from a pTT5 vector. In any of these expression systems, the anti-PD-L1 antibody (or immunocytokine) may be expressed in conjunction with a lipid transfection reagent, and may optionally be expressed in a CHO cell, e.g. an Expi-CHO cell. In any of these expression systems, the anti-PD-L1 antibody (or immunocytokine) may be expressed in conjunction with a PEI transfection reagent, and may optionally be expressed in a CHO cell, e.g. an CHO-E7 EBNA cell. In any of these expression systems, the anti-PD-L1 antibody (or immunocytokine) may be expressed in conjunction with a helper plasmid (e.g. an AKT helper plasmid), and may optionally be expressed in a CHO cell, e.g. an CHO-E7 EBNA cell.

In any of these expression systems, the expression level is between approximately 100 µg/mL and approximately 1500 µg/mL, for example between approximately 100 µg/mL and approximately 1000 µg/mL, or between approximately 200 µg/mL and approximately 1000 µg/mL, or between approximately 350 µg/mL and approximately 1000 µg/mL. In any of these expression systems, the lower limit of expression may be approximately 100 µg/mL, approximately 200 µg/mL, approximately 300 µg/mL, or approximately 400 µg/mL. In another embodiment, the lower limit of expression may be approximately 500 µg/mL, approximately 600 µg/mL, approximately 700 µg/mL, or approximately 800 µg/mL. In any of these expression systems, the upper limit of expression may be approximately

2000 µg/mL, approximately 1800 µg/mL, approximately 1600 µg/mL, or approximately 1500 µg/mL. In another embodiment, the upper limit of expression may be approximately 1250 µg/mL, approximately 1000 µg/mL, approximately 900 µg/mL, or approximately 800 µg/mL.

In another embodiment, the expression system is a Lonza expression system, e.g. Lonza X-Ceed® system. In the Lonza expression system, the expression may be carried out at a scale of approximately 30 mL to 2 L, for example 50 mL to 1 L, or 1 L tp 2 L. In the Lonza expression system, the anti-PD-L1 antibody (or immunocytokine) may be expressed in conjunction with electroporation, and optionally without any helper plasmids. In the Lonza expression system, the anti-PD-L1 antibody (or immunocytokine) may be expressed at a level of approximately 1 g/L, or approximately 900 mg/L, or approximately 800 mg/L, or approximately 700 mg/L. In another embodiment, In the Lonza expression system, the anti-PD-L1 antibody (or immunocytokine) may be expressed at a level of approximately 600 mg/L or approximately 500 mg/L or approximately 400 mg/L. In the Lonza expression system, the anti-PD-L1 antibody (or immunocytokine) may be expressed at a level of between approximately 400 mg/L and approximately 2 g/L, for example between approximately 500 mg/L and approximately 1.5 g/L, or between approximately 500 mg/L and approximately 1 g/L. In another embodiment, the expression level is above 1 g/L.In another embodiment, the anti-PD-L1 antibodies described in the concepts provide improved half-life over other anti-PD-L1 antibodies as further described in Aspect 1 hereinbelow.

Concept 2. The antibody or fragment according to concept 1, wherein X_1 is a hydroxyl-containing amino acid, optionally T.

In one embodiment, the hydroxyl-containing amino acid is Serine. In one embodiment, the hydroxyl-containing amino acid is Cysteine. In one embodiment, the hydroxyl-containing amino acid is Threonine. In one embodiment, the hydroxyl-containing amino acid is Methionine. In one embodiment, the hydroxyl-containing amino acid is Serine or Cysteine. In one embodiment, the hydroxyl-containing amino acid is Serine or Threonine. In one embodiment, the hydroxyl-containing amino acid is Serine or Methionine. In one embodiment, the hydroxyl-containing amino acid is Cysteine or Threonine. In one embodiment, the hydroxyl-containing amino acid is Cysteine or Methionine. In one embodiment, the hydroxyl-containing amino acid is Threonine or Methionine.

In one embodiment, the hydroxyl-containing amino acid is selected from serine, cysteine, threonine and methionine.

Concept 2a. The antibody or fragment according to concept 1a, wherein X_1 is an aliphatic amino acid or an amide amino acid.

In one embodiment, X_1 is selected from Asparagine (N) and valine (V). In one embodiment, X_1 is valine. In one embodiment, X_1 is asparagine.

Concept 2b. The antibody or fragment according to concept 1b, wherein X_1 is an aliphatic amino acid.

In one embodiment, X_1 is selected from alanine (A) or valine (V). In one embodiment, X_1 is valine. In one embodiment, X_1 is alanine.

Concept 3. The antibody or fragment according to concept 1 or concept 2, wherein X_2 is a basic amino acid, optionally K.

In one embodiment, the hydroxyl-containing amino acid is Histidine. In one embodiment, the hydroxyl-containing amino acid is Lysine. In one embodiment, the hydroxyl-containing amino acid is Arginine. In one embodiment, the hydroxyl-containing amino acid is Histidine or Lysine. In one embodiment, the hydroxyl-containing amino acid is Histidine or Arginine. In one embodiment, the hydroxyl-containing amino acid is Lysine or Arginine.

In one embodiment, the hydroxyl-containing amino acid is selected from Histidine, Lysine and Arginine.

Concept 3a. The antibody or fragment according to concept 1a or concept 2a, wherein X_2 is an aliphatic amino acid or an amide amino acid.

In one embodiment, X_2 is selected from leucine (L), isoleucine (I), Valine (V), Asparagine (N) and glutamine (Q). In one embodiment, X_2 is selected from leucine (L), isoleucine (I) and Valine (V). In one embodiment, X_2 is selected from Asparagine (N) and glutamine (Q)In one embodiment, X_2 is selected from leucine (L) and glutamine (Q). In one embodiment, X_2 is leucine (L). In one embodiment, X_2 is glutamine (Q).

Concept 4. The antibody or fragment according to any one of concepts 1 to 3, wherein X_2 is a hydroxyl-containing amino acid, optionally S or T.

In one embodiment, the hydroxyl-containing amino acid is Serine. In one embodiment, the hydroxyl-containing amino acid is Cysteine. In one embodiment, the hydroxyl-containing amino acid is Threonine. In one embodiment, the hydroxyl-containing amino acid is Methionine. In one embodiment, the hydroxyl-containing amino acid is Serine or Cysteine. In one embodiment, the hydroxyl-containing amino acid is Serine or Threonine. In one embodiment, the hydroxyl-containing amino acid is Serine or Methionine. In one embodiment, the hydroxyl-containing amino acid is Cysteine or Threonine. In one embodiment, the hydroxyl-containing amino acid is Cysteine or Methionine. In one embodiment, the hydroxyl-containing amino acid is Threonine or Methionine.

In one embodiment, the hydroxyl-containing amino acid is selected from serine, cysteine, threonine and methionine.

Concept 4a. The antibody or fragment according to any one of concepts 1a, 2a or 3a, wherein X_3 is an aromatic amino acid.

In one embodiment, X_3 is selected from Phenylalanine (F), Tyrosine (Y) and Tryptophan (W). In one embodiment, X_3 is selected from Tyrosine (Y) and Tryptophan (W). In one embodiment, X_3 is Tyrosine (Y). In one embodiment, X_3 is Tryptophan (W).

Concept 5. The antibody or fragment according to any one of concepts 1 to 4, wherein X_3 is an aromatic amino acid, optionally W.

In one embodiment, the hydroxyl-containing amino acid is Phenylalanine. In one embodiment, the hydroxyl-containing amino acid is Tyrosine. In one embodiment, the hydroxyl-containing amino acid is Tryptophan. In one embodiment, the hydroxyl-containing amino acid is Phenylalanine or Tyrosine. In one embodiment, the hydroxyl-containing amino acid is Phenylalanine or Tryptophan. In one embodiment, the hydroxyl-containing amino acid is Tyrosine or Tryptophan.

In one embodiment, the hydroxyl-containing amino acid is selected from Phenylalanine, Tyrosine and Tryptophan.

Concept 5a. The antibody or fragment according to any one of concepts 1a, 2a, 3a or 4a wherein X_4 is an aromatic amino acid.

In one embodiment, X_4 is selected from Phenylalanine (F), Tyrosine (Y) and Tryptophan (W). In one embodiment, X_4 is selected from Tyrosine (Y) and Phenylalanine (F). In one embodiment, X_4 is Tyrosine (Y). In one embodiment, X_4 is Phenylalanine (F).

Concept 6. The antibody or fragment according to any one of concepts 1 to 5, wherein X_4 is absent.

Concept 6a. The antibody or fragment according to any one of concepts 1a, 2a, 3a, 4a or 5a wherein X_5 is an aliphatic amino acid or an hydroxyl-containing amino acid.

In one embodiment, X_5 is selected from leucine (L), isoleucine (I), Valine (V), Serine (S), Cysteine (C) and Threonine (T). In one embodiment, X_5 is selected from leucine (L), isoleucine (I) and Valine (V). In one embodiment, X_5 is selected from Serine (S), Cysteine (C) and Threonine (T). In one embodiment, X_5 is selected from leucine (L) and Serine (S). In one embodiment, X_5 is Serine (S). In one embodiment, X_5 is leucine (L).

Concept 7. The antibody or fragment according to any one of concepts 1 to 5, wherein X_4 is present.

Concept 8. The antibody or fragment according to concept 7, wherein X_4 is an aliphatic amino acid, optionally G.

In one embodiment, the hydroxyl-containing amino acid is selected from Glycine, Alanine, Valine, Leucine and Isoleucine.

In one embodiment, the hydroxyl-containing amino acid is selected from Glycine and Alanine. In one embodiment, the hydroxyl-containing amino acid is selected from Glycine and Valine. In one embodiment, the hydroxyl-containing amino acid is selected from Glycine and Leucine. In one embodiment, the hydroxyl-containing amino acid is selected from Glycine and Isoleucine. In one embodiment, the hydroxyl-containing amino acid is selected from Alanine and Valine. In one embodiment, the hydroxyl-containing amino acid is selected from Alanine and Leucine. In one embodiment, the hydroxyl-containing amino acid is selected from Alanine and Isoleucine. In one embodiment, the hydroxyl-containing amino acid is selected from Valine and Leucine. In one

embodiment, the hydroxyl-containing amino acid is selected from Valine and Isoleucine. In one embodiment, the hydroxyl-containing amino acid is selected from, Leucine and Isoleucine.

In one embodiment, the hydroxyl-containing amino acid selected from three of each of Glycine, Alanine, Valine, Leucine and Isoleucine. In one embodiment, the hydroxyl-containing amino acid selected from four of each of Glycine, Alanine, Valine, Leucine and Isoleucine.

Concept 9. An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 1D05, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:29 or 32, or the CDRH3 sequence of SEQ ID NO:29 or 32 comprising 6 or fewer amino acid substitutions.

Concept 9a: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 84G09, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:9 or 12, or the CDRH3 sequence of SEQ ID NO:9 or 12 comprising 6 or fewer amino acid substitutions.

Concept 9b: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 411B08, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:54 or 57, or the CDRH3 sequence of SEQ ID NO:54 or 57 comprising 6 or fewer amino acid substitutions.

Concept 9c: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 411C04, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID No:74 or 77, or the CDRH3 sequence of SEQ ID NO:74 or 77 comprising 6 or fewer amino acid substitutions.

Concept 9d: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 411D07, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:94 or 97, or the CDRH3 sequence of SEQ ID NO:94 or 97 comprising 3 or fewer amino acid substitutions.

Concept 9e: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 385F01, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:114 or 117, or the CDRH3 sequence of SEQ ID NO:114 or 117 comprising 6 or fewer amino acid substitutions.

Concept 9f: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 386H03, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:144 or 147, or the CDRH3 sequence of SEQ ID NO:144 or 147 comprising 3 or fewer amino acid substitutions.

Concept 9g: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 389A03, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:174 or 177, or the CDRH3 sequence of SEQ ID NO:174 or 177 comprising 6 or fewer amino acid substitutions.

Concept 9h: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 413D08, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:134 or 137, or the CDRH3 sequence of SEQ ID NO:134 or 137 comprising 5 or fewer amino acid substitutions.

Concept 9i: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 413G05, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:240 or 243, or the CDRH3 sequence of SEQ ID NO:240 or 243 comprising 6 or fewer amino acid substitutions.

Concept 9j: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 413F09, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:260 or 263, or the CDRH3 sequence of SEQ ID NO:260 or 263 comprising 6 or fewer amino acid substitutions.

Concept 9k: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 414B06, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:280 or 283, or the CDRH3 sequence of SEQ ID NO:280 or 283 comprising 6 or fewer amino acid substitutions.

Concept 9l: An antibody or a fragment thereof, optionally according to any one of concepts 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 416E01, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID No:345 or 348, or the CDRH3 sequence of SEQ ID No:345 or 348 comprising 6 or fewer amino acid substitutions.

In all of concepts 9, 9a to l, 17, 17a to l, 18, 18a to l, 19, 19a to l, 22, 22a to l, 23, 23a to l, 24 and 24a to l, in one embodiment, the CDR comprises one amino acid substitution, which may be

a conservative amino acid substitution. In all of concepts 9, 9a to l, 17, 17a to l, 18, 18a to l, 19, 19a to l, 22, 22a to l, 23, 23a, 24 and 24a to l, in one embodiment, the CDR comprises two amino acid substitutions, which may be conservative amino acid substitutions. In all of concepts 9, 9a to l, 17, 17a to l, 18, 18a to l, 19, 19a to l, 22, 22a, 22b, 22d, 22f, 22g, 24 and 24a to l, in one embodiment, the CDR comprises three amino acid substitutions, which may be conservative amino acid substitutions. In all of concepts 9, 9a to c, 9e, 9g to l, 17, 17a to c, 17e, 17g to l, 19, 19a, 22, 22d, 22f, 22g, 24 and 24a to l, in one embodiment, the CDR comprises four amino acid substitutions, which may be conservative amino acid substitutions. In all of concepts 9, 9a to c, 9e, 9g to l, 17, 17a to c, 17e, 17g to l, 22d, 22f and 22g, in one embodiment, the CDR comprises five amino acid substitutions, which may be conservative amino acid substitutions. In all of concepts 9, 9a to c, 9e, 9g, 9i to l, 17, 17a to c, 17e, 17g and 17i to l, in one embodiment, the CDR comprises six amino acid substitutions, which may be conservative amino acid substitutions.

Amino acid substitutions include alterations in which an amino acid is replaced with a different naturally-occurring amino acid residue. Such substitutions may be classified as "conservative", in which case an amino acid residue contained in a polypeptide is replaced with another naturally occurring amino acid of similar character either in relation to polarity, side chain functionality or size. Such conservative substitutions are well known in the art. Substitutions encompassed by the present invention may also be "non-conservative", in which an amino acid residue which is present in a peptide is substituted with an amino acid having different properties, such as naturally-occurring amino acid from a different group (e.g. substituting a charged or hydrophobic amino; acid with alanine), or alternatively, in which a naturally-occurring amino acid is substituted with a non-conventional amino acid.

In one embodiment, the conservative amino acid substitutions are as described herein. For example, the substitution may be of Y with F, T with S or K, P with A, E with D or Q, N with D or G, R with K, G with N or A, T with S or K, D with N or E, I with L or V, F with Y, S with T or A, R with K, G with N or A, K with R, A with S, K or P. In another embodiment, the conservative amino acid substitutions may be wherein Y is substituted with F, T with A or S, I with L or V, W with Y, M with L, N with D, G with A, T with A or S, D with N, I with L or V, F with Y or L, S with A or T and A with S, G, T or V.

Concept 10. An antibody or fragment which specifically binds to hPD-L1 and comprises a V_H domain comprising a CDRH3 of from 12 to 20 amino acids and which is derived from the recombination of a human V_H gene segment, a human D gene segment and a human J_H gene segment, wherein the human J_H gene segment is IGHJ5 (e.g. IGHJ5*02).

In one embodiment, the CDRH3 is from 14 to 17 amino acids and the human J_H gene segment is IGHJ5 (e.g. IGHJ5*02).

There is also provided as concept 10a an antibody or fragment which specifically binds to hPD-L1 and comprises a V_H domain comprising a CDRH3 of from 8 to 16 amino acids and which is

derived from the recombination of a human V_H gene segment, a human D gene segment and a human J_H gene segment, wherein the human J_H gene segment is selected from IGHJ4 (e.g. IGHJ4*02), IGHJ5 (e.g. IGHJ5*02) and IGHJ6 (e.g. IGHJ6*02).

In another embodiment, the human J_H gene segment is IGHJ6 (e.g. IGHJ6*02). In another embodiment, the CDRH3 is of from 10 to 17 amino acids and the human J_H gene segment is IGHJ6 (e.g. IGHJ6*02).

In another embodiment, the human J_H gene segment is IGHJ4 (e.g. IGHJ4*02). In another embodiment, the CDRH3 is from 7 to 17 amino acids and the human J_H gene segment is IGHJ4 (e.g. IGHJ4*02).

Optionally, the antibody of concept 10 or 10a has any of the features of concepts 1 to 9, including the binding affinities, Kon and Koff rates, expression levels, half-life etc.

Concept 11. The antibody or fragment according to concept 10 or 10a, wherein the human V_H gene segment is IGHV3 (e.g. IGHV3-9, such as IGHV3-9*01).

There is also provided as concept 11a an antibody or fragment according to concept 10 or 10a, wherein the human V_H gene segment is selected from IGHV3 (e.g. IGHV3-9, such as IGHV3-9*01 or e.g. IGHV3-7, such as IGHV3-7*01 or e.g. IGHV3-33, such as IGHV3-33*01 or e.g. IGHV3-11, such as IGHV3-11*01 or e.g. IGHV3-23, such as IGHV3-23*04), or IGHV4 (e.g. IGHV4-4, such as IGHV4-4*02 or e.g. IGHV4-39, such as IGHV4-39*01).

In one embodiment, the human V_H gene segment is IGHV3 (e.g. IGHV3-7, such as IGHV3-7*01). In one embodiment, the human V_H gene segment is IGHV3 (e.g. IGHV3-33, such as IGHV3-33*01). In one embodiment, the human V_H gene segment is IGHV3 (e.g. IGHV3-11, such as IGHV3-11*01). In one embodiment, the human V_H gene segment is IGHV3 (e.g. IGHV3-23, such as IGHV3-23*04).

In one embodiment, the human V_H gene segment is IGHV4 (e.g. e.g. IGHV4-4, such as IGHV4-4*02). In one embodiment, the human V_H gene segment is IGHV4 (e.g. IGHV4-39, such as IGHV4-39*01).

There is also provided as concept 11b an antibody or fragment according to concept 10, 10a, 11 or 11a, wherein the human D gene segment is selected from IGHD1 (e.g. IGHD1-20, such as IGHD1-20*01), IGHD3 (e.g. IGHD3-10, such as IGHD3-10*01), IGHD4 (e.g. IGHD4-11, such as IGHD4-11*01), IGHD5 (e.g. IGHD5-7, such as IGHD5-18*01), and IGHD6 (e.g. IGHD6-13, such as IGHD6-13*01).

In one embodiment, the human D gene segment is IGHD1 (e.g. IGHD1-20, such as IGHD1-20*01). In one embodiment, the human D gene segment is IGHD3 (e.g. IGHD3-10, such as IGHD3-10*01). In one embodiment, the human D gene segment is IGHD4 (e.g. IGHD4-11, such as IGHD4-11*01). In one embodiment, the human D gene segment is IGHD5 (e.g. IGHD5-18, such as IGHD5-

19*01). In one embodiment, the human D gene segment is IGHD6 (e.g. IGHD6-13, such as IGHD6-13*01).

In any of concepts 10, 11 and 11a, the V_H, D_H and J_H gene segments are as described in the combinations for the antibodies in Table 5 hereinbelow. In one embodiment, the antibody heavy chain is derived from a combination of IGHV3 (e.g. IGHV3-7 such as IGHV3-7*01), IGHD4 (e.g. IGHD4-11 such as IGHD4-11*01) and IGHJ4 (e.g. IGHJ4*02). In one embodiment, the antibody heavy chain is derived from a combination of IGHV4 (e.g. IGHV4-4 such as IGHV4-4*02), IGHD3 (e.g. IGHD3-10 such as IGHD3-10*01) and IGHJ4 (e.g. IGHJ4*02). In one embodiment, the antibody heavy chain is derived from a combination of IGHV4 (e.g. IGHV4-39 such as IGHV4-39*01), IGHD6 (e.g. IGHD6-13 such as IGHD6-13*01) and IGHJ1 (e.g. IGHJ1*01). In one embodiment, the antibody heavy chain is derived from a combination of IGHV3 (e.g. IGHV3-33 such as IGHV3-33*01), IGHD5 (e.g. IGHD5-18 such as IGHD5-18*01) and IGHJ6 (e.g. IGHJ6*02). In one embodiment, the antibody heavy chain is derived from a combination of IGHV3 (e.g. IGHV3-11 such as IGHV3-11*01), IGHD1 (e.g. IGHD1-20 such as IGHD1-20*01) and IGHJ6 (e.g. IGHJ6*02). In one embodiment, the antibody heavy chain is derived from a combination of IGHV3 (e.g. IGHV3-23 such as IGHV3-23*04), IGHD5 (e.g. IGHD5-18 such as IGHD5-18*01) and IGHJ4 (e.g. IGHJ4*02). In one embodiment, the antibody heavy chain is derived from a combination of IGHV3 (e.g. IGHV3-7 such as IGHV3-7*01), IGHD5 (e.g. IGHD5-24 such as IGHD5-24*01) and IGHJ4 (e.g. IGHJ4*02). In one embodiment, the antibody heavy chain is derived from a combination of IGHV3 (e.g. IGHV3-23 such as IGHV3-23*04), IGHD6 (e.g. IGHD6-13 such as IGHD6-13*01) and IGHJ4 (e.g. IGHJ4*02).

Concept 12. The antibody or fragment according to concept 10, 10a, 11, 11a or 11b, wherein the antibody or fragment comprises a V_L domain which is derived from the recombination of a human Vκ gene segment, and a human Jκ gene segment, wherein the human V

- -39*01).

There is also provided as concept 12a an antibody or fragment according to any of concepts 10, 10a, 11, 11a or 11b, wherein the human V gene segment is selected from IG V1-17, suc -17*01 - -9*d01 or e.g. D-12 D-12*02 or - -39*01 - -1*01).

In one embodiment, the human V gene segment is -17, such - 17*01). In one embodiment, the human Vκ gene segment is IGκV1 (- - 9*d01). In one embodiment, the human Vκ gene segment is IGκV1 (- - 12*02). In one embodiment, the human Vκ gene segment is IGκV1 - - 39*01).

In one embodiment, the human Vκ gene segment is IGκV1 -1, such as -1*01)

There is also provided as concept 12b an antibody or fragment according to concept 10, 10a, 11 or 11a, wherein the human gene segment is selected from (e.g. *01) (e.g.), 3 (e.g.) (e.g.) (e.g.).

In one embodiment, the human Jκ gene segment is . In one embodiment, the human Jκ gene segment is IGκJ2 (e.g. IGκJ2*04). In one embodiment, the human Jκ gene segment is IGκJ3 (e.g. IGκJ3*01). In one embodiment, the human Jκ gene segment is IGκJ4

In one embodiment, the human Jκ gene segme

In any of concepts 12 and 12a, the V and J gene segments are as described in the combinations for the antibodies in Table 5 hereinbelow. In one embodiment, the antibody light chain is derived from a combination of IGKV1D (e.g. IGKV1D-12 such as IGKV1D-12*02) and IGKJ3 (e.g. IGKJ3*01). In one embodiment, the antibody light chain is derived from a combination of IGKV4 (e.g. IGKV4-1 such as IGKV14-1*01) and IGKJ2 (e.g. IGKJ2*04). In one embodiment, the antibody light chain is derived from a combination of IGKV1 (e.g. IGKV1-17 such as IGKV1-17*01) and IGKJ1 (e.g. IGKJ1*01). In one embodiment, the antibody light chain is derived from a combination of IGKV1D (e.g. IGKV1D-12 such as IGKV1D-12*02) and IGKJ4 (e.g. IGKJ4*01). In one embodiment, the antibody light chain is derived from a combination of IGKV1 (e.g. IGKV1-9 such as IGKV1-9*d01) and IGKJ5 (e.g. IGKJ5*01). In one embodiment, the antibody light chain is derived from a combination of IGKV1D (e.g. IGKV1D-12 such as IGKV1D-12*02) and IGKJ5 (e.g. IGKJ5*01).

Concept 13. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 1D05 specifically binds.

Concept 13a. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 84G09 specifically binds.

Concept 13b. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 411B08 specifically binds.

Concept 13c. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 411C04 specifically binds.

Concept 13d. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 411D07 specifically binds.

Concept 13e. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 385F01 specifically binds.

Concept 13f. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 386H03 specifically binds.

Concept 13g. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 389A03 specifically binds.

Concept 13h. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 413D08 specifically binds.

Concept 13i. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 413G05 specifically binds.

Concept 13j. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 413F09 specifically binds.

Concept 13k. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 414B06 specifically binds.

Concept 13l. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 416E01 specifically binds.

The antibodies described in these concepts have the sequences as described hereinabove.

In one embodiment, there is provided an antibody which specifically binds to an epitope which is substantially similar to an epitope to which any of the antibodies in concept 13, 13 a to 13l bind.

Contact amino acid residues involved in the interaction of antibody and antigen may be determined by various known methods to those skilled in the art.

In one embodiment, sequential replacement of the amino acids of the antigen sequence (using standard molecular biology techniques to mutate the DNA of the coding sequence of the antigen), in this case hPD-L1 with Alanine (a.k.a Alanine scan), or another unrelated amino acid, may provide residues whose mutation would reduce or ablate the ability of the antibody to recognise the antigen in question. Binding may be assessed using standard techniques, such as, but not limited to, SPR, HTRF, ELISA (which are described elsewhere herein). Other substitutions could be made to enhance the disruption of binding such as changing the charge on the side chain of antigen sequence amino acids (e.g. Lysine change to glutamic acid), switching polar and non-polar residues (e.g. Serine change to leucine). The alanine scan or other amino substitution method may be carried out either with recombinant soluble antigen, or where the target is a cell membrane target, directly on cells using transient or stable expression of the mutated versions.

In one embodiment, protein crystallography may be used to determine contact residues between antibody and antigen (i.e. to determine the epitope to which the antibody binds), crystallography allows the direct visualisation of contact residues involved in the antibody-antigen interaction. As well as standard X-ray crystallography, cryo-electro microscopy has been used to determine contact residues between antibodies and HIV capsid protein (see Lee, Jeong Hyun, "Antibodies to a conformational epitope on gp41 neutralize HIV-1 by destabilizing the Env spike.", Nature communications, 6, (2015)).

In one embodiment, if the antibody recognises a linear epitope, short peptides based on the antigen sequence can be produced and binding of the antibody to these peptides can be assessed using standard techniques, such as, but not limited to, SPR, HTRF, ELISA (which are described elsewhere herein). Further investigation of the epitope could be provided by performing an Alanine scan on any peptides that show binding. Alternative to linear peptides, conformational scans could be carried out using Pepscan technology (http://www.pepscan.com/) using their chemical linkage of

peptides onto scaffolds, which has been used to determine discontinuous epitopes on CD20 targeting antibodies (Niederfellner, Gerhard, "Epitope characterization and crystal structure of GA101 provide insights into the molecular basis for type I/II distinction of CD20 antibodies.", Blood, 118.2, (2011), 358-367.).

In one embodiment, limited proteolytic digestion and mass spectrophotometry can be used to identify binding epitopes. The antibody-antigen complex is digested by a protease, such as, but not limited to, trypsin. The digested complex peptides are compared to antibody-alone and antigen-alone digestion mass spectrophotometry to determine if a particular epitope is protected by the complexation. Further work involving amino acid substitution, competition binding, may then be employed to narrow down to individual amino acid residues involved in the interaction (see, for example, Suckau, Detlev, "Molecular epitope identification by limited proteolysis of an immobilized antigen-antibody complex and mass spectrometric peptide mapping.", Proceedings of the National Academy of Sciences, 87.24, (1990), 9848-9852).

Thus, in one embodiment, the contact residues of the epitope are identified with an unrelated amino acid scan (e.g. alanine scan). In another embodiment, an unrelated amino acid scan (e.g. alanine scan) is carried out using a technique selected from SPR, HTRF, ELISA, X-ray crystallography, cryo-electro microscopy and a combination of limited proteolytic digestion and mass spectrometry. In one embodiment, the unrelated amino acid scan (e.g. alanine scan) is carried out using HTRF. In one embodiment, the unrelated amino acid scan (e.g. alanine scan) is carried out using ELISA.

When the alanine scan is carried out with either ELISA or HTRF, an amino acid residue is identified as contributing to the epitope if the reduction in signal is at least 25%. In one embodiment, the reduction in signal is at least 30%. In one embodiment, the reduction in signal is at least 35%. In one embodiment, the reduction in signal is at least 40%. In one embodiment, the reduction in signal is at least 45%. In one embodiment, the reduction in signal is at least 50%. In one embodiment, the reduction in signal is at least 55%. In one embodiment, the reduction in signal is at least 60%. In one embodiment, the reduction in signal is at least 70%. In one embodiment, the reduction in signal is at least 75%. In one embodiment, the reduction in signal is at least 80%. In one embodiment, the reduction in signal is at least 85%. In one embodiment, the reduction in signal is at least 90%.

When the alanine scan is carried out with SPR, an amino acid residue is identified as contributing to the epitope if there is at least a 10-fold reduction in affinity. In one embodiment, the reduction in affinity is at least 15-fold. In one embodiment, the reduction in affinity is at least 20-fold. In one embodiment, the reduction in affinity is at least 30-fold. In one embodiment, the reduction in affinity is at least 40-fold. In one embodiment, the reduction in affinity is at least 50-fold. In one embodiment, the reduction in affinity is at least 100-fold.

In one embodiment, the contact residues of the epitope are identified by X-ray crystallography. In one embodiment, the contact residues of the epitope are identified by cryo-electro

microscopy. In one embodiment, the contact residues of the epitope are identified by a combination of limited proteolytic digestion and mass spectrometry.

Concept 14. The antibody or fragment according to concept 13, wherein the epitope is identified by unrelated amino acid scanning, or by X-ray crystallography.

Concept 15. The antibody or fragment according to concept 14, wherein the contact residues of the epitope are defined by a reduction in affinity of at least 10-fold in an unrelated amino acid scan, e.g. an alanine scan as determined by SPR.

In one embodiment, the reduction in affinity is at least 15-fold. In one embodiment, the reduction in affinity is at least 20-fold. In one embodiment, the reduction in affinity is at least 30-fold. In one embodiment, the reduction in affinity is at least 40-fold. In one embodiment, the reduction in affinity is at least 50-fold. In one embodiment, the reduction in affinity is at least 100-fold.

SPR may be carried out as described hereinabove.

Concept 16. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 1D05.

Competition may be determined by surface plasmon resonance (SPR), such techniques being readily apparent to the skilled person. SPR may be carried out using Biacore™, Proteon™ or another standard SPR technique. Such competition may be due, for example, to the antibodies or fragments binding to identical or overlapping epitopes of hPD-L1. In one embodiment, competition is determined by ELISA, such techniques being readily apparent to the skilled person. In one embodiment, competition is determined by homogenous time resolved fluorescence (HTRF), such techniques being readily apparent to the skilled person. In one embodiment, competition is determined by fluorescence activated cell sorting (FACS), such techniques being readily apparent to the skilled person. In one embodiment, competition is determined by ForteBio Octet® Bio-Layer Interferometry (BLI) such techniques being readily apparent to the skilled person.

In one embodiment, the antibody or fragment competes (e.g. in a dose-dependent manner) with hPD-1 (or a fusion protein thereof) for binding to cell surface-expressed hPD-L1. In one embodiment, the antibody or fragment competes (e.g. in a dose-dependent manner) with hPD-1 (or a fusion protein thereof) for binding to soluble hPDL-1.

In one embodiment, the antibody or fragment partially or completely inhibits binding of PD-1 and/or CD80 to cell surface-expressed PD-L1, such as hPD-L1. In another embodiment, the antibody or fragment partially or completely inhibits binding of hPD-1 and/or CD80 to soluble hPD-L1. In some embodiments, the antibody or fragment partially or completely increases the secretion of IFN , CD25 and IL-2 from a cell having cell surface-expressed PD-1. In one embodiment, the antibody or fragment partially or completely inhibits binding of CD80 to soluble hPD-L1, but does not show any detectable inhibition of the binding of PD-1 to cell surface-expressed PD-L1. In one embodiment, the antibody or

fragment partially or completely inhibits binding of CD80 to soluble hPD-L1, but does not show any detectable inhibition of the binding of PD-1 to soluble PD-L1.

As used herein, "inhibits", "inhibition", "inhibiting" and the like, as used herein refers to the ability of an antagonist (e.g. an antibody or fragment thereof) to bind to an epitope which either partially or completely prevents the binding of the receptor (e.g. CD80 or PD-1) to the ligand (e.g. PD-L1). If the epitope to which the antagonist binds completely blocks the binding site of the ligand, then ligand binding is completely prevented (which may be a physical blocking – in the case of overlapping epitopes - or steric blocking – where the antagonist is large such that it prevents the ligand binding to its distinct epitope), and the ligand is not removed from circulation. The concentration of circulating ligand may therefore appear to be increased. If the epitope to which the antagonist binds partially blocks the binding site of the ligand, the the ligand may be able to bind, but only weakly (in the case of partial inhibition), or in a different orientation to the natural binding interaction. In this case, some of the ligand may be removed from circulation, but not as much as when the ligand binding site is completely free and available for binding. Inhibition thus refers to the physical interaction of ligand and receptor. Inhibition can be measured by HTRF, which is described in more detail elsewhere herein and in Mathis (1995) Clinical Chemistry 41(9), 1391-1397. Inhibition can also be measured by flow cytometry, where receptor is expressed on cells, or by ELISA, where receptor is adsorbed onto plates.

Concept 16a. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 84G09.

Concept 16b. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 411B08.

Concept 16c. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 411C04.

Concept 16d. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 411D07.

Concept 16e. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 385F01.

Concept 16f. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 386H03.

Concept 16g. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 389A03.

Concept 16h. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 413D08.

Concept 16i. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 413G05.

Concept 16j. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 413F09.

Concept 16k. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 414B06.

Concept 16l. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 416E01.

The antibodies have the sequences as described hereinabove.

Concept 17. The antibody or fragment according to any one of concepts 10 to 16, wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:29 or 32, or the CDRH3 sequence of SEQ ID NO:29 or 32 comprising 6 or fewer amino acid substitutions.

Concept 17a: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13a, and when dependent on concept 16, it is dependent on concept 16a), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:9 or 12, or the CDRH3 sequence of SEQ ID NO:9 or 12 comprising 6 or fewer amino acid substitutions.

Concept 17b: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13b, and when dependent on concept 16, it is dependent on concept 16b), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:54 or 57, or the CDRH3 sequence of SEQ ID NO:54 or 57 comprising 6 or fewer amino acid substitutions.

Concept 17c: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13c, and when dependent on concept 16, it is dependent on concept 16c), wherein the a V_H domain comprises the CDRH3 sequence of SEQ ID NO:74 or 77, or the CDRH3 sequence of SEQ ID NO:74 or 77 comprising 6 or fewer amino acid substitutions.

Concept 17d: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13d, and when dependent on concept 16, it is dependent on concept 16d), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:94 or 97, or the CDRH3 sequence of SEQ ID NO:94 or 97 comprising 3 or fewer amino acid substitutions.

Concept 17e: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13e, and when dependent on concept 16, it is dependent on concept 16e), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:114 or 117, or the CDRH3 sequence of SEQ ID NO:114 or 117 comprising 6 or fewer amino acid substitutions.

Concept 17f: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13f, and when dependent on concept 16, it is dependent on concept 16f), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:144 or 147, or the CDRH3 sequence of SEQ ID NO:144 or 147 comprising 3 or fewer amino acid substitutions.

Concept 17g: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13g, and when dependent on concept 16, it is dependent on concept 16g), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:174 or 177, or the CDRH3 sequence of SEQ ID NO:174 or 177 comprising 6 or fewer amino acid substitutions.

Concept 17h: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13h, and when dependent on concept 16, it is dependent on concept 16h), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:134 or 137, or the CDRH3 sequence of SEQ ID NO:134 or 137 comprising 5 or fewer amino acid substitutions.

Concept 17i: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13i, and when dependent on concept 16, it is dependent on concept 16i), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:240 or 243, or the CDRH3 sequence of SEQ ID NO:240 or 243 comprising 6 or fewer amino acid substitutions.

Concept 17j: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13j, and when dependent on concept 16, it is dependent on concept 16j), wherein the a V_H domain comprises the CDRH3 sequence of SEQ ID NO:260 or 263, or the CDRH3 sequence of SEQ ID NO:260 or 263 comprising 6 or fewer amino acid substitutions.

Concept 17k: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13k, and when dependent on concept 16, it is dependent on concept 16k), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:280 or 283, or the CDRH3 sequence of SEQ ID NO:280 or 283 comprising 6 or fewer amino acid substitutions.

Concept 17l: An antibody or a fragment thereof according to any one of concepts 10 to 16 (but when dependent on concept 13, it is dependent on concept 13l, and when dependent on concept 16, it is dependent on concept 16l), wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:345 or 348, or the CDRH3 sequence of SEQ ID NO:345 or 348 comprising 6 or fewer amino acid substitutions.

Concept 18. The antibody or fragment according to any preceding concept, wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:27 or 30 or the CDRH1 sequence of SEQ ID NO:27 or 30 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18a: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9a, when dependent on concept 13, it is dependent on concept 13a, when dependent on concept 16, it is dependent on concept 16a, and when dependent on concept 17, it is dependent on concept 17a), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:7 or 10, or the CDRH1 sequence of SEQ ID NO:7 or 10 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18b: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9b, when dependent on concept 13, it is dependent on concept 13b, when dependent on concept 16, it is dependent on concept 16b, and when dependent on concept 17, it is dependent on concept 17b), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:52 or 55, or the CDRH1 sequence of SEQ ID NO:52 or 55 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18c: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9c, when dependent on concept 13, it is dependent on concept 13c, when dependent on concept 16, it is dependent on concept 16c, and when dependent on concept 17, it is dependent on concept 17c), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:72 or 75, or the CDRH1 sequence of SEQ ID NO:72 or 75 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18d: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9d, when dependent on concept 13, it is dependent on concept 13d, when dependent on concept 16, it is dependent on concept 16d, and when dependent on concept 17, it is dependent on concept 17d), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:92 or 95, or the CDRH1 sequence of SEQ ID NO:92 or 95 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18e: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9e, when dependent on concept 13, it is dependent on concept 13e, when dependent on concept 16, it is dependent on concept 16e, and when dependent on concept 17, it is dependent on concept 17e), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:112 or 115, or the CDRH1 sequence of SEQ ID NO:112 or 115 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18f: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9f, when dependent on concept 13, it is dependent on concept 13f, when dependent on concept 16, it is dependent on concept 16f, and when dependent on concept 17, it is dependent on concept 17f), wherein the V_H domain comprises the

CDRH1 sequence of SEQ ID NO:142 or 145, or the CDRH1 sequence of SEQ ID NO:142 or 145 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18g: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9g, when dependent on concept 13, it is dependent on concept 13g, when dependent on concept 16, it is dependent on concept 16g, and when dependent on concept 17, it is dependent on concept 17g), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:172 or 175, or the CDRH1 sequence of SEQ ID NO:172 or 175 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18h: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9h, when dependent on concept 13, it is dependent on concept 13h, when dependent on concept 16, it is dependent on concept 16h, and when dependent on concept 17, it is dependent on concept 17h), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:132 or 135, or the CDRH1 sequence of SEQ ID NO:132 or 135 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18i: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9i, when dependent on concept 13, it is dependent on concept 13i, when dependent on concept 16, it is dependent on concept 16i, and when dependent on concept 17, it is dependent on concept 17i), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:238 or 241, or the CDRH1 sequence of SEQ ID NO:238 or 241 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18j: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9j, when dependent on concept 13, it is dependent on concept 13j, when dependent on concept 16, it is dependent on concept 16j, and when dependent on concept 17, it is dependent on concept 17j), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:258 or 261, or the CDRH1 sequence of SEQ ID NO:258 or 261 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18k: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9k, when dependent on concept 13, it is dependent on concept 13k, when dependent on concept 16, it is dependent on concept 16k, and when dependent on concept 17, it is dependent on concept 17k), wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO: 278 or 281, or the CDRH1 sequence of SEQ ID NO: 278 or 281 comprising 3, 2 or 1 amino acid substitution(s).

Concept 18l: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9l, when dependent on concept 13, it is dependent on concept 13l, when dependent on concept 16, it is dependent on concept 16l, and when dependent on concept 17, it is dependent on concept 17l), wherein the V_H domain comprises the CDRH1 sequence

of SEQ ID NO: 343 or 346, or the CDRH1 sequence of SEQ ID NO: 343 or 346 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19. The antibody or fragment according to any preceding concept, wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:28 or 31, or the CDRH2 sequence of SEQ ID NO:28 or 31 comprising 4 or fewer amino acid substitutions.

Concept 19a: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9a, when dependent on concept 13, it is dependent on concept 13a, when dependent on concept 16, it is dependent on concept 16a, when dependent on concept 17, it is dependent on concept 17a, and when dependent on concept 18, it is dependent on concept 18a), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:8 or 11, or the CDRH2 sequence of SEQ ID NO:8 or 11 comprising 4 or fewer amino acid substitutions.

Concept 19b: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9b, when dependent on concept 13, it is dependent on concept 13b, when dependent on concept 16, it is dependent on concept 16b, when dependent on concept 17, it is dependent on concept 17b, and when dependent on concept 18, it is dependent on concept 18b), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:53 or 56, or the CDRH2 sequence of SEQ ID NO:53 or 56 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19c: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9c, when dependent on concept 13, it is dependent on concept 13c, when dependent on concept 16, it is dependent on concept 16c, when dependent on concept 17, it is dependent on concept 17c, and when dependent on concept 18, it is dependent on concept 18c), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:73 or 76, or the CDRH2 sequence of SEQ ID NO:73 or 76 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19d: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9d, when dependent on concept 13, it is dependent on concept 13d, when dependent on concept 16, it is dependent on concept 16d, when dependent on concept 17, it is dependent on concept 17d, and when dependent on concept 18, it is dependent on concept 18d), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:93 or 96, or the CDRH2 sequence of SEQ ID NO:93 or 96 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19e: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9e, when dependent on concept 13, it is dependent on concept 13e, when dependent on concept 16, it is dependent on concept 16e, when dependent on concept 17, it is dependent on concept 17e, and when dependent on concept 18, it is dependent on concept 18e), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:113 or 116, or the CDRH2 sequence of SEQ ID NO:113 or 116 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19f: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9f, when dependent on concept 13, it is dependent on concept 13f, when dependent on concept 16, it is dependent on concept 16f, when dependent on concept 17, it is dependent on concept 17f, and when dependent on concept 18, it is dependent on concept 18f), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:143 or 146, or the CDRH2 sequence of SEQ ID NO:143 or 146 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19g: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9g, when dependent on concept 13, it is dependent on concept 13g, when dependent on concept 16, it is dependent on concept 16g, when dependent on concept 17, it is dependent on concept 17g, and when dependent on concept 18, it is dependent on concept 18g), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:173 or 176, or the CDRH2 sequence of SEQ ID NO:173 or 176 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19h: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9h, when dependent on concept 13, it is dependent on concept 13h, when dependent on concept 16, it is dependent on concept 16h, when dependent on concept 17, it is dependent on concept 17h, and when dependent on concept 18, it is dependent on concept 18h), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:133 or 136, or the CDRH2 sequence of SEQ ID NO:133 or 136 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19i: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9i, when dependent on concept 13, it is dependent on concept 13i, when dependent on concept 16, it is dependent on concept 16i, when dependent on concept 17, it is dependent on concept 17i, and when dependent on concept 18, it is dependent on concept 18i), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:239 or 242, or the CDRH2 sequence of SEQ ID NO:239 or 242 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19j: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9j, when dependent on concept 13, it is dependent on concept 13j, when dependent on concept 16, it is dependent on concept 16j, when dependent on concept 17, it is dependent on concept 17j, and when dependent on concept 18, it is dependent on concept 18j), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:259 or 262, or the CDRH2 sequence of SEQ ID NO:259 or 262 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19k: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9k, when dependent on concept 13, it is dependent on concept 13k, when dependent on concept 16, it is dependent on concept 16k, when

dependent on concept 17, it is dependent on concept 17k, and when dependent on concept 18, it is dependent on concept 18k), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:279 or 282, or the CDRH2 sequence of SEQ ID NO:279 or 282 comprising 3, 2 or 1 amino acid substitution(s).

Concept 19l: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9l, when dependent on concept 13, it is dependent on concept 13l, when dependent on concept 16, it is dependent on concept 16l, when dependent on concept 17, it is dependent on concept 17l, and when dependent on concept 18, it is dependent on concept 18l), wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:344 or 347, or the CDRH2 sequence of SEQ ID NO:344 or 347 comprising 3, 2 or 1 amino acid substitution(s).

Concept 20. The antibody or fragment according to any preceding concept, wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:33, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:33.

Concept 20a: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9a, when dependent on concept 13, it is dependent on concept 13a, when dependent on concept 16, it is dependent on concept 16a, when dependent on concept 17, it is dependent on concept 17a, when dependent on concept 18, it is dependent on concept 18a, and when dependent on concept 19, it is dependent on concept 19a), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:13, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:13.

Concept 20b: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9b, when dependent on concept 13, it is dependent on concept 13b, when dependent on concept 16, it is dependent on concept 16b, when dependent on concept 17, it is dependent on concept 17b, when dependent on concept 18, it is dependent on concept 18b, and when dependent on concept 19, it is dependent on concept 19b), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:58, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:58.

Concept 20c: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9c, when dependent on concept 13, it is dependent on concept 13c, when dependent on concept 16, it is dependent on concept 16c, when dependent on concept 17, it is dependent on concept 17c, when dependent on concept 18, it is dependent on concept 18c, and when dependent on concept 19, it is dependent on concept 19c), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:78, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:78.

Concept 20d: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9d, when dependent on concept 13, it is dependent on concept 13d, when dependent on concept 16, it is dependent on concept 16d, when dependent on concept 17, it is dependent on concept 17d, when dependent on concept 18, it is dependent on concept 18d, and when dependent on concept 19, it is dependent on concept 19d), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:98, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:98.

Concept 20e: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9e, when dependent on concept 13, it is dependent on concept 13e, when dependent on concept 16, it is dependent on concept 16e, when dependent on concept 17, it is dependent on concept 17e, when dependent on concept 18, it is dependent on concept 18e, and when dependent on concept 19, it is dependent on concept 19e), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:118, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:118.

Concept 20f: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9f, when dependent on concept 13, it is dependent on concept 13f, when dependent on concept 16, it is dependent on concept 16f, when dependent on concept 17, it is dependent on concept 17f, when dependent on concept 18, it is dependent on concept 18f, and when dependent on concept 19, it is dependent on concept 19f), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:158, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:158.

Concept 20g: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9g, when dependent on concept 13, it is dependent on concept 13g, when dependent on concept 16, it is dependent on concept 16g, when dependent on concept 17, it is dependent on concept 17g, when dependent on concept 18, it is dependent on concept 18g, and when dependent on concept 19, it is dependent on concept 19g), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:178, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:178.

Concept 20h: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9h, when dependent on concept 13, it is dependent on concept 13h, when dependent on concept 16, it is dependent on concept 16h, when dependent on concept 17, it is dependent on concept 17h, when dependent on concept 18, it is dependent on concept 18h, and when dependent on concept 19, it is dependent on concept 19h),

wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:138, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:138.

Concept 20i: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9i, when dependent on concept 13, it is dependent on concept 13i, when dependent on concept 16, it is dependent on concept 16i, when dependent on concept 17, it is dependent on concept 17i, when dependent on concept 18, it is dependent on concept 18i, and when dependent on concept 19, it is dependent on concept 19i), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:244, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:244.

Concept 20j: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9j, when dependent on concept 13, it is dependent on concept 13j, when dependent on concept 16, it is dependent on concept 16j, when dependent on concept 17, it is dependent on concept 17j, when dependent on concept 18, it is dependent on concept 18j, and when dependent on concept 19, it is dependent on concept 19j), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:264, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:264.

Concept 20k: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9k, when dependent on concept 13, it is dependent on concept 13k, when dependent on concept 16, it is dependent on concept 16k, when dependent on concept 17, it is dependent on concept 17k, when dependent on concept 18, it is dependent on concept 18k, and when dependent on concept 19, it is dependent on concept 19k), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:284, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:284.

Concept 20l: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9l, when dependent on concept 13, it is dependent on concept 13l, when dependent on concept 16, it is dependent on concept 16l, when dependent on concept 17, it is dependent on concept 17l, when dependent on concept 18, it is dependent on concept 18l, and when dependent on concept 19, it is dependent on concept 19l), wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:349, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:349.

In one embodiment, the amino acid sequence is at least 70% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 75% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 95% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 96% identical to the specified Seq ID

No. In one embodiment, the amino acid sequence is at least 97% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 98% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99.5% identical to the specified Seq ID No.

Concept 21. The antibody or fragment according to any preceding concept comprising first and second copies of said V_H domain.

Concept 22. The antibody or fragment according to any preceding concept, comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:37 or 40, or the CRDL1 sequence of SEQ ID NO:37 or 40 comprising 3 or fewer amino acid substitutions.

Concept 22a: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9a, when dependent on concept 13, it is dependent on concept 13a, when dependent on concept 16, it is dependent on concept 16a, when dependent on concept 17, it is dependent on concept 17a, when dependent on concept 18, it is dependent on concept 18a, when dependent on concept 19, it is dependent on concept 19a, and when dependent on concept 20, it is dependent on concept 20a), comprising a V_L domain, which comprises the CDRL1 sequence of SEQ ID NO:17 or 20, or the CDRL1 sequence of SEQ ID NO:17 or 20 comprising 3 or fewer amino acid substitutions.

Concept 22b: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9b, when dependent on concept 13, it is dependent on concept 13b, when dependent on concept 16, it is dependent on concept 16b, when dependent on concept 17, it is dependent on concept 17b, when dependent on concept 18, it is dependent on concept 18b, when dependent on concept 19, it is dependent on concept 19b, and when dependent on concept 20, it is dependent on concept 20b), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:62 or 65, or the CDRL1 sequence of SEQ ID NO:62 or 65 comprising 3 or fewer amino acid substitutions.

Concept 22c: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9c, when dependent on concept 13, it is dependent on concept 13c, when dependent on concept 16, it is dependent on concept 16c, when dependent on concept 17, it is dependent on concept 17c, when dependent on concept 18, it is dependent on concept 18c, when dependent on concept 19, it is dependent on concept 19c, and when dependent on concept 20, it is dependent on concept 20c), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:82 or 85, or the CDRL1 sequence of SEQ ID NO:82 or 85 comprising 2 or 1 amino acid substitution(s).

Concept 22d: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9d, when dependent on concept 13, it is

dependent on concept 13d, when dependent on concept 16, it is dependent on concept 16d, when dependent on concept 17, it is dependent on concept 17d, when dependent on concept 18, it is dependent on concept 18d, when dependent on concept 19, it is dependent on concept 19d, and when dependent on concept 20, it is dependent on concept 20d), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:102 or 105, or the CDRL1 sequence of SEQ ID NO:102 or 105 comprising 5 or fewer amino acid substitutions.

Concept 22e: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9e, when dependent on concept 13, it is dependent on concept 13e, when dependent on concept 16, it is dependent on concept 16e, when dependent on concept 17, it is dependent on concept 17e, when dependent on concept 18, it is dependent on concept 18e, when dependent on concept 19, it is dependent on concept 19e, and when dependent on concept 20, it is dependent on concept 20e), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:122 or 125, or the CDRL1 sequence of SEQ ID NO:122 or 125 comprising 2 or 1 amino acid substitution(s).

Concept 22f: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9f, when dependent on concept 13, it is dependent on concept 13f, when dependent on concept 16, it is dependent on concept 16f, when dependent on concept 17, it is dependent on concept 17f, when dependent on concept 18, it is dependent on concept 18f, when dependent on concept 19, it is dependent on concept 19f, and when dependent on concept 20, it is dependent on concept 20f), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:162 or 165, or the CDRL1 sequence of SEQ ID NO:162 or 165 comprising 5 or fewer amino acid substitutions.

Concept 22g: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9g, when dependent on concept 13, it is dependent on concept 13g, when dependent on concept 16, it is dependent on concept 16g, when dependent on concept 17, it is dependent on concept 17g, when dependent on concept 18, it is dependent on concept 18g, when dependent on concept 19, it is dependent on concept 19g, and when dependent on concept 20, it is dependent on concept 20g), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:182 or 185, or the CDRL1 sequence of SEQ ID NO:182 or 185 comprising 5 or fewer amino acid substitutions.

Concept 22h: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9h, when dependent on concept 13, it is dependent on concept 13h, when dependent on concept 16, it is dependent on concept 16h, when dependent on concept 17, it is dependent on concept 17h, when dependent on concept 18, it is dependent on concept 18h, when dependent on concept 19, it is dependent on concept 19h, and when dependent on concept 20, it is dependent on concept 20h), comprising a V_L domain which

comprises the CDRL1 sequence of SEQ ID NO:142 or 145, or the CDRL1 sequence of SEQ ID NO:142 or 145 comprising 2 or 1 amino acid substitution(s).

Concept 22i: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9i, when dependent on concept 13, it is dependent on concept 13i, when dependent on concept 16, it is dependent on concept 16i, when dependent on concept 17, it is dependent on concept 17i, when dependent on concept 18, it is dependent on concept 18i, when dependent on concept 19, it is dependent on concept 19i, and when dependent on concept 20, it is dependent on concept 20i), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:248 or 251, or the CDRL1 sequence of SEQ ID NO:248 or 251 comprising 2 or 1 amino acid substitution(s).

Concept 22j: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9j, when dependent on concept 13, it is dependent on concept 13j, when dependent on concept 16, it is dependent on concept 16j, when dependent on concept 17, it is dependent on concept 17j, when dependent on concept 18, it is dependent on concept 18j, when dependent on concept 19, it is dependent on concept 19j, and when dependent on concept 20, it is dependent on concept 20j), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:268 or 271, or the CDRL1 sequence of SEQ ID NO:268 or 271 comprising 2 or 1 amino acid substitution(s).

Concept 22k: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9k, when dependent on concept 13, it is dependent on concept 13k, when dependent on concept 16, it is dependent on concept 16k, when dependent on concept 17, it is dependent on concept 17k, when dependent on concept 18, it is dependent on concept 18k, when dependent on concept 19, it is dependent on concept 19k, and when dependent on concept 20, it is dependent on concept 20k), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:288 or 291, or the CDRL1 sequence of SEQ ID NO:288 or 291 comprising 2 or 1 amino acid substitution(s).

Concept 22l: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9l, when dependent on concept 13, it is dependent on concept 13l, when dependent on concept 16, it is dependent on concept 16l, when dependent on concept 17, it is dependent on concept 17l, when dependent on concept 18, it is dependent on concept 18l, when dependent on concept 19, it is dependent on concept 19l, and when dependent on concept 20, it is dependent on concept 20l), comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:353 or 356, or the CDRL1 sequence of SEQ ID NO:353 or 356 comprising 2 or 1 amino acid substitution(s).

Concept 23. The antibody or fragment according to any preceding concept, comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:38 or 41, or the CRDL2

sequence of SEQ ID NO:38 or 41 comprising 2 or 1 amino acid substitution(s), for example a CDRL2 sequence of Seq ID No:50.

Concept 23a: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9a, when dependent on concept 13, it is dependent on concept 13a, when dependent on concept 16, it is dependent on concept 16a, when dependent on concept 17, it is dependent on concept 17a, when dependent on concept 18, it is dependent on concept 18a, when dependent on concept 19, it is dependent on concept 19a, when dependent on concept 20, it is dependent on concept 20a, and when dependent on concept 22, it is dependent on concept 22a), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:18 or 21, or the CDRL2 sequence of SEQ ID NO:18 or 21 comprising 2 or 1 amino acid substitution(s).

Concept 23b: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9b, when dependent on concept 13, it is dependent on concept 13b, when dependent on concept 16, it is dependent on concept 16b, when dependent on concept 17, it is dependent on concept 17b, when dependent on concept 18, it is dependent on concept 18b, when dependent on concept 19, it is dependent on concept 19b, when dependent on concept 20, it is dependent on concept 20b, and when dependent on concept 22, it is dependent on concept 22b), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:63 or 66, or the CDRL2 sequence of SEQ ID NO:63 or 66 comprising one amino acid substitution.

Concept 23c: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9c, when dependent on concept 13, it is dependent on concept 13c, when dependent on concept 16, it is dependent on concept 16c, when dependent on concept 17, it is dependent on concept 17c, when dependent on concept 18, it is dependent on concept 18c, when dependent on concept 19, it is dependent on concept 19c, when dependent on concept 20, it is dependent on concept 20c, and when dependent on concept 22, it is dependent on concept 22c), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:83 or 86, or the CDRL2 sequence of SEQ ID NO:83 or 86 comprising one amino acid substitution.

Concept 23d: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9d, when dependent on concept 13, it is dependent on concept 13d, when dependent on concept 16, it is dependent on concept 16d, when dependent on concept 17, it is dependent on concept 17d, when dependent on concept 18, it is dependent on concept 18d, when dependent on concept 19, it is dependent on concept 19d, when dependent on concept 20, it is dependent on concept 20d, and when dependent on concept 22, it is dependent on concept 22d), comprising a or said V_L domain, which V_L domain comprises the CDRL2

sequence of SEQ ID NO:103 or 106, or the CDRL2 sequence of SEQ ID NO:103 or 106 comprising one amino acid substitution.

Concept 23e: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9e, when dependent on concept 13, it is dependent on concept 13e, when dependent on concept 16, it is dependent on concept 16e, when dependent on concept 17, it is dependent on concept 17e, when dependent on concept 18, it is dependent on concept 18e, when dependent on concept 19, it is dependent on concept 19e, when dependent on concept 20, it is dependent on concept 20e, and when dependent on concept 22, it is dependent on concept 22e), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:123 or 126, or the CDRL2 sequence of SEQ ID NO:123 or 126 comprising one amino acid substitution.

Concept 23f: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9f, when dependent on concept 13, it is dependent on concept 13f, when dependent on concept 16, it is dependent on concept 16f, when dependent on concept 17, it is dependent on concept 17f, when dependent on concept 18, it is dependent on concept 18f, when dependent on concept 19, it is dependent on concept 19f, when dependent on concept 20, it is dependent on concept 20f, and when dependent on concept 22, it is dependent on concept 22f), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:153 or 156, or the CDRL2 sequence of SEQ ID NO:153 or 156 comprising one amino acid substitution.

Concept 23g: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9g, when dependent on concept 13, it is dependent on concept 13g, when dependent on concept 16, it is dependent on concept 16g, when dependent on concept 17, it is dependent on concept 17g, when dependent on concept 18, it is dependent on concept 18g, when dependent on concept 19, it is dependent on concept 19g, when dependent on concept 20, it is dependent on concept 20g, and when dependent on concept 22, it is dependent on concept 22g), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:183 or 186, or the CDRL2 sequence of SEQ ID NO:183 or 186 comprising one amino acid substitution.

Concept 23h: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9h, when dependent on concept 13, it is dependent on concept 13h, when dependent on concept 16, it is dependent on concept 16h, when dependent on concept 17, it is dependent on concept 17h, when dependent on concept 18, it is dependent on concept 18h, when dependent on concept 19, it is dependent on concept 19h, when dependent on concept 20, it is dependent on concept 20h, and when dependent on concept 22, it is dependent on concept 22h), comprising a or said V_L domain, which V_L domain comprises the CDRL2

sequence of SEQ ID NO:143 or 146, or the CDRL2 sequence of SEQ ID NO:143 or 146 comprising one amino acid substitution.

Concept 23i: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9i, when dependent on concept 13, it is dependent on concept 13i, when dependent on concept 16, it is dependent on concept 16i, when dependent on concept 17, it is dependent on concept 17i, when dependent on concept 18, it is dependent on concept 18i, when dependent on concept 19, it is dependent on concept 19i, when dependent on concept 20, it is dependent on concept 20i, and when dependent on concept 22, it is dependent on concept 22i), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:249 or 252, or the CDRL2 sequence of SEQ ID NO:249 or 252 comprising one amino acid substitution.

Concept 23j: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9j, when dependent on concept 13, it is dependent on concept 13j, when dependent on concept 16, it is dependent on concept 16j, when dependent on concept 17, it is dependent on concept 17j, when dependent on concept 18, it is dependent on concept 18j, when dependent on concept 19, it is dependent on concept 19j, when dependent on concept 20, it is dependent on concept 20j, and when dependent on concept 22, it is dependent on concept 22j), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:269 or 272, or the CDRL2 sequence of SEQ ID NO:269 or 272 comprising one amino acid substitution.

Concept 23k: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9k, when dependent on concept 13, it is dependent on concept 13k, when dependent on concept 16, it is dependent on concept 16k, when dependent on concept 17, it is dependent on concept 17k, when dependent on concept 18, it is dependent on concept 18k, when dependent on concept 19, it is dependent on concept 19k, when dependent on concept 20, it is dependent on concept 20k, and when dependent on concept 22, it is dependent on concept 22k), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:289 or 292, or the CDRL2 sequence of SEQ ID NO:289 or 292 comprising one amino acid substitution.

Concept 23l: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9l, when dependent on concept 13, it is dependent on concept 13l, when dependent on concept 16, it is dependent on concept 16l, when dependent on concept 17, it is dependent on concept 17l, when dependent on concept 18, it is dependent on concept 18l, when dependent on concept 19, it is dependent on concept 19l, when dependent on concept 20, it is dependent on concept 20l, and when dependent on concept 22, it is dependent on concept 22l), comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:354 or 357, or the CDRL2 sequence of SEQ ID NO:354 or 357 comprising one amino acid substitution.

Concept 24. The antibody or fragment according to any preceding concept, comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:39 or 42, or the CRDL3 sequence of SEQ ID NO:39 or 42 comprising 4 or fewer amino acid substitutions.

Concept 24a: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9a, when dependent on concept 13, it is dependent on concept 13a, when dependent on concept 16, it is dependent on concept 16a, when dependent on concept 17, it is dependent on concept 17a, when dependent on concept 18, it is dependent on concept 18a, when dependent on concept 19, it is dependent on concept 19a, when dependent on concept 20, it is dependent on concept 20a, when dependent on concept 22, it is dependent on concept 22a, and when dependent on concept 23, it is dependent on concept 23a), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:19 or 22, or the CDRL3 sequence of SEQ ID NO: 19 or 22 comprising 4 or fewer amino acid substitutions.

Concept 24b: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9b, when dependent on concept 13, it is dependent on concept 13b, when dependent on concept 16, it is dependent on concept 16b, when dependent on concept 17, it is dependent on concept 17b, when dependent on concept 18, it is dependent on concept 18b, when dependent on concept 19, it is dependent on concept 19b, when dependent on concept 20, it is dependent on concept 20b, when dependent on concept 22, it is dependent on concept 22b, and when dependent on concept 23, it is dependent on concept 23b), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:64 or 67, or the CDRL3 sequence of SEQ ID NO:64 or 67 comprising 4 or fewer amino acid substitutions.

Concept 24c: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9c, when dependent on concept 13, it is dependent on concept 13c, when dependent on concept 16, it is dependent on concept 16c, when dependent on concept 17, it is dependent on concept 17c, when dependent on concept 18, it is dependent on concept 18c, when dependent on concept 19, it is dependent on concept 19c, when dependent on concept 20, it is dependent on concept 20c, when dependent on concept 22, it is dependent on concept 22c, and when dependent on concept 23, it is dependent on concept 23c), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:84 or 87, or the CDRL3 sequence of SEQ ID NO:84 or 87 comprising 4 or fewer amino acid substitutions.

Concept 24d: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9d, when dependent on concept 13, it is dependent on concept 13d, when dependent on concept 16, it is dependent on concept 16d, when dependent on concept 17, it is dependent on concept 17d, when dependent on concept 18, it is dependent on concept 18d, when dependent on concept 19, it is dependent on concept 19d, when dependent on concept 20, it is dependent on concept 20d, when dependent on concept 22, it is dependent on concept 22d, and when dependent on concept 23, it is dependent on concept 23d),

comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:104 or 107, or the CDRL3 sequence of SEQ ID NO:104 or 107 comprising 4 or fewer amino acid substitutions.

Concept 24e: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9e, when dependent on concept 13, it is dependent on concept 13e, when dependent on concept 16, it is dependent on concept 16e, when dependent on concept 17, it is dependent on concept 17e, when dependent on concept 18, it is dependent on concept 18e, when dependent on concept 19, it is dependent on concept 19e, when dependent on concept 20, it is dependent on concept 20e, when dependent on concept 22, it is dependent on concept 22e, and when dependent on concept 23, it is dependent on concept 23e), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:124 or 127, or the CDRL3 sequence of SEQ ID NO:124 or 127 comprising 4 or fewer amino acid substitutions.

Concept 24f: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9f, when dependent on concept 13, it is dependent on concept 13f, when dependent on concept 16, it is dependent on concept 16f, when dependent on concept 17, it is dependent on concept 17f, when dependent on concept 18, it is dependent on concept 18f, when dependent on concept 19, it is dependent on concept 19f, when dependent on concept 20, it is dependent on concept 20f, when dependent on concept 22, it is dependent on concept 22f, and when dependent on concept 23, it is dependent on concept 23f), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:164 or 167, or the CDRL3 sequence of SEQ ID NO:164 or 167 comprising 4 or fewer amino acid substitutions.

Concept 24g: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9g, when dependent on concept 13, it is dependent on concept 13g, when dependent on concept 16, it is dependent on concept 16g, when dependent on concept 17, it is dependent on concept 17g, when dependent on concept 18, it is dependent on concept 18g, when dependent on concept 19, it is dependent on concept 19g, when dependent on concept 20, it is dependent on concept 20g, when dependent on concept 22, it is dependent on concept 22g, and when dependent on concept 23, it is dependent on concept 23g), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:184 or 187, or the CDRL3 sequence of SEQ ID NO:184 or 187 comprising 4 or fewer amino acid substitutions.

Concept 24h: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9h, when dependent on concept 13, it is dependent on concept 13h, when dependent on concept 16, it is dependent on concept 16h, when dependent on concept 17, it is dependent on concept 17h, when dependent on concept 18, it is

dependent on concept 18h, when dependent on concept 19, it is dependent on concept 19h, when dependent on concept 20, it is dependent on concept 20h, when dependent on concept 22, it is dependent on concept 22h, and when dependent on concept 23, it is dependent on concept 23h), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:144 or 147, or the CDRL3 sequence of SEQ ID NO:144 or 147 comprising 4 or fewer amino acid substitutions.

Concept 24i: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9i, when dependent on concept 13, it is dependent on concept 13i, when dependent on concept 16, it is dependent on concept 16i, when dependent on concept 17, it is dependent on concept 17i, when dependent on concept 18, it is dependent on concept 18i, when dependent on concept 19, it is dependent on concept 19i, when dependent on concept 20, it is dependent on concept 20i, when dependent on concept 22, it is dependent on concept 22i, and when dependent on concept 23, it is dependent on concept 23i), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:250 or 253, or the CDRL3 sequence of SEQ ID NO:250 or 253 comprising 4 or fewer amino acid substitutions.

Concept 24j: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9j, when dependent on concept 13, it is dependent on concept 13j, when dependent on concept 16, it is dependent on concept 16j, when dependent on concept 17, it is dependent on concept 17j, when dependent on concept 18, it is dependent on concept 18j, when dependent on concept 19, it is dependent on concept 19j, when dependent on concept 20, it is dependent on concept 20j, when dependent on concept 22, it is dependent on concept 22j, and when dependent on concept 23, it is dependent on concept 23j), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:270 or 273, or the CDRL3 sequence of SEQ ID NO:270 or 273 comprising 4 or fewer amino acid substitutions.

Concept 24k: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9k, when dependent on concept 13, it is dependent on concept 13k, when dependent on concept 16, it is dependent on concept 16k, when dependent on concept 17, it is dependent on concept 17k, when dependent on concept 18, it is dependent on concept 18k, when dependent on concept 19, it is dependent on concept 19k, when dependent on concept 20, it is dependent on concept 20k, when dependent on concept 22, it is dependent on concept 22k, and when dependent on concept 23, it is dependent on concept 23k), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:290 or 293, or the CDRL3 sequence of SEQ ID NO:290 or 293 comprising 4 or fewer amino acid substitutions.

Concept 24l: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9l, when dependent on concept 13, it is dependent

on concept 13l, when dependent on concept 16, it is dependent on concept 16l, when dependent on concept 17, it is dependent on concept 17l, when dependent on concept 18, it is dependent on concept 18l, when dependent on concept 19, it is dependent on concept 19l, when dependent on concept 20, it is dependent on concept 20l, when dependent on concept 22, it is dependent on concept 22l, and when dependent on concept 23, it is dependent on concept 23l), comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:355 or 358, or the CDRL3 sequence of SEQ ID NO:355 or 358 comprising 4 or fewer amino acid substitutions.

Concept 25. The antibody or fragment according to any preceding concept, comprising a or said V_L domain, which V_L domain comprises an amino acid sequence of SEQ ID NO:43, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:43 (for example the VL domain sequence in the light chain sequence of Seq ID No:50, 51 or 298).

Concept 25a: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9a, when dependent on concept 13, it is dependent on concept 13a, when dependent on concept 16, it is dependent on concept 16a, when dependent on concept 17, it is dependent on concept 17a, when dependent on concept 18, it is dependent on concept 18a, when dependent on concept 19, it is dependent on concept 19a, when dependent on concept 20, it is dependent on concept 20a, when dependent on concept 22, it is dependent on concept 22a, when dependent on concept 23, it is dependent on concept 23a, and when dependent on concept 24, it is dependent on concept 24a), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:23, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:23.

Concept 25b: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9b, when dependent on concept 13, it is dependent on concept 13b, when dependent on concept 16, it is dependent on concept 16b, when dependent on concept 17, it is dependent on concept 17b, when dependent on concept 18, it is dependent on concept 18b, when dependent on concept 19, it is dependent on concept 19b, when dependent on concept 20, it is dependent on concept 20b, when dependent on concept 22, it is dependent on concept 22a, when dependent on concept 23, it is dependent on concept 23b, and when dependent on concept 24, it is dependent on concept 24b), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:68, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:68.

Concept 25c: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9c, when dependent on concept 13, it is dependent on concept 13c, when dependent on concept 16, it is dependent on concept 16c, when dependent on concept 17, it is dependent on concept 17c, when dependent on concept 18, it is dependent on concept 18c, when dependent on concept 19, it is dependent on concept 19c, when

dependent on concept 20, it is dependent on concept 20c, when dependent on concept 22, it is dependent on concept 22c, when dependent on concept 23, it is dependent on concept 23c, and when dependent on concept 24, it is dependent on concept 24c), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:88, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:88.

Concept 25d: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9d, when dependent on concept 13, it is dependent on concept 13d, when dependent on concept 16, it is dependent on concept 16d, when dependent on concept 17, it is dependent on concept 17d, when dependent on concept 18, it is dependent on concept 18d, when dependent on concept 19, it is dependent on concept 19d, when dependent on concept 20, it is dependent on concept 20d, when dependent on concept 22, it is dependent on concept 22d, when dependent on concept 23, it is dependent on concept 23d, and when dependent on concept 24, it is dependent on concept 24d), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:108, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:108.

Concept 25e: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9e, when dependent on concept 13, it is dependent on concept 13e, when dependent on concept 16, it is dependent on concept 16e, when dependent on concept 17, it is dependent on concept 17e, when dependent on concept 18, it is dependent on concept 18e, when dependent on concept 19, it is dependent on concept 19e, when dependent on concept 20, it is dependent on concept 20e, when dependent on concept 22, it is dependent on concept 22e, when dependent on concept 23, it is dependent on concept 23e, and when dependent on concept 24, it is dependent on concept 24e), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:128, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:128.

Concept 25f: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9f, when dependent on concept 13, it is dependent on concept 13f, when dependent on concept 16, it is dependent on concept 16f, when dependent on concept 17, it is dependent on concept 17f, when dependent on concept 18, it is dependent on concept 18f, when dependent on concept 19, it is dependent on concept 19f, when dependent on concept 20, it is dependent on concept 20f, when dependent on concept 22, it is dependent on concept 22f, when dependent on concept 23, it is dependent on concept 23f, and when dependent on concept 24, it is dependent on concept 24f), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:168, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:168.

Concept 25g: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9g, when dependent on concept 13, it is

dependent on concept 13g, when dependent on concept 16, it is dependent on concept 16g, when dependent on concept 17, it is dependent on concept 17g, when dependent on concept 18, it is dependent on concept 18g, when dependent on concept 19, it is dependent on concept 19g, when dependent on concept 20, it is dependent on concept 20g, when dependent on concept 22, it is dependent on concept 22g, when dependent on concept 23, it is dependent on concept 23g, and when dependent on concept 24, it is dependent on concept 24g), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:188, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:188.

Concept 25h: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9h, when dependent on concept 13, it is dependent on concept 13h, when dependent on concept 16, it is dependent on concept 16h, when dependent on concept 17, it is dependent on concept 17h, when dependent on concept 18, it is dependent on concept 18h, when dependent on concept 19, it is dependent on concept 19h, when dependent on concept 20, it is dependent on concept 20h, when dependent on concept 22, it is dependent on concept 22h, when dependent on concept 23, it is dependent on concept 23h, and when dependent on concept 24, it is dependent on concept 24h), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:148, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:148.

Concept 25i: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9i, when dependent on concept 13, it is dependent on concept 13i, when dependent on concept 16, it is dependent on concept 16i, when dependent on concept 17, it is dependent on concept 17i, when dependent on concept 18, it is dependent on concept 18i, when dependent on concept 19, it is dependent on concept 19i, when dependent on concept 20, it is dependent on concept 20i, when dependent on concept 22, it is dependent on concept 22i, when dependent on concept 23, it is dependent on concept 23i, and when dependent on concept 24, it is dependent on concept 24i), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:254, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:254.

Concept 25j: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9j, when dependent on concept 13, it is dependent on concept 13j, when dependent on concept 16, it is dependent on concept 16j, when dependent on concept 17, it is dependent on concept 17j, when dependent on concept 18, it is dependent on concept 18j, when dependent on concept 19, it is dependent on concept 19j, when dependent on concept 20, it is dependent on concept 20j, when dependent on concept 22, it is dependent on concept 22j, when dependent on concept 23, it is dependent on concept 23j, and when dependent on concept 24, it is dependent on concept 24j), wherein the V_L domain comprises an amino

acid sequence of SEQ ID NO:274, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:274.

Concept 25k: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9k, when dependent on concept 13, it is dependent on concept 13k, when dependent on concept 16, it is dependent on concept 16k, when dependent on concept 17, it is dependent on concept 17k, when dependent on concept 18, it is dependent on concept 18k, when dependent on concept 19, it is dependent on concept 19k, when dependent on concept 20, it is dependent on concept 20k, when dependent on concept 22, it is dependent on concept 22k, when dependent on concept 23, it is dependent on concept 23k, and when dependent on concept 24, it is dependent on concept 24k), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:294, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:294.

Concept 25l: An antibody or a fragment thereof according to any preceding concept (but when dependent on concept 9, it is dependent on concept 9l, when dependent on concept 13, it is dependent on concept 13l, when dependent on concept 16, it is dependent on concept 16l, when dependent on concept 17, it is dependent on concept 17l, when dependent on concept 18, it is dependent on concept 18l, when dependent on concept 19, it is dependent on concept 19l, when dependent on concept 20, it is dependent on concept 20l, when dependent on concept 22, it is dependent on concept 22l, when dependent on concept 23, it is dependent on concept 23l, and when dependent on concept 24, it is dependent on concept 24l), wherein the V_L domain comprises an amino acid sequence of SEQ ID NO:359, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:359.

In one embodiment, the amino acid sequence is at least 70% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 75% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 95% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 96% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 97% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 98% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99.5% identical to the specified Seq ID No.

Concept 26. The antibody or fragment according to any one of concepts 12 to 21, comprising first and second copies of a or said V_L domain.

Concept 27. The antibody or fragment according to any preceding concept which specifically binds to cynomolgus PD-L1 as defined by Seq ID No:2.

In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of less than 1 nM (e.g. from 1 nM to 0.01 pM or from 1 nM to 0.1 pM, or from 1 nM to 1pM). In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of less than 10 nM (e.g. from 10 nM to 0.01 pM or from 10 nM to 0.1 pM, or from 10 nM to 1pM). In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of less than 0.1 nM (e.g. from 0.1 nM to 0.01 pM or from 0.1 nM to 0.1 pM, or from 0.1 nM to 1pM). In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of less than 0.01 nM (e.g. from 0.011 nM to 0.01 pM or from 0.01 nM to 0.1 pM).

In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of within 2-fold of the affinity to hPD-L1. In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of within 4-fold of the affinity to hPD-L1. In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of within 5-fold of the affinity to hPD-L1. In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of within 6-fold of the affinity to hPD-L1. In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of within 8-fold of the affinity to hPD-L1. In one embodiment, the antibody or fragment binds to cynomolgus PD-L1 with an affinity of within 10-fold of the affinity to hPD-L1.

In one embodiment, the antibody or fragment does not detectably bind to cynomolgus PD-L1. In one embodiment, the antibody or fragment does not detectably bind to murine PD-L1.

In one embodiment, the antibody or fragment binds to murine PD-L1 with an affinity of less than 1 nM (e.g. from 1 nM to 0.01 pM or from 1 nM to 0.1 pM, or from 1 nM to 1pM). In one embodiment, the antibody or fragment binds to murine PD-L1 with an affinity of less than 10 nM (e.g. from 10 nM to 0.01 pM or from 10 nM to 0.1 pM, or from 10 nM to 1pM). In one embodiment, the antibody or fragment binds to murine PD-L1 with an affinity of less than 0.1 nM (e.g. from 0.1 nM to 0.01 pM or from 0.1 nM to 0.1 pM, or from 0.1 nM to 1pM). In one embodiment, the antibody or fragment binds to murine PD-L1 with an affinity of less than 0.01 nM (e.g. from 0.011 nM to 0.01 pM or from 0.01 nM to 0.1 pM).

Concept 28. The antibody or fragment according to any preceding concept, wherein the antibody or fragment comprises a kappa light chain.

Kappa light chain constant region amino acid and nucleotide sequences can be found in Seq ID Nos:206 to 215.

In one embodiment, the light chain may be a lambda light chain. Lambda light chain constant region amino acid and nucleotide sequences can be found in Seq ID Nos:216 to 237 and Seq ID No:535, Seq ID No:536 and Seq ID No:538.

Concept 29. The antibody or fragment according to any one of concepts 9 to 28, wherein the amino acid substitutions are conservative amino acid substitutions, optionally wherein the conservative

substitutions are from one of six groups (each group containing amino acids that are conservative substitutions for one another) selected from:

1) Alanine (A), Serine (S), Threonine (T);

2) Aspartic acid (D), Glutamic acid (E);

3) Asparagine (N), Glutamine (Q);

4) Arginine (R), Lysine (K);

5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and

6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

Conservative substitutions may be as described above in concept 9.

Concept 30. The antibody or fragment according to any preceding concept, wherein the antibody or fragment comprises a constant region, such as a human constant region, for example an effector-null human constant region, e.g. an IgG4 constant region or an IgG1 constant region, optionally wherein the constant region is IgG4-PE (Seq ID No:199), or a disabled IgG1 as defined in Seq ID No:205.

In other embodiments, the antibody or fragment is any of the isotypes or constant regions as defined hereinabove. In one embodiment, the constant region is wild-type human IgG1 (Seq ID No:340). For example, the constant region is an effector-enabled IgG1 constant region, optionally having ADCC and/or CDC activity. In one embodiment, the constant region is engineered for enhanced ADCC and/or CDC and/or ADCP. In another embodiment, the constant region is engineered for enhanced effector function.

The IgG4 constant region may be any of the IgG4 constant region amino acid sequences, or encoded by any of the nucleic acid sequences of Seq ID Nos:192 to 203. A heavy chain constant region may be an IgG4 comprising both the Leu235Glu mutation and the Ser228Pro mutation. This "IgG4-PE" heavy chain constant region (Seq ID Nos:198, encoded by Seq ID Nos:199, 200 and 201) is effector null.

An alternative effector null human constant region is a disabled IgG1 being an IgG1*01 allele comprising the L235A and/or G237A mutations (e.g. LAGA, Seq ID No:204, encoded by Seq ID No:205). In one embodiment, the antibodies or antibody fragments disclosed herein comprise an IgG1 heavy chain constant region, wherein the sequence contains alanine at position 235 and/or 237 (EU index numbering).

The antibody-dependent cell phagocytosis (ADCP) mechanism is discussed in Gül , "Antibody-Dependent Phagocytosis of Tumor Cells by Macrophages: A Potent Effector Mechanism of Monoclonal Antibody Therapy of Cancer", Cancer Res., 75(23), December 1, 2015.

The potency of Fc-mediated effects may be enhanced by engineering the Fc domain by various established techniques. Such methods increase the affinity for certain Fc-receptors, thus creating potential diverse profiles of activation enhancement. This can be achieved by modification of one or several amino acid residues (e.g. as described in Lazar , 2006, Proc. Natl. Acad. Sci. U.S.A., Mar 14; 103(11):4005-10; the modifications disclosed therein are incorporated herein by reference).

Human IgG1 constant regions containing specific mutations or altered glycosylation on residue Asn297 (e.g. N297Q, EU index numbering) have been shown to enhance binding to Fc receptors. In one embodiment, such mutations are one or more of the residues selected from 239, 332 and 330 for human IgG1 constant regions (or the equivalent positions in other IgG isotypes). In one embodiment, the antibody or fragment comprises a human IgG1 constant region having one or more mutations independently selected from N297Q, S239D, I332E and A330L (EU index numbering).

In another embodiment, the increase in affinity for Fc-receptors is achieved by altering the natural glycosylation profile of the Fc domain by, for example, generating under fucosylated or de-fucosylated variants (as described in Natsume , 2009, Drug Des. Devel. Ther., 3:7–16 or by Zhou Q., Biotechnol. Bioeng., 2008, Feb 15, 99(3):652-65, the modifications described therein are incorporated herein by reference). Non-fucosylated antibodies harbour a tri-mannosyl core structure of complex-type N-glycans of Fc without fucose residue. These glycoengineered antibodies that lack core fucose residue from the Fc N-glycans may exhibit stronger ADCC than fucosylated equivalents due to enhancement of Fc RIIIa binding capacity. For example, to increase ADCC, residues in the hinge region can be altered to increase binding to Fc- RIII (see, for example, Shields , 2001, J. Biol. Chem., Mar 2; 276(9):6591-604; the modifications described therein are incorporated herein by reference). Thus, in one embodiment, the antibody or fragment comprises a human IgG heavy chain constant region that is a variant of a wild-type human IgG heavy chain constant region, wherein the variant human IgG heavy chain constant region binds to human Fc receptors selected from the group consisting of FcyRIIB and FcyRIIA with higher affinity than the wild type human IgG heavy chain constant region binds to the human Fc receptors. In one embodiment, the antibody or fragment comprises a human IgG heavy chain constant region that is a variant of a wild type human IgG heavy chain constant region, wherein the variant human IgG heavy chain constant region binds to human Fc RIIB with higher affinity than the wild type human IgG heavy chain constant region binds to human Fc RIIB. In one embodiment, the variant human IgG heavy chain constant region is a variant human IgG1, a variant human IgG2, or a variant human IgG4 heavy chain constant region. In one embodiment, the variant human IgG heavy chain constant region comprises one or more amino acid mutations selected from G236D, P238D, S239D, S267E, L328F, and L328E (EU index numbering system). In another embodiment, the variant human IgG heavy chain constant region comprises a set of amino acid mutations selected from the group consisting of: S267E and L328F; P238D and L328E; P238D and one or more substitutions selected from the group consisting of E233D, G237D, H268D, P271G, and A330R; P238D, E233D, G237D, H268D, P271G, and A330R; G236D and S267E; S239D and S267E; V262E, S267E, and L328F; and V264E, S267E, and L328F (EU index numbering system). In another embodiment, the variant human IgG heavy chain constant region further comprises one or more amino acid mutations that reduce the affinity of the IgG for human Fc RIIIA, human Fc RIIA, or human Fc RI. In one embodiments, the Fc RIIB is expressed on a cell selected from the group consisting of macrophages, monocytes, B-cells, dendritic cells, endothelial cells, and activated T-cells. In one embodiment, the variant human IgG heavy chain constant region comprises one or more of

the following amino acid mutations G236A, S239D, F243L, T256A, K290A, R292P, S298A, Y300L, V305I, A330L, I332E, E333A, K334A, A339T, and P396L (EU index numbering system). In one embodiment, the variant human IgG heavy chain constant region comprises a set of amino acid mutations selected from the group consisting of: S239D; T256A; K290A; S298A; I332E; E333A; K334A; A339T; S239D and I332E; S239D, A330L, and I332E; S298A, E333A, and K334A; G236A, S239D, and I332E; and F243L, R292P, Y300L, V305I, and P396L (EU index numbering system). In one embodiment, the variant human IgG heavy chain constant region comprises a S239D, A330L, or I332E amino acid mutations (EU index numbering system). In one embodiment, the variant human IgG heavy chain constant region comprises an S239D and I332E amino acid mutations (EU index numbering system). In one embodiment, the variant human IgG heavy chain constant region is a variant human IgG1 heavy chain constant region comprising the S239D and I332E amino acid mutations (EU index numbering system). In one embodiment, the antibody or fragment comprises an afucosylated Fc region. In another embodiment, the antibody or fragment thereof is defucosylated. In another embodiment, the antibody or fragment is under fucosylated.

In another embodiment, the antibodies and fragments disclosed herein may comprise a triple mutation (M252Y/S254T/T256E) which enhances binding to FcRn. See Dall ., Immunol 2002; 169:5171-5180 for a discussion of mutations affection FcRn binding in table 2, the mutations described therien are incorporated herein by reference.

Equally, the enhancement of CDC may be achieved by amino acid changes that increase affinity for C1q, the first component of the classic complement activation cascade (see Idusogie , J. Immunol., 2001, 166:2571–2575; the modifications described are incorporated herein by reference). Another approach is to create a chimeric Fc domain created from human IgG1 and human IgG3 segments that exploit the higher affinity if IgG3 for C1q (Natsume , 2008, Cancer Res., 68: 3863–3872; the modifications are incorporated herein by reference). In another embodiment, the antibody or antibody fragments disclosed herein may comprise mutated amino acids at residues 329, 331 and/or 322 to alter the C1q binding and/or reduced or abolished CDC activity. In another embodiment, the antibodies or antibody fragments disclosed herein may contain Fc regions with modifications at residues 231 and 239, whereby the amino acids are replaced to alter the ability of the antibody to fix complement. In one embodiment, the antibody or fragment has a constant region comprising one or more mutations selected from E345K, E430G, R344D and D356R, in particular a double mutation comprising R344D and D356R (EU index numbering system).

An antibody may have a heavy chain constant region that binds one or more types of Fc receptor but does not induce cellular effector functions, i.e. which does not mediate ADCC, CDC or ADCP activity. Such a constant region may be unable to bind the particular Fc receptor(s) responsible for triggering ADCC, CDC or ADCP activity. An antibody may have a heavy chain constant region that does not bind Fc receptors. Thus, in one embodiment, the constant region may comprise a Leu235Glu mutation (EU index numbering system).

In another embodiment, the antibodies and fragments disclosed herein are modified to increase or decrease serum half-life. In one embodiment, one or more of the following mutations: T252L, T254S or T256F are introduced to increase biological half-life of the antibody. Biological half-life can also be increased by altering the heavy chain constant region CH_1 domain or CL region to contain a salvage receptor binding epitope taken from two loops of a CH_2 domain of an Fc region of an IgG, as described in U.S. Patent Numbers. 5,869,046 and 6,121,022, the modifications described therein are incorporated herein by reference. In another embodiment, the Fc hinge region of an antibody or antigen-binding fragment of the invention is mutated to decrease the biological half-life of the antibody or fragment. One or more amino acid mutations are introduced into the CH_2-CH_3 domain interface region of the Fc-hinge fragment such that the antibody or fragment has impaired Staphylococcyl protein A (SpA) binding relative to native Fc-hinge domain SpA binding. Other methods of increasing serum half-life are known to those skilled in the art. Thus, in one embodiment, the antibody or fragment is PEGylated. In another embodiment, the antibody or fragment is fused to an albumin-bidnig domain, e.g. an albumin binding single domain antibody (dAb). In another embodiment, the antibody or fragment is PASylated (i.e. genetic fusion of polypeptide sequences composed of PAS (XL-Protein GmbH) which forms uncharged random coil structures with large hydrodynamic volume). In another embodiment, the antibody or fragment is XTENylated®/rPEGylated (i.e. genetic fusion of non-exact repeat peptide sequence (Amunix, Versartis) to the therapeutic peptide). In another embodiment, the antibody or fragment is ELPylated (i.e. genetic fusion to ELP repeat sequence (PhaseBio)). These various half-life extending fusions are described in more detail in Strohl, BioDrugs (2015) 29:215–239, which fusions, e.g. in Tables 2 and 6, are incorporated herein by reference.

The antibody may have a modified constant region which increases stabililty. Thus, in one embodiment, the heavy chain constant region comprises a Ser228Pro mutation. In another embodiment, the antibodies and fragments disclosed herein comprise a heavy chain hinge region that has been modified to alter the number of cysteine residues. This modification can be used to facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

Concept 31. The antibody or fragment according to concept 30, wherein the constant region is a murine constant region.

In other embodiments, the constant region may be of any non-human mammalian origin, e.g. rat, mouse, hamster, guinea pig, dog, cat, horse, chicken, llama, dromedary, etc. In one embodiment, the constant region is a rat constant region. In another embodiment, the constant region is a llama constant region. The murine constant region may be any of the isotypes or alleles described hereinabove.

Concept 32. The antibody or fragment according to concept 30 or concept 31, wherein the constant region has CDC and/or ADCC activity.

Concept 33. The antibody according to any preceding concept wherein the:

a) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

b) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:33, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:43;

c) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

d) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

e) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

f) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:342 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

g) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

h) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

i) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

j) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

k) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:342 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

l) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

m) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

n) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

o) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

p) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:342 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

q) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

r) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

s) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

t) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

u) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:342 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

v) V_H domain comprises an amino acid sequence of SEQ ID No:58 and the V_L domain comprises an amino acid sequence of SEQ ID No:68;

w) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:58, and the V_L domain comprise an amino acid sequence that is at least 85% identical to SEQ ID No:68;

x) V_H domain comprises an amino acid sequence of SEQ ID No:78 and the V_L domain comprises an amino acid sequence of SEQ ID No:88;

y) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:78, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:88;

z) V_H domain comprises an amino acid sequence of SEQ ID No:98 and the V_L domain comprises an amino acid sequence of SEQ ID No:108;

aa) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:98, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:108;

bb) V_H domain comprises an amino acid sequence of SEQ ID No:118 and the V_L domain comprises an amino acid sequence of SEQ ID No:128;

cc) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:118, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:128;

dd) V_H domain comprises an amino acid sequence of SEQ ID No:158 and the V_L domain comprises an amino acid sequence of SEQ ID No:168;

ee) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:158, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:168;

ff) V_H domain comprises an amino acid sequence of SEQ ID No:178 and the V_L domain comprises an amino acid sequence of SEQ ID No:188;

gg) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:178, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:188;

hh) V_H domain comprises an amino acid sequence of SEQ ID No:138 and the V_L domain comprises an amino acid sequence of SEQ ID No:148;

ii) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:138 and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:148;

jj) V_H domain comprises an amino acid sequence of SEQ ID No:244 and the V_L domain comprises an amino acid sequence of SEQ ID No:254;

kk) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:244, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:254;

ll) V_H domain comprises an amino acid sequence of SEQ ID No:264 and the V_L domain comprises an amino acid sequence of SEQ ID No:274;

mm) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:264, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:274;

nn) V_H domain comprises an amino acid sequence of SEQ ID No:284 and the V_L domain comprises an amino acid sequence of SEQ ID No:294; and

oo) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:284, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:294;

pp) V_H domain comprises an amino acid sequence of SEQ ID No:349 and the V_L domain comprises an amino acid sequence of SEQ ID No:359; and

qq) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:349, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:359.

In one embodiment, the amino acid sequence is at least 70% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 75% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 95% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 96% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 97% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 98% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99.5% identical to the specified Seq ID No.

Concept 34. The antibody according to any preceding concept wherein the antibody comprises a heavy chain and a light chain, and

a) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

b) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:45;

c) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:47 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

d) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:48 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

e) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:49 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

f) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:342 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

g) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

h) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:47 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

i) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:48 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

j) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:49 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

k) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:342 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

l) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

m) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:47 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

n) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:48 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

o) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:49 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

p) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:342 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

q) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

r) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:47 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

s) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:48 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

t) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:49 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

u) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:342 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

v) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:60 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:70;

w) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:60, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:70;

x) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:80 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:90;

y) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:80, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:90;

z) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:100 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:110;

aa) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:100, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:110;

bb) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:120 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:130;

cc) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:120, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:130;

dd) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:160 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:170;

ee) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:160, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:170;

ff) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:180 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:190;

gg) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:180, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:190

hh) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:140 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:150;

ii) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:140, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:150;

jj) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:246 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:256;

kk) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:246, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:256;

ll) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:266 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:276;

mm) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:266, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:276;

nn) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:286 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:296; and

oo) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:286, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:296;

pp) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:351 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:361; and

qq) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:351, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:361.

In one embodiment, the amino acid sequence is at least 70% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 75% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 95% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 96% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 97% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 98% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99.5% identical to the specified Seq ID No.

Concept 35. The antibody or fragment according to any preceding concept which competes for binding to hPD-L1 with the antibody 1D05, optionally wherein the competition for binding to hPD-L1 is conducted using SPR.

SPR may be carried out as described hereinabove, or as described in concept 16.

Concept 36. The antibody or fragment according to any preceding concept wherein the antibody or fragment is capable of inhibiting PD-L1-mediated suppression of T-cells, optionally wherein the suppression of T-cells is measured by an increase in one or more of IFN , IL-2, CD25 or proliferation of T-cells in an assay that provides co-stimulation by either direct CD3/CD28 stimulation, superantigen stimulation or provides co-stimulation by co-incubation with cells capable of inducing a T-cell response.

The measurements may be carried out with any suitable technique. For example, the measurements may be taken with ELISA, HTRF, BRDU incorporation (proliferation), electrochemiluminescence (ECL) or flow cytometry (e.g. FACS). These techniques are well-known to those skilled in the art and are described elsewhere herein. In one embodiment, the assay is flow cytometry. In one embodiment, the assay is ELISA. In one embodiment, the assay is HTRF.

In one embodiment, the suppression of T-cells is measured by an increase in IFN . In one embodiment, the suppression of T-cells is measured by an increase in IL-2. In one embodiment, the suppression of T-cells is measured by an increase in CD25. In one embodiment, the suppression of T-cells is measured by an increase in IFN and IL-2. In one embodiment, the suppression of T-cells is measured by an increase in IFN and CD25. In one embodiment, the suppression of T-cells is measured by an increase in CD25 and IL-2. In one embodiment, the suppression of T-cells is measured by an increase in IFN , IL-2 and CD25.

In one embodiment, the co-stimulation is provided by direct CD3/CD28 stimulation.

In one embodiment, the co-stimulation is provided by a superantigen, such as staphylococcal enterotoxin B (SEB).

In one embodiment, the assay provides co-stimulation by co-incubation with cells capable of inducing a T-cell response. Such cells may be antigen-presenting cells (APCs), for example monocytes, B-cells or dendritic cells. In one embodiment, the assay provides co-stimulation by co-incubation with APCs. In one embodiment, the assay provides co-stimulation by co-incubation with monocytes. In one embodiment, the assay provides co-stimulation by co-incubation with B-cells. In one embodiment, the assay provides co-stimulation by co-incubation with dendritic cells.

Concept 37. A bispecific antibody or fusion protein comprising an antibody or fragment thereof as defined in any preceding concept.

Concept 37a. A dual binding antibody or fusion protein comprising an antibody or fragment thereof as defined in any preceding concept.

A dual binding antibody has the meaning as set out above.

Concept 38. The bispecific antibody according to concept 37, wherein the bispecific format is selected from DVD-Ig, mAb^2, FIT-Ig, mAb-dAb, dock and lock, SEEDbody, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH_3, Diabody-CH_3, minibody, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, in particular mAb^2, knob-in-holes, knob-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs and FIT-Ig, e.g. mAb^2 and FIT-Ig.

In one embodiment, the bispecific format is selected from DVD-Ig, mAb^2, FIT-Ig, mAb-dAb, dock and lock, Fab-arm exchange, SEEDbody, Triomab, LUZ- -body, orthogonal Fab, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART,

TandAb, scDiabody, scDiabody-CH_3, Diabody-CH_3, Triple body, Miniantibody, minibody, TriBi minibody, scFv-CH_3 KIH, scFv-CH-CL-scFv, F(ab')$_2$-scFv, scFv-KIH, Fab-scFv-Fc, tetravalent HCab, ImmTAC, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, DT-IgG, DutaMab, IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv, scFv4-Ig and zybody.

In one embodiment, the bispecific format is selected from DVD-Ig, FIT-Ig, mAb-dAb, dock and lock, Fab-arm exchange, SEEDbody, Triomab, LUZ- -body, orthogonal Fab, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH_3, Diabody-CH_3, Triple body, Miniantibody, minibody, TriBi minibody, scFv-CH_3 KIH, scFv-CH-CL-scFv, F(ab')$_2$-scFv, scFv-KIH, Fab-scFv-Fc, tetravalent HCab, ImmTAC, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, DT-IgG, DutaMab, IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv, scFv4-Ig and zybody, for example DVD-Ig, FIT-Ig, mAb-dAb, dock and lock, SEEDbody, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH_3, Diabody-CH_3, minibody, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, in particular knob-in-holes, knob-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs and FIT-Ig, e.g. FIT-Ig.

In one embodiment, the bispecific format is selected from DVD-Ig, mAb^2, mAb-dAb, dock and lock, Fab-arm exchange, SEEDbody, Triomab, LUZ- -body, orthogonal Fab, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH_3, Diabody-CH_3, Triple body, Miniantibody, minibody, TriBi minibody, scFv-CH_3 KIH, scFv-CH-CL-scFv, F(ab')$_2$-scFv, scFv-KIH, Fab-scFv-Fc, tetravalent HCab, ImmTAC, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, DT-IgG, DutaMab, IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv, scFv4-Ig and zybody, for example DVD-Ig, mAb^2, mAb-dAb, dock and lock, SEEDbody, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH_3, Diabody-CH_3, minibody, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, in particular mAb^2, knob-in-holes, knobs-in-holes with common light chain and charge pairs, and knob-in-holes with common light chain, e.g. mAb^2.

In one embodiment, the bispecific format is selected from DVD-Ig, mAb-dAb, dock and lock, Fab-arm exchange, SEEDbody, Triomab, LUZ- -body, orthogonal Fab, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb,

scDiabody, scDiabody-CH_3, Diabody-CH_3, Triple body, Miniantibody, minibody, TriBi minibody, scFv-CH_3 KIH, scFv-CH-CL-scFv, F(ab')$_2$-scFv, scFv-KIH, Fab-scFv-Fc, tetravalent HCab, ImmTAC, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, DT-IgG, DutaMab, IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv, scFv4-Ig and zybody, for example DVD-Ig, mAb-dAb, dock and lock, SEEDbody, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH_3, Diabody-CH_3, minibody, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, in particular knob-in-holes, knobs-in-holes with common light chain and charge pairs, and knob-in-holes with common light chain.

Concept 39. The bispecific antibody according to concept 37 or concept 38, wherein the bispecific antibody specifically binds to hPD-L1 and another target antigen selected from immune checkpoint inhibitors (such as PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. TIGIT, TIM-3 and LAG-3), immune modulators (such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD , CXCL11 and CD155, e.
and CSF1R), immune activators (such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies), CD27, CD3, ICOS (e.g. agonistic anti-ICOS antibodies), for example. ICOS, CD137, GITR and OX40).

Concept 39a. A bispecific antibody which binds to hPD-L1 with a V_H, a V_L, or a paired V_H and V_L comprising one or more of the CDRs (e.g. CDRH3 and CDRL3) or variable region sequences of any of the antibodies described in Aspect 1a hereinbelow, and another target antigen selected from immune checkpoint inhibitors (such as PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. TIGIT, TIM-3 and LAG-3), immune modulators (such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10, CXCL11
CXCR4, BTLA, hVEM and CSF1R), immune activators (such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies), CD27, CD3, ICOS (e.g. agonistic anti-ICOS antibodies), for example. ICOS, CD137, GITR and OX40).

Concept 39b. The bispecific antibody according to concept 37 or concept 38, wherein the bispecific antibody specifically binds to hPD-L1 and another target antigen selected from immune checkpoint inhibitors (such as PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. TIGIT, TIM-3 and LAG-3), immune modulators (such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10 and CD155, e.g. GARP, SIRPα, CXCR4, BTLA, hVEM and CSF1R), immune activators (such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies), CD3, ICOS (e.g. agonistic anti-ICOS antibodies), for example. ICOS, CD137, GITR and OX40).

In one embodiment, the another target antigen is an immune checkpoint inhibitor, such as PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. TIGIT, CTLA-4, TIM-3 and LAG-3. In one embodiment, the another target antigen is an immune modulator, such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD , CXCL11 and CD155, or such as such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, and CD155 e.g. GARP, SIRPα, CXCR4, BTLA, hVEM and CSF1R. In one embodiment, the another target antigen is an immune activator, such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies), CD27, CD3 and ICOS (e.g. agonistic anti-ICOS antibodies), or CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies), CD3 and ICOS (e.g. agonistic anti-ICOS antibodies), for example ICOS, CD137, GITR and OX40). In one embodiment, the another target antigen is CTLA-4. In one embodiment, the another target antigen is TIGIT. In one embodiment, the another target antigen is TIM-3. In one embodiment, the another target antigen is LAG-3. In one embodiment, the another target antigen is GITR. In one embodiment, the another target antigen is VISTA. In one embodiment, the another target antigen is CD137. In one embodiment, the another target antigen is In one embodiment, the another target antigen is CXCL10. In one embodiment, the another target antigen is CD155. In one embodiment, the another target antigen is CD40.

In another embodiment, the bispecific antibody binds another target antigen which is PD-1 and the binding to PD-1 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CTLA4 and the binding to CTLA4 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is TIGIT and the binding to TIGIT is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is TIM-3 and the binding to TIM-3 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is LAG3 and the binding to LAG3 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is VISTA and the binding to VISTA is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is BTLA and the binding to BTLA is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is hHVEM and the binding to hHVEM is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CSF1R and the binding to CSF1R is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CCR4 and the binding to CCR4 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD39 and the binding to CD39 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD40 and the binding to CD40 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD73 and the binding to CD73 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD96 and the binding to CD96 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CXCR2 and the binding to CXCR2 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CXCR4 and the binding to CXCR4 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD200 and the binding to CD200 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is GARP and the binding to GARP is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is SIRPα and the binding to -binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CXCL9 and the binding to CXCL9 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CXCL10 and the binding to CXCL10 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CXCL11 and the binding to CXCL11 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD155 and the binding to CD155 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD137 and the binding to CD137 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is GITR and the binding to GITR is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is OX40 and the binding to OX40 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD40 and the binding to CD40 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CXCR3 and the binding to CXCR3 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD27 and the binding to CD27 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is CD3 and the binding to CD3 is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in Aspect 1A hereinbelow.

In another embodiment, the bispecific antibody binds another target antigen which is ICOS and the binding to ICOS is provided by an antigen-binding domain (for example, a V_H, a V_L or a paired V_H and V_L) having any of the sequences, including CDR sequences (for example CDRH3 and/or CDRL3) or variable region sequences as described in arrangement 5 and arrangement 5a hereinbelow, and any of the anti-ICOS antibodies described in sentences 1 to 102 and sentences 1a to 21a.

In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs

and variable regions – as defined in Aspect 1a hereinbelow) and a Fab which binds GITR (optionally wherein the GITR Fab has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow). In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds GITR (optionally wherein the GITR antibody has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow) and a Fab which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow). In one embodiment, the FIT-Ig is effector-enabled (e.g. as described in any of concepts 30 to 32). In another embodiment, the FIT-Ig is effector-disabled (e.g. is an IgG4 format, or as described in any of concepts 30 to 31).

In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow) and a Fab which binds ICOS (e.g. binds with agonistic activity and optionally wherein the ICOS Fab has a sequence – including CDRs and variable regions - as defined in arrangement 5, or in arrangement 5a, or in sentences 1 to 102, or in sentences 1a to 21a hereinbelow). In one embodiment, the ICOS Fab has a sequence of any of the ICOS antibodies described herein in sentences 1 to 102 or in sentences 1a to 21a) In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds ICOS (e.g. binds with agonistic activity or optionally wherein the ICOS antibody has a sequence – including CDRs and variable regions - as defined in arrangement 5, or in arrangement 5a, or in sentences 1 to 102, or in sentences 1a to 21a hereinbelow) and a Fab which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1A hereinbelow). In one embodiment, the FIT-Ig is effector-enabled (e.g. as described in any of concepts 30 to 32). In another embodiment, the FIT-Ig is effector-disabled (e.g. is an IgG4 format, or as described in any of concepts 30 or 31).

In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow) and a Fab which binds TIM-3 (optionally wherein the TIM-3 Fab has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow). In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a

full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds TIM-3 (optionally wherein the TIM-3 antibody has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow) and a Fab which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow). In one embodiment, the FIT-Ig is effector-enabled (e.g. as described in any of concepts 30 to 32). In another embodiment, the FIT-Ig is effector-disabled (e.g. is an IgG4 format, or as described in any of concepts 30 or 31).

In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow) and a Fab which binds CD137 (optionally wherein the CD137 Fab has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow). In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds CD137 (optionally wherein the CD137 antibody has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow) and a Fab which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow). In one embodiment, the FIT-Ig is effector-enabled (e.g. as described in any of concepts 30 to 32). In another embodiment, the FIT-Ig is effector-disabled (e.g. is an IgG4 format, or as described in any of concepts 30 or 31).

In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow) and a Fab which binds CD3 (optionally wherein the CD3 Fab has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow). In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds CD3 (optionally wherein the CD3 antibody has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow) and a Fab which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow). In one embodiment, the FIT-Ig is effector-enabled (e.g. as described in

any of concepts 30 to 32). In another embodiment, the FIT-Ig is effector-disabled (e.g. is an IgG4 format, or as described in any of concepts 30 or 31).

Any of the targets listed above (and the Fabs and/or full antibodies described in more detail in Aspect 1A) may be applied to the FIT-Ig structure.

Concept 40. The bispecific antibody according to concept 39, wherein the another target antigen is TIGIT or LAG3.

In any of concepts 37 to 40, if the antibody or fragment thereof has the heavy and light variable region sequences of 84G09, then the bispecific antibody shall be interpreted as not including a mAb^2 format wherein the Fcab has binding affinity to LAG3.

In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and CL and a heavy chain comprising V_H, C_H1, C_H2 and C_H3) which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow) and a Fab which binds TIGIT (optionally wherein the TIGIT Fab has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow). In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds TIGIT (optionally wherein the TIGIT antibody has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow) and a Fab which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow). In one embodiment, the FIT-Ig is effector-enabled (e.g. as described in any of concepts 30 to 32). In another embodiment, the FIT-Ig is effector-disabled (e.g. is an IgG4 format, or as described in any of concepts 30 or 31).

In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and CL and a heavy chain comprising V_H, C_H1, C_H2 and C_H3) which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow) and a Fab which binds LAG3 (optionally wherein the LAG3 Fab has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow). In one embodiment, the bispecific antibody has a FIT-Ig format which comprises a full antibody (e.g. an antibody comprising a light chain comprising a V_L and C_L and a heavy chain comprising V_H, CH_1, CH_2 and CH_3) which binds LAG3 (optionally wherein the LAG3 antibody has a sequence – including CDRs and variable regions - as defined in Aspect 1a hereinbelow) and a Fab which binds hPD-L1 (optionally wherein the antibody has a structure as defined in any one of concepts 1 to 40, or wherein the antibody has a sequence – including CDRs and variable regions – as defined in Aspect 1a hereinbelow). In one embodiment, the FIT-Ig is effector-enabled (e.g. as described in

any of concepts 30 to 32). In another embodiment, the FIT-Ig is effector-disabled (e.g. is an IgG4 format, or as described in any of concepts 30 or 31).

Concept 41. An antibody or fragment as defined in any preceding concept for use in treating or preventing a hPD-L1-mediated disease or condition, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma). (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

Concept 42. Use of an antibody or fragment as defined in any one of concepts 1 to 40 in the manufacture of a medicament for administration to a human for treating or preventing a hPD-L1 mediated disease or condition in the human, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

Concept 43. A method of treating or preventing a hPD-L1 mediated disease or condition, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas) in a human, comprising administering to said human a therapeutically effective amount of an antibody or fragment as defined in any one of concepts 1 to 40, wherein the hPD-L1 mediated disease or condition is thereby treated or prevented.

In any of concepts 41 to 43, the hPD-L1 mediated disease may be any of those as described herein. In one embodiment, in any of concepts 41 to 43, the hPD-L1 mediated disease is a virally induced cancer, such as cervical cancer and nasopharyngeal cancer, for example cervical cancers caused by HPV infection. In one embodiment, in any of concepts 41 to 43, the hPD-L1 mediated disease is a chronic viral infection. In one embodiment, in any of concepts 41 to 43, the hPD-L1 mediated disease is a neoplastic disease. In one embodiment, in any of concepts 41 to 43, the hPD-L1 mediated disease is a non-neoplastic disease. In one embodiment, in any of concepts 41 to 43, the hPD-L1 mediated disease is a malignant tumour. In one embodiment, in any of concepts 41 to 43, the hPD-L1 mediated disease is a cancer which is known to be responsive to PD-L1 therapy, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma. In one embodiment, in any of concepts 41 to 43, the hPD-L1 mediated disease is a cancer which is a soft tissue sarcoma.

Concept 44. The antibody or fragment according to concept 41, the use according to concept 42 or the method according to concept 43, wherein the hPD-L1-mediated disease or condition is cancer.

Concept 44a. The antibody or fragment according to concept 41, the use according to concept 42 or the method according to concept 43, wherein the hPD-L1-mediated disease or condition is a neurodegenerative disease, disorder or condition, optionally wherein the neurodegenerative disease, disorder or condition is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, corticobasal degeneration, Rett syndrome, a retinal degeneration disorder selected from age-related macular degeneration and retinitis pigmentosa; anterior ischemic optic neuropathy, glaucoma, uveitis, depression, trauma-associated stress or post-traumatic stress disorder, frontotemporal dementia, Lewy body dementias, mild cognitive impairments, posterior cortical atrophy, primary progressive aphasia and progressive supranuclear palsy or aged-related dementia, in particular Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease, and e.g. Alzheimer's disease.

In concept 44a, the therapeutically effective amount of an antibody or fragment may comprise an antigen-binding site that specifically binds PD-L1, e.g. hPD-L1.

In one embodiment, the antigen-binding site specifically binds PD-L1, e.g. hPD-L1. In one embodiment, the PD-L1 antigen-binding site comprises the CDRH1, CDRH2, CDR3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from any one of the anti-PD-L1 antibodies selected from atezolizumab (Roche), avelumab (Merck), BMS-936559/MDX-1105 (BMS), durvalumab/Medi4736 (Medimmune), KN-035, CA-170, FAZ-053 M7824, ABBV-368, LY-3300054, GNS-1480, YW243.55.S70, REGN3504 and any of the PD-L1 antibodies disclosed in WO2017/034916, WO2017/020291, WO2017/020858, WO2017/020801, WO2016/111645, WO2016/197367, WO2016/061142, WO2016/149201, WO2016/000619, WO2016/160792, WO2016/022630,

WO2016/007235, WO2015/179654, WO2015/173267, WO2015/181342, WO2015/109124, WO2015/112805, WO2015/061668, WO2014/159562, WO2014/165082, WO2014/100079, WO2014/055897, WO2013/181634, WO2013/173223, WO2013/079174, WO2012/145493, WO2011/066389, WO2010/077634, WO2010/036959, WO2010/089411 or WO2007/005874, which antibodies and sequences are incorporated herein by reference.

In another embodiment of concept 44a, the PD-L1 antigen-binding site comprises the CDRH1, CDRH2, CDR3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from any one of the anti-PD-L1 antibodies selected from an anti-PD-L1 antibody disclosed herein, particularly the anti-PD-L1 antibody clones disclosed in concepts 16a through 16l, and more particularly anti-PD-L1 antibody clone 84G09.

In another embodiment of concept 44a, the PD-L1 antigen-binding site comprises the CDRH1, CDRH2, CDR3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from anti-PD-L1 antibody clone 84G09 and the hPD-L1-mediated disease or condition is Alzheimer's disease.

Concept 45. The antibody or fragment, the use or the method according to concept 44, wherein the cancer is selected from melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or is selected from virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas.

Concept 46. The antibody or fragment, use or the method according to any one of concepts 41 to 45, further comprising administering to the human a further therapy, for example a further therapeutic agent, optionally wherein the further therapeutic agent is independently selected from the group consisting of:

a. other immune checkpoint inhibitors (such as anti-TIM-3 antibodies, anti-CTLA-4 antibodies, anti-TIGIT antibodies and anti-LAG-3 antibodies);
b. immune stimulators (such as anti-OX40 antibodies, anti-GITR antibodies, anti-CD137 antibodies, anti-ICOS antibodies and anti-CD40 antibodies);
c. chemokine receptor antagonists (such as CXCR4, CCR4 and CXCR2);
d. targeted kinase inhibitors (such as CSF-1R or VEGFR inhibitors);
e. angiogenesis inhibitors (such as anti-VEGF-A or Delta-like Ligand-4);
f. immune stimulating peptides or chemokines (such as CXCL9 or CXCL10);
g. cytokines (such as IL-15 and IL-21);
h. bispecific T-cell engagers (BiTEs) having at least one specificity against CD3 (e.g. CD3/CD19 BiTE);
i. other bi-specific molecules (for example IL-15-containing molecules targeted towards tumour associated antigens, for example Epidermal growth factor receptors such as EGFR, Her-2,

New York Esophageal Cancer-1 (NY-ESO-1), GD2, EpCAM or Melanoma Associated Antigen-3 (MAGE-A3));

j. oncolytic viruses (such as HSV virus (optionally which secretes GMCSF), Newcastle disease virus and Vaccinia virus);

k. vaccination with tumour associated antigens (such as New York Esophageal Cancer-1 [NY-ESO-1], Melanoma Associated Antigen-3 [MAGE-3]);

l. cell-based therapies (such as chimeric Antigen Receptor-T-cells (CAR-T) for example expressing anti-CD19, anti-EpCam or anti-mesothelin);

m. bi-specific NK cell engagers having a specificity against an activating MK receptor such as NKG2D or CD16a; and

n. adoptive transfer of tumour specific T-cells or LAK cells,

or optionally wherein the further therapy is chemotherapy, radiotherapy and surgical removal of tumours.

Radiotherapy may be single dose or in fractionated doses, either delivered to affected tissues directly or to the whole body.

Chemotherapeutic agents may any as described hereinabove, in particular, agents that induce immunogenic cell death, for example platinum therapies, such as oxaliplatin. In one embodiment, the chemotherapy is a standard of care cytotoxic chemotherapy for the cancer being treated.

In this aspect, the bispecific molecules include "bispecific antibodies" and antibody fusion proteins, including those formats and molecules described in concepts 37 to 40.

The antibodies may be any of the sequences or antibodies described in arrangement 5, 5a or detailed in Aspect 1a.

The further therapeutic agents of this concept may be delivered by any method, which methods are well-known to those skilled in the art. For example, the further therapeutic agents may be delivered orally, systemically or locally (to the tumour environment). In one embodiment, the further therapeutic agent is delivered orally. In one embodiment, the further therapeutic agent is delivered systemically (e.g. intravenously). In one embodiment, the further therapeutic agent is delivered locally to the tumour environment.

Compositions and routes of administration are described in more detail hereinbelow.

Concept 47. The antibody or fragment, use or the method according to concept 46, wherein the further therapeutic agent is administered sequentially or simultaneously with the anti-hPD-L1 antibody or fragment.

Concept 48. A pharmaceutical composition comprising an antibody of fragment as defined in any one of concepts 1 to 40 and a pharmaceutically acceptable excipient, diluent or carrier and optionally further comprising a further therapeutic agent independently selected from the group consisting of:

a) other immune checkpoint inhibitors (such as anti-TIM-3 antibodies, anti-CTLA-4 antibodies, anti-TIGIT antibodies and anti-LAG-3 antibodies);

b) immune stimulators (such as anti-OX40 antibodies, anti-GITR antibodies, anti-CD137 antibodies, anti-ICOS antibodies and anti-CD40 antibodies);

c) chemokine receptor antagonists (such as CXCR4, CCR4 and CXCR2);

d) targeted kinase inhibitors (such as CSF-1R or VEGFR inhibitors);

e) angiogenesis inhibitors (such as anti-VEGF-A or Delta-like Ligand-4);

f) immune stimulating peptides or chemokines (such as CXCL9 or CXCL10);

g) cytokines (such as IL-15 and IL-21);

h) bispecific T-cell engagers (BiTEs) having at least one specificity against CD3 (e.g. CD3/CD19 BiTE);

i) other bi-specific molecules (for example IL-15-containing molecules targeted towards tumour associated antigens, for example Epidermal growth factor receptors such as EGFR, Her-2, New York Esophageal Cancer-1 (NY-ESO-1), GD2, EpCAM or Melanoma Associated Antigen-3 (MAGE-A3));

j) oncolytic viruses (such as HSV virus (optionally which secretes GMCSF), Newcastle disease virus and Vaccinia virus);

k) vaccination with tumour associated antigens (such as New York Esophageal Cancer-1 [NY-ESO-1], Melanoma Associated Antigen-3 [MAGE-3]);

l) cell-based therapies (such as chimeric Antigen Receptor-T-cells (CAR-T) for example expressing anti-CD19, anti-EpCam or anti-mesothelin);

m) bi-specific NK cell engagers having a specificity against an activating MK receptor such as NKG2D or CD16a; and

n) adoptive transfer of tumour specific T-cells or LAK cells.

Pharmaceutical formulations are well-known to those skilled in the art. In one embodiment, the antibody or fragment is administered intravenously. In one embodiment, the antibody or fragment is administered subcutaneously.

In an example, an antibody or fragment as disclosed herein is contained in a medical container, e.g. a vial, syringe, IV container or an injection device (such as an intraocular or intravitreal injection device). In an example, the antibody or fragment is , for example, in a sterile container.

In one embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as

lignocamne to ease pain at the site of the injection. Such compositions, however, may be administered by a route other than intravenous.

Generally, the ingredients of compositions are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

In this aspect, the bispecific molecules include "bispecific antibodies" and antibody fusion proteins, including those formats and molecules described in concepts 37 to 40.

The further therapeutic agents of this concept may be delivered by any method, which methods are well-known to those skilled in the art. For example, the further therapeutic agents may be delivered orally, systemically or locally (to the tumour environment). In one embodiment, the further therapeutic agent is delivered orally. In one embodiment, the further therapeutic agent is delivered systemically (e.g. intravenously). In one embodiment, the further therapeutic agent is delivered locally to the tumour environment.

The antibodies may have any of the sequences or may be any of the antibodies described in arrangement 5, 5a or detailed in aspect 1a.

Concept 49. A pharmaceutical composition according to concept 48, or a kit comprising a pharmaceutical composition as defined in concept 48, wherein the composition is for treating and/or preventing a hPD-L1-mediated condition or disease, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease, diffuse large B-cell lymphoma.

Concept 50. A pharmaceutical composition according to concept 48 or concept 49 in combination with, or kit according to concept 49 comprising, a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g. an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the antibody or fragment.

Concept 51. A method of modulating PD-1/PD-L1 interaction in a patient, comprising administering an effective amount of an antibody or fragment as defined in any one of concepts 1 to 40 to said patient.

In another embodiment, there is provided a method of modulating CD80/PD-L1 interaction in a patient, comprising administering an effective amount of an antibody or fragment as defined in any one of concepts 1 to 40 to said patient. In another embodiment, the antibody or fragment modulates CD80/PD-L1 interaction, but does not modulate PD-1/PD-L1 interaction. In another embodiment, the antibody or fragment blocks CD80/PD-L1 interaction, but does not block PD-1/PD-L1 interaction. In another embodiment, the antibody or fragment inhibits CD80/PD-L1 interaction, but does not inhibit PD-1/PD-L1 interaction.

Concept 52. A method of inhibiting PD-L1 activity in a patient, comprising administering an effective amount of an antibody or fragment as defined in any one of concepts 1 to 40 to said patient.

In one embodiment, the antibody or fragment blocks or inhibits PD-1 binding to PD-L1. In one embodiment, the antibody or fragment blocks or inhibits CD80 binding to PD-L1.

Concept 53. A method of treating a proliferative disease in an animal (e.g. a human), comprising administering an effective amount of an antibody or fragment as defined in any one of concepts 1 to 40 to said patient.

Proliferative diseases may be any as described elsewhere herein.

Concept 54. A method of detecting PD-L1 expression in a sample, comprising contacting the sample with an antibody or fragment as defined in any one of concepts 1 to 40.

Concept 55. A method comprising contacting a biological sample with an antibody or fragment as defined in any one of concepts 1 to 40 to form a complex with PD-L1 present in the sample and measuring the presence, absence or level of the complex in the biological sample.

Concept 56. The method according to concept 55, wherein the presence, absence and/or level of PD-L1 expression is detected prior to treatment and a high level of surface expressed PD-L1 is indicative of successful treatment.

Concept 57. The method according to concept 55, wherein the presence, absence and/or level of PD-L1 expression is detected during treatment as an early response biomarker.

Concept 58. The method according to concept 55 or concept 57, wherein the presence, absence and/or level of PD-L1 expression is detected during or after treatment to help determine one or more of: whether treatment has been successful, whether treatment should continue, and/or whether treatment should be modified.

Concept 59. The method according to any one of concepts 55 to 58, wherein therapy comprises treatment with an anti-PD-L1 antibody, optionally as defined in any one of concepts 1 to 40.

Concept 60. A method for monitoring therapy efficacy, the method comprising detecting expression of surface expressed PD-L1 in a patient prior to therapy, and during or after therapy, wherein an antibody or fragment as defined in any one of concepts 1 to 40 is used to detect expression of surface expressed PD-L1.

Concept 61. The method according to concept 60, wherein surface expressed PD-L1 expression is detected .

Concept 62. The method according to concept 60, wherein surface expressed PD-L1 expression is detected in a tissue sample .

Concept 63. A method for identifying binding partners for PD-L1, the method comprising immunoprecipitating an intact protein complex comprising PD-L1 using an antibody or fragment as defined in any one of concepts 1 to 40.

Concept 64. A method of diagnosing a disease in a human subject associated with altered PD-L1 expression comprising the steps of contacting a biological sample from the human subject with an antibody as defined in concepts 1 to 40 to form a complex between the antibody and PD-L1 present in the sample; and detecting the amount of the complex.

Concept 65. A nucleic acid that encodes the CDRH3 of an antibody or fragment as defined in any one of concepts 1 to 40.

Concept 65a. There is also provided a nucleic acid that encodes the CDRH2 of an antibody or fragment as defined in any one of concepts 1 to 40.

Concept 65b. There is also provided a nucleic acid that encodes the CDRH1 of an antibody or fragment as defined in any one of concepts 1 to 40.

Concept 65c. There is also provided a nucleic acid that encodes the CDRL1 of an antibody or fragment as defined in any one of concepts 1 to 40.

Concept 65d. There is also provided a nucleic acid that encodes the CDRL2 of an antibody or fragment as defined in any one of concepts 1 to 40.

Concept 65e. There is also provided a nucleic acid that encodes the CDRL3 of an antibody or fragment as defined in any one of concepts 1 to 40.

In one embodiment, the nucleic acid is an isolated and purified nucleic acid.

Concept 66. A nucleic acid that encodes a V_H domain and/or a V_L domain of an antibody or fragment as defined in any one of concepts 1 to 40.

The V_H and V_L domain nucleic acid sequences of the invention are provided in the sequence listing. In one embodiment, the nucleic acid sequence is at least 70% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 75% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 95% identical to the specified Seq

ID No. In one embodiment, the nucleic acid sequence is at least 96% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 97% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 98% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 99% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 99.5% identical to the specified Seq ID No.

Concept 67. The nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:36 and/or SEQ ID NO:46.

Concept 67a. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:16 and/or SEQ ID NO:26.

Concept 67b. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:61 and/or SEQ ID NO:71.

Concept 67c. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:81 and/or SEQ ID NO:91.

Concept 67d. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:101 and/or SEQ ID NO:111.

Concept 67e. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:121 and/or SEQ ID NO:131.

Concept 67f. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:161 and/or SEQ ID NO:171.

Concept 67g. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:181 and/or SEQ ID NO:191.

Concept 67h. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:141 and/or SEQ ID NO:151.

Concept 67i. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:247 and/or SEQ ID NO:257.

Concept 67j. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:267 and/or SEQ ID NO:277.

Concept 67k. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:287 and/or SEQ ID NO:297.

Concept 67l. A nucleic acid according to concept 66 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:352 and/or SEQ ID NO:362.

In one embodiment, the nucleic acid sequence is at least 70% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 75% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 95% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 96% identical to the specified Seq

ID No. In one embodiment, the nucleic acid sequence is at least 97% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 98% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 99% identical to the specified Seq ID No. In one embodiment, the nucleic acid sequence is at least 99.5% identical to the specified Seq ID No.

Concept 68. A nucleic acid that encodes a heavy chain or a light chain of an antibody as defined in any one of concepts 1 to 40.

Concept 69. A vector comprising the nucleic acid of any one of concepts 65 to 68; optionally wherein the vector is a CHO or HEK293 vector.

Concept 70. A host comprising the nucleic acid of any one of concepts 65 to 68 or the vector of concept 69.

3. Immunocytokines

The inventors have described immunocytokines which comprise an antibody which binds to an immune checkpoint inhibitor, such as PD-L1 fused to either the N-terminus or C-terminus of the heavy chain or the light chain (for example, the C-terminus of the heavy or light chain, and in particular the light chain). The immunocytokines comprise a cytokine molecule, which may be IL-2 or a variant thereof (including variant having a 1 to 10 amino acid deletion at the N-terminus). The antibodies as described hereinabove may be used in any immunocytokine described herein.

Without being bound by theory, immunocytokines of the invention may provide one or more of the following advantageous properties:

synergistic activity (by virtue of the therapeutic activity of antibody Fab portion in combination with the cytokine)
improved tumour targeting
ability to retain effector functions such as CDC, ADCC and/or ADCP
reduced off-target effects
reduced toxicity (e.g. compared to free cytokine or cytokine when fused to the heavy chain of an immunocytokine)
reduced immunogenicity
lower dose/frequency of dosing, in particular due to improved half life of light chain cytokine fusions as compared to heavy chain fusion equivalents
Specificity for blocking only one of the ligands of PD-L1 (e.g. blocks CD80/PD-L1 interaction, but not PD-1/PD-L1 interaction)
Solubility
Stability
Ease of formulation

Frequency of dosing and/or route of administration

Manufacturability (e.g. expression, ease of purification, isoforms)

1D05 ICK comprises a heavy chain amino acid sequence of Seq ID No:299, and a light chain amino acid sequence of Seq ID No:300. The light chain comprises a V_L domain comprising the CDRs and V_L sequence of antibody 1D05 described hereinabove, fused at the heavy chain to full length, wild-type, human IL-2 cytokine. It does not contain a linker peptide. The heavy chain comprises a V_H domain comprising the CDRs and V_H sequence of antibody 1D05 described hereinabove, fused to a disabled IgG constant region (Seq ID No:205).

1D05 D5-9 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D5-9 (Seq ID No:303), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D1-9 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D1-9 (Seq ID No:304), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D5-7 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D5-7 (Seq ID No:305), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D1 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D1 (Seq ID No:306), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D1-2 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at

the C-terminus to IL-2 D1-2 (Seq ID No:307), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D1-3 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D1-3 (Seq ID No:308), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D1-4 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D1-4 (Seq ID No:309), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D1-5 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D1-5 (Seq ID No:310), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D1-6 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D1-6 (Seq ID No:311), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D1-7 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D1-7 (Seq ID No:312), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D1-8 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at

the C-terminus to IL-2 D1-8 (Seq ID No:313), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D9 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D9 (Seq ID No:314), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D9-8 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D9-8 (Seq ID No:315), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D9-7 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D9-7 (Seq ID No:316), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D9-6 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D9-6 (Seq ID No:317), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D9-4 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D9-4 (Seq ID No:318), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D9-3 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at

the C-terminus to IL-2 D9-3 (Seq ID No:319), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D9-2 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D9-2 (Seq ID No:320), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D2-6 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D2-6 (Seq ID No:321), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D3-7 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D3-7 (Seq ID No:322), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

1D05 D4-8 ICK comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:33 (comprising the CDRs of 1D05 as described hereinabove) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D4-8 (Seq ID No:323), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

In any of the ICK constructs above, the IL-2 binding portion may be a variant IL-2, in particular an IL-2 having an R38A mutation (as described in amino acids 21-133 of the variant IL-2 described as SEQ ID NO:517) or an R38Q mutation (as described in amino acids 21-133 of the variant IL-2 described as SEQ ID NO:518).

In any of the ICK constructs above, the V_H region of the 1D05 antibody may be exchanged for the V_H region of mutated 1D05 – Heavy Chain mutant 1 (Seq ID No:47), mutated 1D05 – Heavy Chain mutant 2 (Seq ID No:48), mutated 1D05 – Heavy Chain mutant 3 (Seq ID No:49) or mutated 1D05 – Heavy Chain mutant 4 (Seq ID No:342). A preferred mutated heavy chain V_H region of 1D05 is mutated 1D05 – Heavy Chain mutant 4 (Seq ID No:342).

Thus, certain ICK constructs comprise:

Mutated 1D05 – Heavy Chain mutant 4 D5-9 ICK, which comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:342 (comprising the CDRs of mutated 1D05 – Heavy Chain mutant 4 as described herein) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D5-9 (Seq ID No:303), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

Mutated 1D05 – Heavy Chain mutant 4 D1-9 ICK, which comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:342 (comprising the CDRs of mutated 1D05 – Heavy Chain mutant 4 as described herein) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D1-9 (Seq ID No:304), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

Mutated 1D05 – Heavy Chain mutant 4 D1-8 ICK, which comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:342 (comprising the CDRs of mutated 1D05 – Heavy Chain mutant 4 as described herein) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D1-8 (Seq ID No:313), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

Mutated 1D05 – Heavy Chain mutant 4 D9-7 ICK, which comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:342 (comprising the CDRs of mutated 1D05 – Heavy Chain mutant 4 as described herein) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D9-7 (Seq ID No:316), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

Mutated 1D05 – Heavy Chain mutant 4 D9-2 ICK, which comprises a heavy chain comprising a V_H region amino acid sequence of Seq ID No:342 (comprising the CDRs of mutated 1D05 – Heavy Chain mutant 4 as described herein) fused to a disabled IgG1 constant region with an amino acid sequence of Seq ID No:205. The light chain comprises a V_L amino acid sequence of Seq ID No:43 (comprising the CDRs of 1D05 as described hereinabove) directly fused at the C-terminus to IL-2 D9-2 (Seq ID No:320), which is directly fused to amino acids 21 to 133 of hIL-2 (Seq ID No:324).

In any of the ICK constructs above, the V_L region of the 1D05 antibody may be exchanged for the V_L region of mutated 1D05 – Light Chain mutant 1 (Seq ID No:50), mutated 1D05 – Light Chain mutant 2 (Seq ID No:51) or mutated 1D05 – Light Chain mutant 3 (Seq ID No:298).

In any of the ICK constructs above, both the V_H and V_L region of the 1D05 antibody may be exchanged for both the V_H and V_L regions of any of the other antibodies described herein, i.e. 84G09, 411B08, 411C04, 411D07, 385F01, 413D08, 386H03, 389A03, 413G05, 413F09 and 414B06.

In any of the ICK constructs above, the heavy chain constant region of Seq ID No:205 may be exchanged for any of the heavy chain constant regions of Seq ID Nos:193, 195, 197, 199, 203, 205, 340, 524, 526, 528, 530, 532 or 534.

Immunocytokines may be described in the following sentences or aspects. Unless otherwise apparent, the features of any of the concepts described hereinabove apply to any of the aspects hereinbelow.

Aspect 1. An immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

d) A light chain constant region, (C_L);

e) Optionally, a linker, (L); and

f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to hPD-L1 as defined by Seq ID No:1, and competes for binding to said hPD-L1 with the antibody 1D05; and

wherein the immunocytokine comprises a V_H domain which comprises a CDRH3 comprising the motif $X_1GSGX_2YGX_3X_4FD$, wherein X_1, X_2 and X_3 are independently any amino acid, and X_4 is either present or absent, and if present, may be any amino acid.

In the aspects described herein, CDR sequences may be determined according to any method known to those skilled in the art, such as using the Kabat method, the IMGT method or the Chothia method, each of which are described in more detail herein. In one embodiment, the CDR regions are human CDR regions.

In addition to the CDR regions, the V_H and/or V_L domains may further comprise framework regions, such as FW1, FW2 and FW3. The V_H and/or V_L domains may be of any origin described herein, and may be for example, fully human, humanised, murine or camelid. In one embodiment, the V_H and/or V_L domains are human V_H and/or V_L domains. CDRs may be of a non-human origin (e.g. mouse origin) and be grafted onto human framework regions. In another embodiment, the CDRs are synthetic.

In another embodiment, V_H regions may be selected from the group consisting of an antibody variable domain (e.g. a V_L or a V_H, an antibody single variable domain (domain antibody or dAb), a camelid V_{HH} antibody single variable domain, a shark immunoglobulin single variable domain (NARV), a Nanobody™ or a camelised V_H single variable domain); a T-cell receptor binding domain; an immunoglobulin superfamily domain; an agnathan variable lymphocyte receptor; a fibronectin domain

(e.g. an Adnectin™); an antibody constant domain (e.g. a CH_3 domain, e.g. a CH_2 and/or CH_3 of an Fcab™) wherein the constant domain is not a functional CH_1 domain; an scFv; an (scFv)2; an sc-diabody; an scFab; a centyrin and an epitope binding domain derived from a scaffold selected from CTLA-4 (Evibody™); a lipocalin domain; Protein A such as Z-domain of Protein A (e.g. an Affibody™ or SpA); an A-domain (e.g. an Avimer™ or Maxibody™); a heat shock protein (such as and epitope binding domain derived from GroEI and GroES); a transferrin domain (e.g. a trans-body); ankyrin repeat protein (e.g. a DARPin™); peptide aptamer; C-type lectin domain (e.g. Tetranectin™); human - crystallin or human ubiquitin (an affilin); a PDZ domain; scorpion toxin; and a kunitz type domain of a human protease inhibitor.

The constant region comprises at least two heavy chain constant region domains selected from CH_1, CH_2, CH_3 and CH_4. In one embodiment, the constant region comprises (or consists of) a CH_1 domain and a CH_2 domain. In one embodiment, the constant region comprises (or consists of) a CH_1 domain, a hinge region and a CH_2 domain. In one embodiment, the constant region comprises (or consists of) a CH_1 domain and a CH_3 domain, and optionally a hinge region. In one embodiment, the constant region comprises (or consists of) a CH_1 domain and a CH_4 domain, and optionally a hinge region. In one embodiment, the constant region comprises (or consists of) a CH_1 domain, a CH_2 domain and a CH_3 domain, and optionally a hinge region. In one embodiment, the constant region comprises (or consists of) a CH_1 domain, a CH_2 domain and a CH_4 domain, and optionally a hinge region. In one embodiment, the constant region comprises (or consists of) a CH_1 domain, a CH_3 domain and a CH_4 domain, and optionally a hinge region. In one embodiment, the constant region comprises (or consists of) a full constant region.

The constant region may be of any isotype described herein, e.g. IgA, IgD, IgE, IgG, and IgM. In one embodiment, the constant region is of any origin described herein, and may be for example, human, murine or camelid. In one embodiment, the constant region is a (full) human constant region. In one embodiment, the constant region is a human IgG constant region. In one embodiment, the constant region is a (full) human IgG1 constant region. In one embodiment, the constant region is an effector null (full) human IgG1 constant region. In one embodiment, the constant region has CDC and/or ADCC and/or ADCP activity. In one embodiment, the constant region is engineered to enhance the CDC and/or ADCC and/or ADCP activity. The constant region may be any of the constant regions described in concepts 30 to 32 hereinabove.

The light chain constant region may be a kappa or lambda light chain constant region. The light chain constant region may be as described in concept 28 hereinabove.

An IL-2 cytokine is a cytokine molecule which confers IL-2 activity on one or both of the intermediate affinity IL-2 Receptor (-2 receptor ( ). An IL-2 cytokine includes variant IL-2 cytokines. An IL-2 cytokine may be of human origin or of non-human origin, for example of a non-human mammal, including, but not limited to, primates (e.g. monkeys such a rhesus macaque or cynomolgus), rodents (such as mice, rats and guinea pigs) farm animals, (such as cattle,

sheep, pigs, goats, horses, chickens, turkeys, ducks and geese), and domestic mammals (such as dogs and cats). In one embodiment, an IL-2 cytokine is a human IL-2 cytokine.

As used herein, a "variant IL-2 cytokine" is a cytokine having up to 10 amino acids deleted from the N terminal sequence, in combination with up to 5 amino acid substitutions, deletions or additions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 10 (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 5 (e.g. 1, 2, 3, 4 or 5) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 10 (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) amino acid deletions from the N-terminal sequence (e.g. within the first 15 amino acids of the wild-type IL-2 sequence in question), in combination with up to 5 (e.g. 1, 2, 3, 4 or 5) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 10 (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) amino acid deletions from the N-terminal sequence (e.g. within the first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 5 (e.g. 1, 2, 3, 4 or 5) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 10 (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 10 (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 3 (e.g. 1, 2 or 3) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 10 (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 2 (e.g. 1 or 2) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 10 (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with 1 amino acid substitution elsewhere in the IL-2 cytokine.

In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 9 (e.g. 1, 2, 3, 4, 5, 6, 7, 8 or 9) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 9 (e.g. 1, 2, 3, 4, 5, 6, 7, 8 or 9) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 3 (e.g. 1, 2 or 3) amino acid

substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 9 (e.g. 1, 2, 3, 4, 5, 6, 7, 8 or 9) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 2 (e.g. 1 or 2) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 9 (e.g. 1, 2, 3, 4, 5, 6, 7, 8 or 9) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with one amino acid substitution elsewhere in the IL-2 cytokine.

In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 8 (e.g. 1, 2, 3, 4, 5, 6, 7 or 8) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 8 (e.g. 1, 2, 3, 4, 5, 6, 7 or 8) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 3 (e.g. 1, 2 or 3) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 8 (e.g. 1, 2, 3, 4, 5, 6, 7 or 8) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 2 (e.g. 1 or 2) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 8 (e.g. 1, 2, 3, 4, 5, 6, 7 or 8) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with one amino acid substitution elsewhere in the IL-2 cytokine.

In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 7 (e.g. 1, 2, 3, 4, 5, 6 or 7) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 7 (e.g. 1, 2, 3, 4, 5, 6 or 7) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 3 (e.g. 1, 2 or 3) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 7 (e.g. 1, 2, 3, 4, 5, 6 or 7) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 2 (e.g. 1 or 2) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 7 (e.g. 1, 2, 3, 4, 5, 6 or 7) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10

amino acids of the wild-type IL-2 sequence in question), in combination with one amino acid substitution elsewhere in the IL-2 cytokine.

In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 6 (e.g. 1, 2, 3, 4, 5 or 6) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 6 (e.g. 1, 2, 3, 4, 5 or 6) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 3 (e.g. 1, 2 or 3) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 6 (e.g. 1, 2, 3, 4, 5 or 6) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 2 (e.g. 1 or 2) amino acid substitutions elsewhere in the IL-2 cytokine.

In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 5 (e.g. 1, 2, 3, 4 or 5) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 5 (e.g. 1, 2, 3, 4 or 5) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 5 (e.g. 1, 2, 3, 4 or 5) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 6 (e.g. 1, 2, 3, 4, 5 or 6) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with one amino acid substitution elsewhere in the IL-2 cytokine.

In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 4 (e.g. 1, 2, 3 or 4) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 4 (e.g. 1, 2, 3 or 4) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 3 (e.g. 1, 2 or 3) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 4 (e.g. 1, 2, 3 or 4) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first

10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 2 (e.g. 1 or 2) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 4 (e.g. 1, 2, 3 or 4) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with one amino acid substitution elsewhere in the IL-2 cytokine.

In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 3 (e.g. 1, 2 or 3) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 3 (e.g. 1, 2 or 3) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 3 (e.g. 1, 2 or 3) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 3 (e.g. 1, 2 or 3) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 2 (e.g. 1 or 2) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) up to 3 (e.g. 1, 2 or 3) amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with one amino acid substitution elsewhere in the IL-2 cytokine.

In one embodiment, the variant IL-2 cytokine comprises (or consists of) 1 or 2 amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 4 (e.g. 1, 2, 3 or 4) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) 1 or 2 amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 3 (e.g. 1, 2 or 3) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) 1 or 2 amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with up to 2 (e.g. 1 or 2) amino acid substitutions elsewhere in the IL-2 cytokine. In one embodiment, the variant IL-2 cytokine comprises (or consists of) 1 or 2 amino acid deletions from the N-terminal sequence (e.g. within the first 20, or first 15, or first 10 amino acids of the wild-type IL-2 sequence in question), in combination with one amino acid substitution elsewhere in the IL-2 cytokine.

Substitutions elsewhere in the IL-2 cytokine are defined further in aspect 44 hereinbelow.

Particular IL-2 cytokines and variant IL-2 cytokines are further defined in aspects 40 to 45 hereinbelow.

The amino acid sequence of the -chain of human IL-2 is provided in Seq ID No:327. The -chain of human IL-2 is provided in Seq ID No:328. The amino acid sequence of the -chain of human IL-2 is provided in Seq ID No:239.

In any of the aspects or concepts herein, an immunocytokine or anti-PDL1 antibody or fragment may have a half-life of at least 4 hours, 5 hours, 6 hours, 7 hours or 8 hours. In another embodiment, the half-life of any of the immunocytokines or anti-PD-L1 antibodies or fragments provided herein is at least 9 hours, or at least 10 hours, or at least 11 hours, or at least 12 hours. In another embodiment, the half-life of any of the immunocytokines or anti-PD-L1 antibodies or fragments provided herein is at least 13 hours, or at least 14 hours, or at least 15 hours, or at least 16 hours. In another embodiment, the half-life of any of the immunocytokines or anti-PD-L1 antibodies or fragments provided herein is at least 17 hours, or at least 18 hours, or at least 19 hours, or at least 20 hours. In another embodiment, the half-life of any of the immunocytokines or anti-PD-L1 antibodies or fragments provided herein is at least 21 hours, or at least 22 hours, or at least 23 hours, or at least 24 hours. In another embodiment, the half-life of any of the immunocytokines or anti-PD-L1 antibodies or fragments provided herein is at least 25 hours, or at least 26 hours, or at least 27 hours, or at least 30 hours. In another embodiment, the half-life of any of the immunocytokines or anti-PD-L1 antibodies or fragments provided herein is at least 32 hours, or at least 34 hours, or at least 36 hours, or at least 40 hours. In one embodiment, the half-life is determined in a mouse model (for example a human PD-L1 knock-in mouse, e.g. as described in Example 22 hereinbelow, or in an immunocompromised mouse xenografted with human T-cells). In another embodiment, the half life is determined in a single dose study in cynomolgus monkeys (e.g. as described in Example 18 or Example 23 hereinbelow). In another embodiment, the half life is determined in an extended single dose study in cynomolgus monkeys (e.g. as described in Example 19 or Example 26 hereinbelow).

Aspect 1a. An immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

d) A light chain constant region, (C_L);

e) Optionally, a linker, (L); and

f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to an antigen selected from: an immune checkpoint inhibitor (such as PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. TIGIT, TIM-3 and LAG-3), an immune modulator (such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10, CXCL11 and CD155, e.g. GARP, SIRPα, CXCR4, BTLA, hVEM and CSF1R), and an immune activator

(such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic activity against CXCR3), CD27, CD3 and ICOS (e.g. agonistic activity against ICOS), for example, ICOS, CD137, GITR and OX40).

In another embodiment, the antigen-binding site that specifically binds to an antigen selected from: an immune checkpoint inhibitor (such as PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. TIGIT, TIM-3 and LAG-3), an immune modulator (such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10 and CD155, e.g. GARP, SIRPα, CXCR4, BTLA, hVEM and CSF1R), and an immune activator (such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic activity against CXCR3), CD3 and ICOS (e.g. agonistic activity against ICOS), for example, ICOS, CD137, GITR and OX40).

Any of the embodiments of aspect 1 apply to aspect 1a. Any of the features or embodiments of aspects 2 to 54 apply to aspect 1a. Any of the features of the antibodies or other embodiments or features of concepts 1 to 70 apply to aspect 1a.

In one embodiment, the antigen-binding site specifically binds PD-L1, e.g. hPD-L1. In one embodiment, the PD-L1 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from any one of the anti-PD-L1 antibodies selected from atezolizumab/MPDL3280A (Roche), avelumab/MSB0010718C (Merck), BMS-936559/MDX-1105 (BMS), durvalumab/Medi4736 (Medimmune), KN-035, CA-170, FAZ-053 M7824, ABBV-368, LY-3300054, GNS-1480, YW243.55.S70, REGN3504 and any of the PD-L1 antibodies disclosed in WO2017/034916, WO2017/020291, WO2017/020858, WO2017/020801, WO2016/111645, WO2016/050721, WO2016/197367, WO2016/061142, WO2016/149201, WO2016/000619, WO2016/160792, WO2016/022630, WO2016/007235, WO2015/179654, WO2015/173267, WO2015/181342, WO2015/109124, WO2015/195163, WO2015/112805, WO2015/061668, WO2014/159562, WO2014/165082, WO2014/100079, WO2014/055897, WO2013/181634, WO2013/173223, WO2013/079174, WO2012/145493, WO2011/066389, WO2010/077634, WO2010/036959, WO2010/089411 or WO2007/005874, which antibodies and sequences are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds ICOS, e.g. hICOS. In one embodiment, the antigen-binding site specifically binds ICOS, e.g. hICOS and is an agonist to ICOS, e.g. hICOS. In one embodiment, the antigen-binding site specifically binds ICOS, e.g. hICOS and is an antagonist to ICOS, e.g. hICOS. In one embodiment, the ICOS antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from any one of the anti-ICOS antibodies described in arrangement 5 and arrangement 5a hereinbelow, and any of the anti-ICOS antibodies described in sentences 1 to 102 and sentences 1a to 21a.

In any of the following embodiments, a particular antigen-binding site specifically binds to a human target. In one embodiment, the antigen-binding site specifically binds an immune checkpoint inhibitor. In one embodiment, the antigen-binding site specifically binds an immune checkpoint

inhibitor selected from PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA. In one embodiment, the antigen-binding site specifically binds an immune checkpoint inhibitor selected from TIGIT, CTLA-4, TIM-3 and LAG-3.

In one embodiment, the antigen-binding site specifically binds PD-1, e.g. human PD-1. In one embodiment, the PD-1 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from pembrolizumab (Keytruda®/MK-3475), nivolumab (Opdivo®/BMS-936558/MDX-1106), MEDI-0680/AMP514, PDR001, Lambrolizumab, BMS-936558, REGN2810, BGB-A317, BGB-108, PDR-001, SHR-1210, JS-001, JNJ-63723283, AGEN-2034, PF-06801591, genolimzumab, MGA-012, IBI-308, BCD-100, TSR-042 ANA011, AUNP-12, KD033, MCLA-134, mDX400, muDX400, STI-A1110, AB011, 244C8, 388D4, XCE853, or pidilizumab/CT-011, or from any one of the anti-PD-1 antibodies described in WO2015/112800 & US2015/0203579 (including the antibodies in Tables 1 to 3), US9,394,365, US5,897,862 and US7,488,802, WO2017/087599 (including antibody SSI-361 and SHB-617), WO2017/079112, WO2017/071625 (including deposit C2015132, hybridoma LT004, and antibodies 6F5/6 F5 (Re), 6F5H1 L1 and 6F5 H2L2), WO2017/058859 (including PD1AB-1 to PD1AB-6), WO2017/058115 (including 67D9, c67D9, and hu67D9), WO2017/055547 (including 12819.15384, 12748.15381, 12748.16124, 12865.15377, 12892.15378, 12796.15376, 12777.15382, 12760.15375 and 13112.15380), WO2017/040790 (including AGEN2033w, AGEN2034w, AGEN2046w, AGEN2047w, AGEN2001w and AGEN2002w), WO2017/025051 & WO2017/024515 (including 1.7.3 hAb, 1.49.9 hAb, 1.103.11 hAb, 1.103.11-v2 hAb, 1.139.15 hAb and 1.153.7 hAb), WO2017/025016 & WO2017/024465 (including antibody A to antibody I), WO2017/020858 & WO2017/020291 (including 1.4.1, 1.14.4, 1.20.15 and 1.46.11), WO2017/019896 & WO2015/112900 & US2015/0210769 (including BAP049-hum01 to BAP049-hum16 and BAP049-Clone-A to BAP049-Clone-E), WO2017/019846 (including PD-1 mAb 1 to PD-1 mAb 15), WO2017/016497 (including MHC723, MHC724, MHC725, MHC728, MHC729, m136-M13, m136-M19, m245-M3, m245-M5 and m136-M14), WO2016/201051 (including antibody EH12.2H7, antibody hPD-1 mAb2, antibody hPD-1 mAb7, antibody hPD-1 mAb9, antibody hPD-1 mAb15, or an anti-PD-1 antibody selected from Table 1), WO2016/197497 (including DFPD1-1 to DFPD1-13), WO2016/197367 (including 2.74.15 and 2.74.15.hAb4 to 2.74.15.hAb8), WO2016/196173 (including the antibodies in Table 5, and Figures 1-5), WO2016/127179 (including R3A1, R3A2, R4B3, and R3D6), WO2016/077397 (including the antibodies described in Table 1 of Example 9), WO2016/106159 (including the murine antibodies in Table 3 of Example 2 and the humanised antibodies in Tables 7, 8 and 9 of Example 3), WO2016/092419 (including C1, C2, C3, EH12.1, mAb7-G4, mAb15-G4, mAb-AAA, mAb15-AAA), WO2016/068801 (including clone A3 and its variants and the other antibodies described in Figures 1 to 4), WO2016/014688 (including 10D1, 4C10, 7D3, 13F1, 15H5, 14A6, 22A5, 6E1, 5A8, 7A4, and 7A4D and the humanised antibodies of Examples 9/10), WO2016/015685 (including 10F8, BA08-1, BA-08-2 and 15H6), WO2015/091911 & WO2015/091910 (including the anti-canine PD-1 antibodies in Examples 2, 3 and 4) , WO2015/091914 (including the anti-canine PD-1 antibodies in Table 3), WO2015/085847 (including mAb005, H005-1 to H005-4), WO2015/058573

(including cAB7), WO2015/036394 (including LOPD180), WO2015/035606 (including the antibodies in Table 1 of Example 2, in Tables 14, 15 and 16 of Example 7 and in tables 20, 21 and 22 of Example 11), WO2014/194302 (including GA2, RG1B3, RG1H10, RG2A7, RG2H10, SH-A4, RG4A6, GA1, GB1, GB6, GH1, A2, C7, H7, SH-A4, SH-A9, RG1H11, and RG6B), WO2014/179664 (including 9A2, 10B11, 6E9, APE1922, APE1923, APE1924, APE1950, APE1963 and APE2058), WO2014/206107 (including clone 1, 10, 11, 55, 64, 38, 39, 41 and 48), WO2012/135408 (including h409A11, h409A16, and h409A17), WO2012/145493 (including antibodies 1E3, 1E8, 1H3 and h1H3 Var 1 to h1H3 Var 14), WO2011/110621 (including antibody 949 and the modified versions disclosed in Figures 1 to 11), WO2011/110604 (including antibody 948 and the modified versions disclosed in Figures 3 to 11), WO2010/089411 (including CNCM deposit number 1-4122, 1-4080 or 1-4081), WO2010/036959 (including the antibodies in Table 1 of Example 1), WO2010/029435 & WO2010/029434 (including clones 2, 10 and 19), WO2008/156712 (including hPD-1.08A, hPD-1.09A, h409A11, h409A16 and h409A17 and the antibodies described in Example 2, Table H, Example 4 and table IV), WO2006/121168 (including clones 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, and 2D3), WO2004/004771 or WO2004/056875 (including PD1-17, PD1-28, PD1-33, PD1-35, PD1-F2 and the Abs described in Table 1); the sequences and features of the anti-PD-1 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CTLA-4, e.g. hCTLA-4. In one embodiment, the CTLA-4 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from ipilimumab (MDX-010, CAS No. 477202-00-9), tremelimumab (ticilimumab/ CP-675,206), antibody clone 2F1, clone 1F4 (Abnova Corporation), clone 9H10 (EMD Millipore), clone BNU3 (GeneTex), clone 1 E2, clone AS32 (Lifespan Biosciences) clone A3.4H2.H12 (Acris Antibodies), clone 060 (Sino Biological), clone BU5G3 (Creative Diagnostics), clone MIH8 (MBL International), clone A3.6B10.G1, or clone L3D10 (BioLegend) or from any one of the anti-CTLA-4 antibodies described in WO2017/087588 (ISVs disclosed in Figure 2), WO2017/084078 (clones C2, C4, C10, C11, C12 and C13, and figures 4-7), WO2016/196237 (including AGEN1884w, AGEN2041w, the sequences in Figures 19A, 19B and Tables 1-6), WO2016/130986 & WO2016/130898 (including E8, F7 and the Abs described in Table 4), WO2016/015675 (including hybridoma LT001 and anitbodies 8D2, 8D2H1L1, 8D2H2L2, 8D2H3L3, 8D2H2L15 and 8D2H2L17), WO2012/120125 (including 3B10, 8H5, and the Abs identified in Examples 1, 2, 3 and 5), WO2010/097597 (including JMW-3B3 and the variants and fragments disclosed), WO2009/100140 (including 10D1, 1H5, 3A4, 6C10 and the antibodies described in Figures 1 to 6), WO2007/008463 & WO2006/101692 & WO2006/101691 & WO2006/048749 & WO2005/09238, (including 4.1.1, 4.8.1, 4.10.2, 4.13.1, 4.14.3, 6.1.1, 11.2.1, 11.6.1, 11.7.1, 12.3.1.1 , 12.9.1.1, and 10D1), WO2006/096491 (including ATCC Deposit No. 11.2.1 11.2.1.4 PTA-5169 and 4.1.1 4.1.1.1 PTA-5166), WO2006/066568 (including TGN2122.C, TGN2422.C, 4.8H10H5 and 4.3F6B5 and the antibodies described in tables 3 to 14), WO2006/029219 (including L3D10, L1B11, K4G4, KM10, and YL2), WO2004/029069 (including ATCC deposit number PTA-4537), WO01/54732 (including antibodies 25, 26, 27, 29, 33, 34, 35, 36 and 38), WO01/14424 (including 3A4, 9A5, 2E2, 2E7, 4B6, 4E10, 5C4, 5G1, 11E8, and 11G1 and the

antibodies identified in Examples 3 and 4 and table 3) and WO00/37504 (including 3.1.1, 4.1.1, 4.8.1, 4.10.2, 4.13.1, 4.14.3, 6.1.1, 11.2.1, 11.6.1, 11.7.1, 12.3.1.1, and 12.9.1.1); the sequences and features of the anti-CTLA-4 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds TIGIT, e.g. human TIGIT. In one embodiment, the TIGIT antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from RG-6058 (MTIG-7192A) or from any one of the anti-TIGIT antibodies described in WO2017/053748 (including 1A4, 1D3, 4A3, 10A7, 4.1D3.Q1E, h10A7.K4G3, 4.1D3 and the other antibodies described in Examples 1 and 2), WO2017/037707 (including VSIG9#1 and 258-csl#4), WO2017/030823 (including 14D7, 26B10 and humanized versions in Example 3), WO2016/191643 (including 313R11, 313R12, 313R14, 313R19, 313R20, ATCC PTA-122180 and ATCC PTA-122181), WO2016/106302 (including 14B2, 13E6, 6F9, 11G11, 10C9, 16F6, 11C9, 27A9, 10D7, 20G6, 24E8, 24G1, 27F1, 15A6, 4E4, 13D1, 9B11, 10B8, 22G2, 19H2, 8C8, 17G4, 25E7, 26D8 and 16A8), WO2016/028656 (including 14A6, 28H5 or 31C6 and humanized versions from Example 6), and WO2009/126688 (US2013/0251720, including 10A7 and 1F4); the sequences and features of the anti-TIGIT antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds TIM-3, e.g. human TIM-3. In one embodiment, the TIM-3 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from F38-2E2 (BioLegend), clone 2E2 (Merck Millipore), clone 6B6E2, clone 024 (Sino Biological) clone 344801 (R&D Systems), clone E-18, clone H-191 (Santa Cruz Biotechnology), or clone 13A224 (United States Biological), TSR-022 (Tesaro) or from any one of the anti-TIM-3 antibodies described in WO2017/079115 (including anti-TIM3 antibodies listed in tables 30-38), WO2017/055404 (including PD1TIM3-0389, PD1TIM3-0168, PD1TIM3-0166, TIM3-0038, TIM3-0018, TIM3-0028, TIM3-0438 – Table C), WO2017/031242 (Table 10), WO2016/179194 (including antibodies in Figure 1b, including mAb F38-2E2 and 2E2), WO2016/171722 (including 344823 and antibodies from the hybridomas 7D11, 10G12, 11G8, 8B.2C12 and 25F.1D6), WO2016/161270 (including APE5137 and APE5121), WO2016/111947 (including mAb5, mAb13, mAb15, mAb17, mAb21, mAb22, mAb26, mAb27, mAb48, mAb58 and mAb91), WO2016/071448 (including TIM3-0016, TIM3-0018, TIM3-0021, TIM3-0022, TIM3-0026, TIM3-0028, TIM3-0030, TIM3-0033, TIM3-0038, TIM3-0433, TIM3-0434, TIM3-0438 and TIM3-0443), WO2016/068802 (including 1B9, 1H9, 1H10, 2C7, 2F4, 2G6, 1D9, 1F4 and 2C8 – Figures 1, 2 & 3), WO2016/068803 (including A3, B10, G6, G7, G9, A11 and A11_gl – Figure 1, 2 & 3), WO2015/117002 (including ABTIM3, ABTIM3-hum02, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum12, ABTIM-hum01, ABTIM-hum04, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum04, ABTIM3-hum21, ABTIM3-hum03, ABTIM3-hum11 and antibodies listed in Table 9), WO2015/048312 (including 5D12), WO2014/022332 (including 2C12), WO2013/006490 (including antibodies in Table 1), WO2011/155607 (including 512, 644, 4545, 4177, 8213, 344823 and 34823), WO2003/063792 (including antibody 8B.2C12 and 25F.1D6), WO2017/019897 (including antibody

molecules disclosed in Tables 1-4, including ABTIM3, ABTIM3-hum20, ABTIM3-hum22 and ABTIM3-hum23), WO2016/079050 & WO2016/079050 (including Tim3_0022, Tim3_0016, Tim3_0018, Tim3_00122, Tim3_0022, Tim3_0021, Tim3_0028, Tim3_0026, Tim3_0033, Tim3_0038, Tim3_0030, 1.7.E10, F38-2EL and 27-12E12); the sequences and features of the anti-TIM-3 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds LAG-3, e.g. human LAG-3. In one embodiment, the LAG-3 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from antibody clone 17B4 (Enzo Life Sciences), or clone 333210 (R&D Systems), or clone 14L676 (United States Biological), or C9B7W (PharMingen), or 11E, or IMO321, or mAb C9B7W (BioXcell) or from any one of the anti-LAG-3 antibodies described in WO95/30750, WO2004/078928, WO2008/132601 (including IMP731 Lag-3 Ab, IMP321, A9H12 Lag-3 mAb and 31G11), WO2010/019570 (including 25F7, 26H10, 25E3, 8B7, 11F2 and 17E5), WO2014/140180 (including H5L7, H5L7BW, IMP731 and antibodies in Tables 3 & Table 7), WO2014/179664 (including APE03109), WO2014/008218 (including Lag3.1, Lag3.5, Lag3.6, Lag3.7 and Lag3.8), WO2015/042246, WO2015/116539 (including BMS-986016), WO2015/138920 (including BAP050-hum01 to BAP050-hum20, huBAP050(Ser), BAP050-hum01-Ser to BAP050-hum20-Ser, BAP050-Clone-F, BAP050-Clone-G, BAP050-Clone-H, BAP050-Clone- I, BAP050-Clone-J, BAP050 and BAP050-chi), WO2015/198312 , WO2016/028672 (including Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8 and Ab9), WO2016/126858, WO2016/200782 (including LAG-3 mAb1 to LAG-3 mAb6), WO2017/015560 (including L32D10, L3E3, L3C5, L35D4, L35G6, L33H11, L32A9, L32A4, L3A1 and the antibodies listed in Table 3), WO2017/062888 (including mAb1, H4H15477P, H4H15483P, H4H15484P, H4H15491, H4H17823P, H4H17826P2, H4H17828P2, H4sH15460P, H4sH15462P, H4sH15463P, H4sH15464P, H4sH15466P, H4sH15467P, H4sH15470P, H4sH15475P, H4sH15479P, H4sH15480P, H4sH15482P, H4sH15488P, H4sH15496P2, H4sH15498P2, H4sH15505P2, H4sH15518P2, H4sH15523P2, H4sH15530P2, H4sH15555P2, H4sH15558P2, H4sH15567P2 and H4H17819P), WO2017/019894, WO2017/037203 (including 8E2, 13E2, 34F4, 17B4 and IMP761), WO2017/087589 (including 11B09) or WO2017/087901; the sequences and features of the anti-LAG-3 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds VISTA, e.g. human VISTA. In one embodiment, the VISTA antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from any one of the anti-VISTA antibodies described in WO2016/207717 & WO2015/097536 (including VSTB50, VSTB53, VSTB60, VSTB95, VSTB112, VSTB116, VSTB174, VSTB175, VSTB149, VSTB140 and the antibodies in Table 1A and Examples 7 and 8) and WO2014/190356 (including clone 2D3 and 18C3); the sequences and features of the anti-VISTA antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds an immune modulator. In one embodiment, the antigen-binding site specifically binds an immune modulator selected from BTLA,

hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10, CXCL11 and CD155, or from BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10 and CD155. In one embodiment, the antigen-binding site specifically binds an immune modulator selected from GARP, SIRPα, CXCR4, BTLA, hVEM and CSF1R.

In one embodiment, the antigen-binding site specifically binds GARP, e.g. human GARP. In one embodiment, the GARP antigen-binding site comprises the CDRH1, CDRH2, CDR3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from G14D9, Plato-1, 272, G6, 50 G10 or 7B11 or from any of one of the anti-GARP antibodies described in WO2007/113301 & WO2015/015003 (including MHGARP8, LHG-10, LHG-10-D, LHG-10.3-D, LHG-10.4-D, LHG-10.5-D, LHG-10.6-D, LHG-10.3, LHG-10.4, LHG-10.5, LHG-10.6, 27E10, MHGARP1, MHGARP2, MHGARP3, MHGARP4, MHGARP5, MHGARP6, MHGARP7 and MHGARP9), WO2017/051888 (including 110F, 105F, c151D, c198D, h198D, h151D, h151D-H1L1 and h198D-H3L4); the sequences and features of the anti-GARP antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds SIRP , e.g. human SIRP . In one embodiment, the SIRP antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from ED9 (ThermoFisher), or 602411 (Novus Biologicals), or from any one of the anti-SIRP antibodies described in WO97/48723, WO00/24869 (including 10C4), WO00/66159 (including ED9 and ED17), WO01/40307, WO02/092784 (including SE5A5, SE7C2 and SE12C3), WO2004/108923 (including SE12C3 and 2F34), WO2009/046541 (including P84), WO2011/076781, WO2012/172521, WO2012/040207 (including SE5A5 and mouse P84), WO2013/056352 (including 29-AM4-5, Ab AM4-5, AM5-1, AM5-3, AM5-5, AM5-6, SIRPalpha-AM3-35, AM4-1, SIRP29-AM3-35, SIRP29-AM4-5, SIRP29-AM4-1, 29-AM2-2, 29-AM4-4, 29-AM4-1, 29-AM4-5, 29-AM3-35 and SIRP29-AM3-63), WO2016/063233, WO2016/205042 (including P362) or WO2015/138600 (including KWAR23); the sequences and features of the anti-SIRP antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CXCR4, e.g. human CXCR4. In one embodiment, the CXCR4 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region of ulocuplumab/BMS-936564, clone 44717.111 or PF-06747143 or from any one of the anti-CXCR4 antibodies described in WO97/49424 (including MAB12G5), WO99/50461, WO01/42308, WO03/066830 & WO2003/066830 (including Ab124 and Ab125), WO2004/059285 (including ALX40-4C), WO2006/089141 (including mAbs 2N, 6R, 18, 19, 20, 33 and 48), WO2007/005605, WO2008/142303 (including MAB170, MAB171, MAB173 and MAB172), WO2008/060367 & WO2013/071068 & WO2015/015401 (including BMS-936564/MDX-1338), WO2009/140124 (including antibody I, II, III, IV and V), WO2009/117706 (including 701, 708, 716, 717, 718 and 4G10), WO2011/161266 (including 4CXCR100, 4CXCR103, 4CXCR104, 4CXCR101, 4CXCR238D2 and 4CXCR238D4), WO2011/098762 (including C-9P21 (Table 1), B-1M22 (Table 2),

C1124 (Table 3), D-1K21 (Table 4) and 9N10 (Table 5)), WO2012/175576, WO2013/013025 (including 2A4, 6C7, 4C1, 7C8, 5C9 and 5E1), WO2013/017566 (including Mab 427aB1 and 515H7), WO2013/017562 (including 1-3859 Mab and 515H7), WO2015/069874 (including antibodies corresponding to Seq ID numbers 25 and 29), WO2015/015401 (including 12A11, 6B6, 3G10, m3G10.hlgG1, m3G10.hlgG4, h3G10.A57.hlgG1, h3G10.A57.A58A.hlgG1, h3G10.1.91.A58A.hlgG1, h3G10.1.91.A58B.hlgG1 and h3G10.2.37.2.72.hlgG1), WO2016/156570 (including 281F12, 281A6 and 281D4), WO2016/109872 (including antibodies listed in tables 1, 2, 9 & 12, -114- -272- -523- - - - -746 and -1121), WO2017/071625, WO2012/175576, WO2010/125162 & WO2012/055980 & WO2011/121040 & WO2010/037831 (including c414H5 (414H5), c515H7 (515H7) and 301aE5), WO2009/138519 (including ALX40-4C, 238D2, 238D4, 237B5 antibodies and sequences listed in table 1, table 1.1, table A-I, table B-1.1 & B-5), WO2011/042398 (including 238D2 and 238D4), WO2011/083140 (including those disclosed in Tables C-2, C-3, C-4 & C-5, Figure 2 and ALX-0651, 15H3, 10E12, 10G10, 238B6, 10E9, 281E10, 10A10, 14A2 and 15A1) or WO2011/083141; the sequences and features of the anti-CXCR4 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds BTLA, e.g. hBTLA. In one embodiment, the BTLA antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from antibody clone 1B7, clone 2G8, clone 4C5 (Abnova Corporation), clone 4B8 (antibodies-online), clone MIH26 (Thermo Scientific Pierce Antibodies), clone UMAB61 (OriGene Technologies), clone 330104 (R&D Systems), clone 1B4 (Lifespan Biosciences), clone 440205, clone 5E7 (Creative Diagnostics) or from any one of the anti-BTLA antibodies described in WO2016/176583 (including clone 6F4), WO2011/014438 (including 8D5, 8A3, 20H4, 21H6, 15C5, 19A7 and 4C7), WO2010/106051 (including CNCM deposit number 1-4123) and WO2008/076560 (including 1B4, E4H9, 3C2, 3C2a, 6A5, 11E2, E8D9, 10H6 and 4C9 as detailed in Example 2); the sequences and features of the anti-BTLA antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds hVEM, e.g. human hVEM. In one embodiment, the HVEM antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from any one of the anti-HVEM antibodies described in WO2008/083169 (including LBH1); the sequences and features of the anti-BTLA antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CSF1R. In one embodiment, the CSF1R antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from any one of the anti-CSF1R antibodies described in WO2009/026303 (including 1.2, 1.109, 2.360 and 1.2.SM and the antibodies in figures 1 and 2), WO2009/112245 (including CXIIG6), WO2011/070024 (including Mab 2F11, 2E10, 2H7 and 1G10, and their derivatives), WO2011/107553 (including 7H5.2G10/DSM ACC2922), WO2011/123381

(including antibody 1 and antibody 2), WO2011/131407 (including 7G5.3B6/DSM ACC2921), WO2011/140249 (including 0301, 0302, and 0311 their derivatives and the antibodies in tables 2, 3 and 5), WO2013/169264 & WO2014/036357 & WO2016/106180 & WO2016/168149 (including huAb1 to huAb16), WO2012/110360 & WO2013/057281 (including CXIIG6, H19K12, H27K5 and H27K15 and the humanised antibodies of tables 1 and 2), WO2013/087699 (including 9D11.2E8 and 10H2.2F12), WO2014/072441 (including H27K15), WO2014/173814 & WO2013/132044 (including Mab 2F11, Mab 2E10, Mab 2H7, Mab 1G10 and sc2-4A5 and the antibodies in Table 3 and 3b), WO2015/028455 & WO2015/028454 (including Ab535, Ab969, and derivatives, e.g. Ab969.g2), WO2015/036511 & WO2016/207312 (including 2F11, 2E10 and the derivatives described in embodiment 33) and WO2017/049038 (including ALM-423 and the antibodies listed in Table 2); the sequences and features of the anti-CSF1R antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CD39, e.g. human CD39. In one embodiment, the CD39 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from BY40, BY12, BA54g (Biolegend), BU61 (Santa Cruz Biotech), A1 (Ebiosciences), AC2 (Immunotech), 22A9 (Abcam), 24DMS1 or any one of the anti-CD39 antibodies described in WO96/32471, WO00/04041, WO01/10205 (including CD39L4), WO2009/09547 (including CNCM-I-3889/BY40), WO2014/169255, WO2012/085132 (including antibodies VY12, BY40 and BA54g), WO2016/073845 (including R29-5-13A, R29-5-71A, R29-5-165C and R29-9-8B), WO2017/089334 (including 1-391, 1-392 and antibodies produced from hybridomas I-3889 and CNCM I-41171) and WO2009/095478; the sequences and features of the anti-CD39 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CD40, e.g. human CD40. In one embodiment, the CD40 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from BMS3h-56-269, CP-870,893, dacetuzumab, SEA-CD40, ADC-1013, RO7009789 and Chi Lob 7/4, or from any one of the anti-CD40 antibodies described in WO2017/059243, WO2017/059196, WO2017/040932, WO2017/040566, WO2017/004016, WO2017/004006, WO2016/196314, WO2016/028810, WO2016/023960, WO2016/023875, WO2015/134988, WO2015/091853, WO2014/070934, WO2014/065403, WO2014/065402, WO2014/04298, WO2013/164789, WO2013/034904, WO2012/149356, WO2012/145673, WO2012/125569, WO2012/111762, WO2012/075111, WO2012/065950, WO2012/041635, WO2011/123489, WO2010/123012, WO2010/104761, WO2010/121231, WO2009/062125, WO2010/104747, WO2010/104748, WO2010/104749, WO2010/024676, WO2009/094391, WO2009/062054, WO2008/091954, WO2007/130493, WO2007/129895, WO2007/124299, WO2007/053767, WO2007/053661, WO2006/128103, WO2006/073443, WO2005/063981, WO2005/063289 (US2012/0263732), WO2005/044855, WO2005/044306, WO2005/044294, WO2005/044307, WO2005/044304, WO2005/044854, WO2005/044305, WO03/040170 (US7,563,442B, US7,618,633B, US7,338,660B, US7,288,251B, US7,626,012B,

US8,388,971B, US2013/0024956), WO03/029296, WO02/088186, WO01/83755, WO02/28905, WO02/28480, WO02/28481, WO02/28904, WO01/37870, WO01/16180, WO00/75348 WO99/61057, WO99/42075, WO97/31025, WO95/17202 and WO95/09653; the sequences and features of the anti-CD40 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CD73, e.g. human CD73. In one embodiment, the CD73 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from 1E9 (Santa Cruz Biotechnology), AD2, 7G2, 4G4 or from any one of the anti-CD73 antibodies described in WO2017/064043 (including 7H10, 12F9, 15D7, 4B11, 11D9 and 9D2), WO2016/081748 (including 4C3, 7A11, 6E11, 5F8, 4C3, 11F11, 11A6, CD73.4-1, CD73.4-2, CD73.3, 11F11-1, 11F11-2, 11F11, 4C3-1, 4C3-2, 4C3-3, 4D4, 10D2-1, 10D2-2, 11A6, 24H2, 5F8-1, 5F8-2 and 5F8-3), WO2016/131950 (including 11E1, 8C7, 3C12 and 6E1), WO2016/075176 (including MEDI9447, clone 10.3 and clone 2C5) & WO2016/075099 (including CD730004, CD730008, CD7300011, CD730021, CD730042, CD730046, CD730047, CD730068 and CD730069), WO2016/055609 (including 11E1, 6E1, 3C12 and 8C7); the sequences and features of the anti-CD73 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CD96, e.g. human CD96. In one embodiment, the CD96 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region of 6A6, or NK92.39 (E bioscience), 1C8, 3H8, MAA6359 or from any one of the anti-CD96 antibodies described in WO2008/073316, WO2009/007124, WO2013/184912, WO2014/089169, WO2014/149310 (including antibody 3.3), WO2015/024060 or WO2015/024042, WO2015/024060 (including mAb 3.3); the sequences and features of the anti-CD96 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CXCR2, e.g. human CXCR2. In one embodiment, the CXCR2 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from any one of the anti-CXCR2 antibodies described in WO2015/169811 (including HY29 and HY29GL), WO2014/170317 (including CX2-Mab#1 to #19), WO2012/062713, WO2013/168108 (including 163D2-127D1, 163E3-127D1, 163E3-54B12, 163D2-54B12, 2B2-163E3, 2B2-163D2, 97A9-2B2, 97A9-54B12, 127D1-163D2, 127D1-163E3, 2B2-97A9, 54B12-163D2, 54B12-163E3, 163D2-2B2, 163E3-2B2, 127D1-97A9, 54B12-97A9, 97A9-127D1 and derivatives thereof), WO2009/117706 (including 48311.211, 5E8/CXCR2, clone 19 and derivatives thereof), WO2009/120186 (including RII115, 48311 and derivatives thereof) and WO2002/26249; the sequences and features of the anti-CXCR2 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CD200, e.g. human CD200. In one embodiment, the CD200 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from DX-109, samalizumab/ALXN-6000, TTI-200.7 or from any one of the anti-CD200 antibodies described in WO99/24565 (including

M3B5 and the antibodies in Examples 4 and 5), WO02/11762 (including 3B6 and the antibodies in the Examples), WO2004/060295 (US2004/0213783), WO2004/078938 (including scFv-9), WO2006/020266 (US8,840,885B2, including CG1R3A10, cG2aR3A10, cG2aR3B7, dGlR3A5, dGlR3B5, and dGlR3B10 and the antibodies described in Figures 9A-9C, Figures 21A and 21B), WO2007/084321 (US8,709,415B2, including ALXN5200, hB7VH3VL2, C2aB7G1, C2aB7G2/G4, V3V2-G1 and V3V2-G2/G4), WO2009/014745 (including OX90mG2a (Fig. 10), OX90NE and OX90NE-AG), and WO2011/100538 & US2013/0189258 (including Antibody 1 and Antibody 2); the sequences and features of the anti-CD200 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CCR4, e.g. human CCR4. In one embodiment, the CCR4 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from mogamulizumab, KM3060 (see Niwa ., 2004, Cancer Research 64, 2127-2133), and KW-0761 (see Ishida ., Annals of Oncology 2008, vol 19, supplement 4, 513) or from any one of the anti-CCR4 antibodies described in WO2016/178779 & WO2016/057488 (including mAb2-3, 1-44, 1-49, 2-1 and 2-2), WO2015/179236 (including KW-0761), WO2013/166500 (including mAb1567, c1567, h1567, mAb 1-4 and 2-3 and the antibodies in Examples 6 and 13), WO2012/076883 (including antibodies 208, 306, 308, 406, 501, 503, 601, 603 and 803 – Tables 1-9), WO2010/142952 (including 17G, 9E, 11F, 9E10, 9E10J and 9E1D – see Tables 1-16), WO2009/086514 (including mAb1567 and the humanised mAbs in Example 14), WO2005/035582 (including the DG44/CCR4 antibody and the Ms705/CCR4 antibody (FERM BP-8467)), WO2005/053741 & WO01/64754 (US6,989,145B, US7,666,418B, US8,197,814B, US8,632,996B, including KM2160 (FERM BP-10090), KM2760 (FERM deposit BP-7054)), WO2003/018635 (including KM2160, KM8759 (FERM BP-8129) and KM8760 (FERM BP-8130), WO00/42074 (US6,488,930B, US7,138,117B, including 2B10, 10E4, 1G1 and the antibodies deposited as ATCC accession number HB-12624 and HB-12625) and WO00/41724 (US6,881,406B, US6,245,332B, including 1G1 and the antibody deposited under ATCC accession number HB-12624); the sequences and features of the anti-CCR4 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CXCL9, e.g. human CXCL9. In one embodiment, the CXCL9 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from mAb 392-100 or AF392 (R&D Systems).

In one embodiment, the antigen-binding site specifically binds CXCL10, e.g. human CXCL10. In one embodiment, the CXCL10 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region of mAb266 (R & D systems) or from any one of the anti-CXCL10 antibodies described in WO017/8708 (including CR.G (IP-10) (IgG1) (PharMingen) ande IP-10 (IgG)(A.Luster), WO02/15932, WO03/006045, WO2004/082714, WO2004/045525, WO2004/045526, WO2004/101511 (including antibodies in table 1 and AIP12, HuAIP12, MuAIP12, AIP13, HuAIP13, MuAIP13, AIP6, AIP8, AIP14, AIP18, AIP21, AIP22, AIP5 and

AIP17), WO2005/060457 (including AIP5, AIP6, AIP8, AIP10, AIP12, AIP13, AIP14, AIP17, AIP18, AIP21, AIP22, AIP32 and AIP36), WO2005/011605, WO2005/023201, WO2005/058815 (including 1D4, 1E1, 2G1, 3C4, 6A5, 6A8, 6B10, 7C10, 8F6, 10A12 and 10A12S13C4), WO2005/084708, WO2006/039819, WO2006/118085, WO2008/047486, WO2008/044824 (including antibodies #124, #31, #28, #43 and #137), WO2008/106200, WO2009/023566, WO2012/149320 (including MSX-1100 and 6A5), WO2014/003742 (including the antibody of Example 14), WO2013/170735, WO2014/189306, WO2015/063187; the sequences and features of the anti-CXCL10 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CD155, e.g. human CD155. In one embodiment, the CD155 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from clone SKII.4 (BioLegend).

In one embodiment, the antigen-binding site specifically binds an immune activator. In one embodiment, the antigen-binding site specifically binds an immune activator selected from CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic activity against CXCR3), CD3 and ICOS (e.g. agonistic activity against ICOS). In one embodiment, the antigen-binding site specifically binds an immune activator selected from ICOS, CD137, GITR and OX40.

In one embodiment, the antigen-binding site specifically binds CD137, e.g. hCD137. In one embodiment, the CD137 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from urelumab, BMS-663513, PF-05082566 (Pfizer), 1D8 and 3E1, 4B4 (BioLegend 309809), H4-1BB-M127 (BD Pharmingen 552532), BBK.2 (Thermo Fisher M S621PABX), 145501 (Leinco Technologies B591), the antibody produced by cell line deposited as ATCC No. HB-11248 (US Patent 6974863) or XmAb-5592, or from any one of the anti-CD137 antibodies described in WO2017/04945, WO2016/134358, WO2015/179236, WO2012/177788, WO2012/145183, WO2012/032433, WO2009/135019, WO2005/035584, US Patent 6974863, WO2004/055513 and WO2004/010947; the sequences and features of the anti-CD137 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds GITR, e.g. hGITR. In one embodiment, the GITR antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from MK4166, TRX518, TRX385, MAB689 (R & D Systems), YGITR765 (Novus Biologicals) or 1D8 (Novus Biologicals), or from any one of the anti-GITR antibodies described in WO2015/187835 (including 28F3, 3C3-1, 3C3- -1, 9G7- - -2, 19D3, 18E10, and 6G10), WO2015/184099 (including 1042-7, 32-15, 1039-45, 1333-21, 231-1039-45, 231-32-15, Hum231#1, Hum231#2, m6C8, pab1964, to pab1973, pab1975 to pab1977, pab1979 to pab1981, pab1983, pab2159, pab2160, pab2161 and the antibodies in tables 1 and 2), WO2015/031667 (including antibodies Ab1 to Ab59 in table 1), WO2015/026684 (including an antibody with a CDR sequence of Seq ID 1-66), WO2013/039954 (including, 2155, 1718, 1649, 1362, 954, 827, 698, 706 and antibodies listed in Tables 1 & 3), WO2011/051726 (including

antibodies containing CDRs a-f listed on page 17), WO2011/028683 (including antibodies 36E5, 61F6, 61G6, 3D6, 6H6, 1D8, 17F10, 35D8, 49A1, 9E5, 31H6 and antibodies from hybridomas PTA-9889, PTA-9890, PTA-9891, PTA-9892, PTA-9893, PTA-10286, PTA-10287, PTA-10288, PTA-10289, PTA-10290, and PTA-10291), WO2009/009116 (including antibody 2F8), WO2007/133822 (including antibodies listed in Table 1), WO2006/105021 (including 6C8, 2F8, HuN6C8-Agly, HuQ6C8-Gly, and HuQ6C8-Agly), WO2006/050172 & WO2004/084942 (including DTA-1), WO03/006058 (including anti-GITR/TNFRSF18# AF524), WO2016/054638 (including mAb #1-81, #3-167, #5-139, #7-192, #10-116, #11-126, #12-46, #13-169, #14-182, #15-68 and #17-60), WO2016/196792 (including 6G10, 28F3, 19D3, 18E10, 3C3, 2G6, 8A6, 9G7, 14E3 and 19H8), WO2017/087678 (including 28F3, 19D3, 18E10, 3C3-1, 3C3-2, 2G6, 8A6, 9G7-1, 9G7-2, 14E3, 19H8-1, 19H8-2 and 6G10); the sequences and features of the anti-GITR antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds OX40, e.g. hOX40. In one embodiment, the OX40 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from GSK3174998, L106 BD (Pharmingen Product # 340420), ACT35 (Santa Cruz Biotechnology, Catalog # 20073), MOXR0916, MEDI-6469, MEDI-0562, 9B12 (Weinberg, A.D., J Immunother 29, 575-585 (2006)), the humanised anti-OX40 Ab described in Morris ., Mol Immunol. May 2007; 44(12):3112-3121, or from any one of the anti-OX40 antibodies described in WO2017/077085 (including SAP9, SAP28.2, SAP15.3, SAP29-50, SAP25-29 and SAP29-23 and humanised versions described in Examples 4 and 5), WO2017/063162 (including O3, O19, O21 and the affinity matured version in Example 5 – Table 2, including 21#H28H33, 21#H65, 21#H96, 21#VHnew-L80, 21#H96-L80), WO2017/050729 (including SP197), WO2017/021912 & WO2017/021910 (including ANTIBODY 106-222, OX86, and the antibodies described in Figures 6 and 7), WO2016/200836 & WO2016/200835 (including MOXR0916/1A7.gr1 IgG1), WO2016/196228 (including 3F4, 14B6-1, 14B6-2, 23H3, 18E9, 8B11, 20B3, 20C1, 6E1-1, 6E1-2, 14A2, 14A2-1, 14A2-2, L106, OX40.1, OX40.5, OX40.8, OX40.6, and OX40.16 and OX40.21 – Figures 1 to 10), WO2016/179517 (including 11D4, pab1949, pab1949-1, pab2044, pab2193-1, Tables 1 to 4), WO2016/057667 (including 9B12 and OX40mAb24), WO2015/153513 (including 3C8, 1D2, 1A7 and their variants described in the sequence listing, including A1A7.gr1 and 3C8.gr.5, the antibodies described in Figure 1), WO2014/148895 (including ACT35, 12H3, 12H3 (Fig 25) - and humanised versions VL1H1, VL1VH2, VL1VH3, VL2H1, VL2VH2 and VL2VH3 (Fig 43 & 44) and 20E5 (Fig 24)), WO2013/068563 (including A26 [Fig 2]), WO2013/038191 (including ACT35, 12H3 and 12H3), WO2013/028231 (including 119-122, 119-43-1, 106-222 and the antibodies in Table 1), WO2013/008171 (including 2F8, 1D4 and their derivatives, including VH6/VL9, and the antibodies in Figures 4 and 5 and tables 6 and 7), WO2012/027328 (including 119-122, 119-43-1, Hu106 and Hu106-222), WO2010/096418 (including A26), WO2008/106116 (including the antibodies in Tables 1 and 2, and A10 (inc A10A-F), B66 – Fig14 – B2, B24, B36, B37, and B39) and WO2007/062245 (including 112V8 (ATCC No. PTA-7219), 112Y55 (ATCC No. PTA-7220), 112Y131

(ATCC No. PTA-7218), 112F32 (ATCC No. PTA-7217) and 112Z5 (ATCC No. PTA-7216); the sequences and features of the anti-OX40 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CXCR3, e.g. CXCR3. In one embodiment, the CXCR3 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from GSK3174998 or from any one of the anti-CXCR3 antibodies described in WO2016/200836, WO2016/200835, WO2016/196228, WO2016/179517, WO2016/057667, WO2015/153513, WO2014/148895, WO2013/068563, WO2013/038191, WO2013/028231, WO2013/008171, WO2012/027328, WO2010/096418, WO2011/073180, WO2008/106116 and WO2007/062245; the sequences and features of the anti-CXCR3 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CD27, e.g. hCD27. In one embodiment, the CD27 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from any one of the anti-CD27 antibodies described in WO2016/145085 (including 1F5), WO2015/016718 (including hCD27.15 and 1F5), WO2014/140374 (including 2F2, 5F24, 5F32, 10F13, 10F31, 11F26, 1052 to 015, F2A4B2 and their derivatives, including hz5F24VH+V5Q, hz5F24VL+K45Q), WO2013/138586 (including C2177, C2186, C2191, and C2192 and the derivatives in Examples 8 to 12, and tables 7 to 42), WO2012/004367 (including hCD27.15/ATCC number PTA-11008), WO2011/130434 (including 1G5, 1H8, 3H12, 3H8, 2G9, 1F5, 3A10, 2C2, ms 1A4, ms 9F4 and ms M-T271), WO2011/081164 & WO2010/001908 (including KM4027, KM4028, KM4026, KM4030, KM4032 and derivatives thereof), WO2008/051424 (including LG3A10 and AT124-1); the sequences and features of the anti-CD27 antibodies are incorporated herein by reference.

In one embodiment, the antigen-binding site specifically binds CD3, e.g. hCD3. In one embodiment, the CD3 antigen-binding site comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region from OKT3 antibody, otelixizumab, teplizumab or visilizumab, or from any one of the anti-CD3 antibodies described in WO2017/010874, WO2017/009442, WO2016/204966, WO2016/180721, WO2016/179003, WO2016/116626, WO2016/014974, WO2015/104346, WO2015/095392, WO2015/001085, WO2014/047231, WO2013/188693, WO2013/186613, WO2013/158856, WO2012/173819, WO2012/162067, WO2005/118635, WO2004/108158, WO2004/052397, WO2004/024771, WO01/51644, WO00/05268, WO97/44362, WO93/19196, WO92/06193 and WO91/09968; the sequences and features of the anti-CD3 antibodies are incorporated herein by reference.

Aspect 1b. An immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

b) A heavy chain constant region;

c) Optionally, a linker, (L); and

d) An IL-2 cytokine;

and wherein the light chain comprises in N- to C-terminal direction:

e) A V_L domain comprising CDRL1, CDRL2 and CDRL3; and

f) A light chain constant region, (C_L);

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to an antigen selected from: an immune checkpoint inhibitor (such as PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. TIGIT, TIM-3 and LAG-3), an immune modulator (such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD
CXCL10 and CD155, e.g. GARP, SIRPα, CXCR4, BTLA, hVEM and CSF1R), and an immune activator (such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies), CD27, CD3 and ICOS (e.g. agonistic anti-ICOS antibodies), for example ICOS, CD137, GITR and OX40).

In another embodiment, the antigen-binding site that specifically binds to an antigen selected from: an immune checkpoint inhibitor (such as PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. TIGIT, TIM-3 and LAG-3), an immune modulator (such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10
CXCR4, BTLA, hVEM and CSF1R), and an immune activator (such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies), CD3 and ICOS (e.g. agonistic anti-ICOS antibodies), for example ICOS, CD137, GITR and OX40).

Any of the embodiments of aspect 1 and/or aspect 1a apply to aspect 1b. Any of the features or embodiments of aspects 2 to 54 apply to aspect 1b. Any of the features of the antibodies or other embodiments or features of concepts 1 to 70 apply to aspect 1b.

In one embodiment, the antigen binding site specifically binds any of the antigens as set out in aspect 1a.

In one embodiment, the antigen-binding site specifically bind to hPD-L1 as defined by Seq ID No:1, and competes for binding to said hPD-L1 with the antibody 1D05; and wherein the immunocytokine comprises a V_H domain which comprises a CDRH3 comprising the motif X1GSGX2YGX3X4FD, wherein X_1, X_2 and X_3 are independently any amino acid, and X_4 is either present or absent, and if present, may be any amino acid.

In either of aspect 1 or 1a, the wording of part f) may be substituted to read: "f) a cytokine, e.g. selected from IL-7, IL-15, IL-21, IL-12, GM-CSF, TNF , CXCL9, CXCL10 and interferon- ". In 1b, the wording of part d) may be substituted for "d) a cytokine, e.g. selected from IL-7, IL-15, IL-21, IL-12, GM-CSF, TNF , CXCL9, CXCL10 and interferon- ". Thus, the immunocytokines as disclosed herein may contain cytokines other than a cytokine having IL-2 cytokine activity. In one embodiment, the cytokine is IL-7 (Seq ID No:330). In one embodiment, the cytokine is IL-15 (Seq ID No:331). In one embodiment, the cytokine is IL-21 (Seq ID No:332). In one embodiment, the cytokine is IL-12, comprising the -chain (Seq ID No:336 -chain (Seq ID No:337). In one

embodiment, the cytokine is GM-CSF (Seq ID No:333). In one embodiment, the cytokine is TNF (Seq ID No:335). In one embodiment, the cytokine is TGFβ. In one embodiment, the cytokine is CXCL9 (Seq ID No:338). In one embodiment, the cytokine is CXCL10 (Seq ID No:339). In one embodiment, the cytokine is interferon- (Seq ID No:334).

In another embodiment, the cytokine is an immune-stimulating cytokine. In another embodiment, the cytokine is a T-cell stimulating cytokine.

Aspect 2. An immunocytokine according to aspect 1, wherein X_1 is a hydroxyl-containing amino acid, optionally T.

Aspect 3. An immunocytokine according to aspect 1 or aspect 2, wherein X_2 is a basic amino acid, optionally K.

Aspect 4. An immunocytokine according to any one of aspects 1 to 3, wherein X_2 is a hydroxyl-containing amino acid, optionally S or T.

Aspect 5. The immunocytokine according to any one of claims 1 to 4, wherein X_3 is an aromatic amino acid, optionally W.

Aspect 6. An immunocytokine according to any one of aspects 1 to 5, wherein X_4 is absent.

Aspect 7. An immunocytokine according to any one of aspects 1 to 5, wherein X_4 is present.

Aspect 8. An immunocytokine according to aspect 7, wherein X_4 is an aliphatic amino acid, optionally G.

The features of aspects 2 to 7 may be as defined in any of concepts 2 to 7 hereinabove.

Aspect 9. An immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and
b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;
d) A light chain constant region, (C_L);
e) Optionally, a linker, (L); and
f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 1D05, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:29 or 32, or the CDRH3 sequence of SEQ ID NO:29 or 32 comprising 6 or fewer amino acid substitutions, optionally, wherein the immunocytokine is according to any one of aspects 2 to 8.

In this aspect, any of the features of CDRH3 described in concepts 9, and 9a to l, and any of the embodiments of concept 9 apply .

Aspect 10. An immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

d) A light chain constant region, (C_L);

e) Optionally, a linker, (L); and

f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to hPD-L1; and

wherein the V_H domain comprises a CDRH3 of from 12 to 20 amino acids and which is derived from the recombination of a human V_H gene segment, a human D gene segment and a human J_H gene segment, wherein the human J_H gene segment is IGHJ5 (e.g. IGHJ5*02).

In this aspect, any of the features of CDRH3 described in concepts 10 and 10a apply .

Aspect 11. An immunocytokine according to aspect 10, wherein the human V_H gene segment is IGHV3 (e.g. IGHV3-9, such as IGHV3-9*01).

In this aspect, any of the features of the gene segments described in concept 11, 11a or 11b apply .

Aspect 12. An immunocytokine according to aspect 10 or aspect 11, wherein the antibody or fragment comprises a V_L domain which is derived from the recombination of a human Vκ gene segment, and a human Jκ gene segment, wherein the human V_L gene segment is IGκV1D (e.g. IGκV1D-39, such as -39*01).

In this aspect, any of the features of the gene segments described in concept 12, 12a or 12b apply .

Aspect 13. An immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

d) A light chain constant region, (C_L);

e) Optionally, a linker, (L); and

f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to an epitope that is identical to an epitope to which the antibody 1D05 specifically binds.

In this aspect, any of the features of the epitopes, assays and other embodiments described in any of concepts 13 and 13a to 13l apply .

Aspect 14. An immunocytokine according to aspect 13, wherein the epitope is identified by an unrelated amino acid scan, or by X-ray crystallography.

Aspect 15. An immunocytokine according to aspect 14, wherein the contact residues of the epitope are defined by a reduction in affinity of at least 10-fold in an unrelated amino acid scan, e.g. an alanine scan as determined by SPR.

In this aspect, any of the features of concept 15 apply .

Aspect 16. An immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

d) A light chain constant region, (C_L);

e) Optionally, a linker, (L); and

f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site which competes for binding to hPD-L1 with the antibody 1D05.

In this aspect, any of the features of the antibodies of concepts 16a to 16l or any of the competitive assays and other embodiments described in concept 16, or the features of concept 35 apply .

Aspect 17. An immunocytokine according to any one of aspects 10 to 16, wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:29 or 32, or the CDRH3 sequence of SEQ ID NO:29 or 32 comprising 6 or fewer amino acid substitutions.

In this aspect, any of the features of the antibodies of concepts 17a to 17l apply .

Aspect 18. An immunocytokine according to any preceding aspect, wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:27 or 30 or the CDRH1 sequence of SEQ ID NO:27 or 30 comprising 3, 2 or 1 amino acid substitution(s).

In this aspect, any of the features of the antibodies of concepts 18a to 18l apply .

Aspect 19. An immunocytokine according to any preceding aspect, wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:28 or 31, or the CDRH2 sequence of SEQ ID NO:28 or 31 comprising 4 or fewer amino acid substitutions.

In this aspect, any of the features of the antibodies of concepts 19a to 19l apply .

Aspect 20. An immunocytokine according to any preceding aspect, wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:33, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:33 (for example the V_H domain sequence in any of the heavy chain sequences of Seq ID Nos:47 to 49).

In this aspect, any of the features of the antibodies of concepts 20a to 20l or any of the embodiments of concept 20 apply .

Aspect 21. An immunocytokine according to any preceding aspect comprising first and second copies of said heavy chain.

Aspect 22. An immunocytokine according to any preceding aspect, comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:37 or 40, or the CRDL1 sequence of SEQ ID NO:37 or 40 comprising 3 or fewer amino acid substitutions.

In this aspect, any of the features of the antibodies of concepts 22a to 22l apply .

Aspect 23. An immunocytokine according to any preceding aspect, comprising a V_L domain which comprises the CDRL2 sequence of SEQ ID NO:38 or 41, or the CRDL2 sequence of SEQ ID NO:38 or 41 comprising 2 or 1 amino acid substitution(s), for example a CDRL2 sequence of Seq ID No:50.

In this aspect, any of the features of the antibodies of concepts 23a to 23l apply .

Aspect 24. An immunocytokine according to any preceding aspect, comprising a V_L domain which comprises the CDRL3 sequence of SEQ ID NO:39 or 42, or the CRDL3 sequence of SEQ ID NO:39 or 42 comprising 4 or fewer amino acid substitutions.

In this aspect, any of the features of the antibodies of concepts 24a to 24l apply .

Aspect 25. An immunocytokine according to any preceding aspect, comprising a V_L domain which comprises an amino acid sequence of SEQ ID NO:43, or a light chain variable domain amino acid

sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:43 (for example the V_L domain sequence in the light chain sequence of Seq ID No:50 or 51).

In this aspect, any of the features of the antibodies of concepts 25a to 25l or any of the embodiments of concept 25 apply .

Aspect 26. An immunocytokine according to any preceding aspect comprising first and second copies of said light chain.

Aspect 27. An immunocytokine according to any preceding aspect which specifically binds to cynomolgus PD-L1 as defined by Seq ID No:2.

In this aspect, any of embodiments of concept 27 apply .

Aspect 28. An immunocytokine according to any preceding aspect, wherein the antibody or fragment comprises a kappa light chain.

In this aspect, any of the embodiments of concept 28 apply .

Aspect 29. An immunocytokine according to any one of aspects 9 to 28, wherein the amino acid substitutions are conservative amino acid substitutions, optionally wherein the conservative substitutions are from one of six groups (each group containing amino acids that are conservative substitutions for one another) selected from:

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

In this aspect, any of the embodiments of concept 9 apply .

Aspect 30. An immunocytokine according to any preceding aspect, wherein the antibody or fragment comprises a constant region, e.g. an IgG1 constant region, optionally wherein the constant region is a disabled IgG1 as defined in Seq ID No:205.

In this aspect, any of the features or the embodiments of concepts 30, 31 or 32 apply .

Aspect 31. An immunocytokine according to any preceding aspect wherein the:

A) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;
B) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:33, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:43;

C) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

D) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

E) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

F) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

G) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

H) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

I) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

J) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

K) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

L) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

M) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

N) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

O) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

P) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

Q) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

R) V_H domain comprises an amino acid sequence of SEQ ID No:58 and the V_L domain comprises an amino acid sequence of SEQ ID No:68;

S) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:58, and the V_L domain comprise an amino acid sequence that is at least 85% identical to SEQ ID No:68;

T) V_H domain comprises an amino acid sequence of SEQ ID No:78 and the V_L domain comprises an amino acid sequence of SEQ ID No:88;

U) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:78, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:88;

V) V_H domain comprises an amino acid sequence of SEQ ID No:98 and the V_L domain comprises an amino acid sequence of SEQ ID No:108;

W) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:98, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:108;

X) V_H domain comprises an amino acid sequence of SEQ ID No:118 and the V_L domain comprises an amino acid sequence of SEQ ID No:128;

Y) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:118, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:128;

Z) V_H domain comprises an amino acid sequence of SEQ ID No:158 and the V_L domain comprises an amino acid sequence of SEQ ID No:168;

AA) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:158, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:168;

BB) V_H domain comprises an amino acid sequence of SEQ ID No:178 and the V_L domain comprises an amino acid sequence of SEQ ID No:188;

CC) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:178, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:188;

DD) V_H domain comprises an amino acid sequence of SEQ ID No:138 and the V_L domain comprises an amino acid sequence of SEQ ID No:148;

EE) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:13, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:148;

FF) V_H domain comprises an amino acid sequence of SEQ ID No:244 and the V_L domain comprises an amino acid sequence of SEQ ID No:254;

GG) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:244, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:254;

HH) V_H domain comprises an amino acid sequence of SEQ ID No:264 and the V_L domain comprises an amino acid sequence of SEQ ID No:274;

II) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:264, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:274;

JJ) V_H domain comprises an amino acid sequence of SEQ ID No:284 and the V_L domain comprises an amino acid sequence of SEQ ID No:294;

KK) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:284, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:294;

LL) V_H domain comprises an amino acid sequence of SEQ ID No:13 and the V_L domain comprises an amino acid sequence of SEQ ID No:23; and

MM) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:13, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:23;

NN) V_H domain comprises an amino acid sequence of SEQ ID No:349 and the V_L domain comprises an amino acid sequence of SEQ ID No:359; and

OO) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:349, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:359.

In one embodiment, the amino acid sequence is at least 70% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 75% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 95% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 96% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 97% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 98% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99.5% identical to the specified Seq ID No.

Aspect 32. An immunocytokine according to any preceding aspect wherein the:

A) V_H and the constant region comprise an amino acid sequence of SEQ ID No:299 and V_L and C_L comprise an amino acid sequence of SEQ ID No:45;

B) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:299, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:45;

C) V_H and the constant region comprise an amino acid sequence of SEQ ID No:47 and V_L and C_L comprise an amino acid sequence of SEQ ID No:45;

D) V_H and the constant region comprise an amino acid sequence of SEQ ID No:48 and V_L and C_L comprise an amino acid sequence of SEQ ID No:45;

E) V_H and the constant region comprise an amino acid sequence of SEQ ID No:49 and V_L and C_L comprise an amino acid sequence of SEQ ID No:45;

F) V_H and the constant region comprise an amino acid sequence of SEQ ID No:342 and V_L and C_L comprise an amino acid sequence of SEQ ID No:45;

G) V_H and the constant region comprise an amino acid sequence of SEQ ID No:238 and V_L and C_L comprise an amino acid sequence of SEQ ID No:50;

H) V_H and the constant region comprise an amino acid sequence of SEQ ID No:47 and V_L and C_L comprise an amino acid sequence of SEQ ID No:50;

I) V_H and the constant region comprise an amino acid sequence of SEQ ID No:48 and V_L and C_L comprise an amino acid sequence of SEQ ID No:50;

J) V_H and the constant region comprise an amino acid sequence of SEQ ID No:49 and V_L and C_L comprise an amino acid sequence of SEQ ID No:50;

K) V_H and the constant region comprise an amino acid sequence of SEQ ID No:342 and V_L and C_L comprise an amino acid sequence of SEQ ID No:50;

L) V_H and the constant region comprise an amino acid sequence of SEQ ID No:299 and V_L and C_L comprise an amino acid sequence of SEQ ID No:51;

M) V_H and the constant region comprise an amino acid sequence of SEQ ID No:47 and V_L and C_L comprise an amino acid sequence of SEQ ID No:51;

N) V_H and the constant region comprise an amino acid sequence of SEQ ID No:48 and V_L and C_L comprise an amino acid sequence of SEQ ID No:51;

O) V_H and the constant region comprise an amino acid sequence of SEQ ID No:49 and V_L and C_L comprise an amino acid sequence of SEQ ID No:51;

P) V_H and the constant region comprise an amino acid sequence of SEQ ID No:342 and V_L and C_L comprise an amino acid sequence of SEQ ID No:51;

Q) V_H and the constant region comprise an amino acid sequence of SEQ ID No:299 and V_L and C_L comprise an amino acid sequence of SEQ ID No:298;

R) V_H and the constant region comprise an amino acid sequence of SEQ ID No:47 and V_L and C_L comprise an amino acid sequence of SEQ ID No:298;

S) V_H and the constant region comprise an amino acid sequence of SEQ ID No:48 and V_L and C_L comprise an amino acid sequence of SEQ ID No:298;

T) V_H and the constant region comprise an amino acid sequence of SEQ ID No:49 and V_L and C_L comprise an amino acid sequence of SEQ ID No:298;

U) V_H and the constant region comprise an amino acid sequence of SEQ ID No:342 and V_L and C_L comprise an amino acid sequence of SEQ ID No:298;

V) V_H and the constant region comprise an amino acid sequence of SEQ ID No:60 and V_L and C_L comprise an amino acid sequence of SEQ ID No:70;

W) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:60, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:70;

X) V_H and the constant region comprise an amino acid sequence of SEQ ID No:80 and V_L and C_L comprise an amino acid sequence of SEQ ID No:90;

Y) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:80, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:90;

Z) V_H and the constant region comprise an amino acid sequence of SEQ ID No:100 and V_L and C_L comprise an amino acid sequence of SEQ ID No:110;

AA) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:100, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:110;

BB) V_H and the constant region comprise an amino acid sequence of SEQ ID No:120 and V_L and C_L comprise an amino acid sequence of SEQ ID No:130;

CC) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:120, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:130;

DD) V_H and the constant region comprise an amino acid sequence of SEQ ID No:160 and V_L and C_L comprise an amino acid sequence of SEQ ID No:170;

EE) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:160, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:170;

FF) V_H and the constant region comprise an amino acid sequence of SEQ ID No:180 and V_L and C_L comprise an amino acid sequence of SEQ ID No:190;

GG) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:180, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:190;

HH) V_H and the constant region comprise an amino acid sequence of SEQ ID No:140 and V_L and C_L comprise an amino acid sequence of SEQ ID No:150;

II) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:140, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:150;

JJ) V_H and the constant region comprise an amino acid sequence of SEQ ID No:246 and V_L and C_L comprise an amino acid sequence of SEQ ID No:256;

KK) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:246, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:256;

LL) V_H and the constant region comprise an amino acid sequence of SEQ ID No:266 and V_L and C_L comprise an amino acid sequence of SEQ ID No:276;

MM) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:266, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:276;

NN) V_H and the constant region comprise an amino acid sequence of SEQ ID No:286 and V_L and C_L comprise an amino acid sequence of SEQ ID No:296; and

OO) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:286, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:296;

PP) V_H and the constant region comprise an amino acid sequence of SEQ ID No:15 and V_L and C_L comprise an amino acid sequence of SEQ ID No:25; and

QQ) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:15, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:25;

RR) V_H and the constant region comprise an amino acid sequence of SEQ ID No:351 and V_L and C_L comprise an amino acid sequence of SEQ ID No:361; and

SS) V_H and the constant region comprise an amino acid sequence that is at least 85% identical to SEQ ID No:351, and the V_L and C_L comprise an amino acid sequence that is at least 85% identical to SEQ ID No:361.

In one embodiment, the amino acid sequence is at least 70% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 75% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 95% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 96% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 97% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 98% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99% identical to the specified Seq ID No. In one embodiment, the amino acid sequence is at least 99.5% identical to the specified Seq ID No.

Aspect 33. An immunocytokine according to any preceding aspect wherein the antigen-binding site specifically binds PD-L1, whilst the IL-2 cytokine) IL-2 receptor (IL-2R).

In one embodiment, the antigen binding site binds PD-L1 simultaneously to the IL-2 cytokine binding the IL-2R. In one embodiment, the antigen binding site binds PD-L1 sequentially to the IL-2 cytokine binding the IL-2R. In one embodiment, the IL-2 cytokine additionally binds the intermediate ( ) IL-2R.

Aspect 34. An immunocytokine according to any preceding aspect wherein the immunocytokine is capable of inhibiting PD-L1-mediated suppression of T-cells.

In one embodiment, the immunocytokine inhibits PD-L1-mediated suppression of T-cells. In one embodiment, the immunocytokine inhibits PD-L1-mediated suppression of T-cells in an assay. In another embodiment, the antigen binding site has any of the features or embodiments of concept 51 or 52.

In another embodiment, the antigen binding site blocks or inhibits PD-1 binding to PD-L1. In one embodiment, the antigen binding site blocks or inhibits CD80 binding to PD-L1.

Aspect 35. An immunocytokine according to any preceding aspect wherein the immunocytokine is capable of increasing IL-2R-mediated T-cell activation.

In one embodiment, the immunocytokine increases IL-2R-mediated T-cell activation. In one embodiment, the immunocytokine increases IL-2R-mediated T-cell activation in an assay.

Aspect 36. An immunocytokine according to aspect 34 or aspect 35, wherein the suppression of T-cells or the increase in IL-2R-mediated T-cell activation is measured by an increase in one or more of IFN , IL-2, CD25 or proliferation of T-cells in an assay that provides co-stimulation by either direct CD3/CD28 stimulation, superantigen stimulation or provides co-stimulation by co-incubation with cells capable of inducing a T-cell response.

The measurements may be carried out with any suitable technique. For example, the measurements may be taken with ELISA, HTRF, BRDU incorporation (proliferation), electrochemiluminescence (ECL) or flow cytometry (e.g. FACS). These techniques are well-known to those skilled in the art and are described elsewhere herein. In one embodiment, the assay is flow cytometry. In one embodiment, the assay is ELISA. In one embodiment, the assay is HTRF.

In this aspect, when aspect 36 is dependent on aspect 34, any of the features or embodiments of concept 36 apply .

When Aspect 36 is dependent on Aspect 35, in one embodiment, the increase in IL-2R-mediated T-cell activation is measured by an increase in one or both of IFN and CD25.

When Aspect 36 is dependent on Aspect 35, in one embodiment, the co-stimulation is provided by direct CD3/CD28 stimulation.

When Aspect 36 is dependent on Aspect 35, in one embodiment, the co-stimulation is provided by a superantigen, such as staphylococcal enterotoxin B (SEB).

When Aspect 36 is dependent on Aspect 35, in one embodiment, the assay provides co-stimulation by co-incubation with cells capable of inducing a T-cell response. Such cells may be antigen-presenting cells (APCs), for example monocytes, B-cells or dendritic cells. In one embodiment, the assay provides co-stimulation by co-incubation with APCs. In one embodiment, the assay provides co-stimulation by co-incubation with monocytes. In one embodiment, the assay provides co-stimulation by co-incubation with B-cells. In one embodiment, the assay provides co-stimulation by co-incubation with dendritic cells.

Aspect 37. An immunocytokine according to any preceding aspect which does not comprise a linker (L), or an immunocytokine according to any preceding claim wherein the C_L of d) is directly fused to the cytokine of f).

In one embodiment, the C_L of the light chain or the heavy chain is directly fused to the cytokine.

In one embodiment of aspect 1b, the C_L of b) is directly fused to the cytokine of d).

Aspect 38. An immunocytokine according to any one of aspects 1 to 37, wherein the linker is a peptide linker of 1 to 20 amino acids in length.

In one embodiment, the linker is peptide linker of 1 to 15 amino acids in length. In one embodiment, the linker is peptide linker of 1 to 10 amino acids in length. In one embodiment, the linker is peptide linker of 1 to 5 amino acids in length.

In one embodiment, the linker may be a chemical linker. In the case of recombinant fusion proteins, the linkers are encoded by nucleic acid sequences located in frame, in between the coding regions for the different immunocytokine portions. In the case of synthetic proteins, the linker peptides are introduced during synthesis.

Linkers are well-known to those skilled in the art. For example, see described in Denardo , 1998, Clin. Cancer Res., 4(10):2483-90; Peterson , 1999, Bioconjug. Chem. 10(4):553-7; and Zimmerman , 1999, Nucl. Med. Biol., 26(8):943-50, the modifications described therein are incorporated herein by reference.

Aspect 39. An immunocytokine according to aspect 38, wherein the linker peptide is selected from poly-G or $(G_4S)_X$, wherein X is 1, 2, 3 or 4.

In other embodiments, the linker may be selected from STG, GSTG, RS, TVAAPS, GGGGS, GSTVAAPS, TVAAPSGS or GSTVAAPSGS. In another embodiment, the linker is Gln–Arg–Val–Asp (derived from N-terminus of canine kappa constant region). In another embodiment, the linker is GGNGT or YGNGT.

Aspect 40. An immunocytokine according to any preceding aspect wherein the IL-2 cytokine is human IL-2 (hIL-2) or a variant thereof.

IL-2 variants are as described in aspect 1.

There is also provided a variant cytokine, which may be any of the non-IL-2 cytokines described herein (including the non-IL-2 cytokines described in aspect 1, e.g. selected from IL-7, IL-15, IL-21, IL-12, GM-CSF, TNF , CXCL9, CXCL10 and interferon-). The definition of a variant IL-2 cytokine applies to the other cytokines (including immune stimulating cytokines and T-cell stimulating cytokines) described herein, e.g. comprising any of the N-terminal deletions described for IL-2 in aspect 1.

Aspect 41. An immunocytokine according to aspect 40, wherein the hIL-2 comprises or consists of the amino acid sequence of Seq ID No:301.

Aspect 42. An immunocytokine according to aspect 40, wherein the hIL-2 comprises a variant of IL-2 which comprises a modification at the N-terminus, optionally a deletion of from 1 to 10 amino acids.

As used in this aspect, a modification at the N-terminus of any of the cytokines described herein (including the non-IL-2 cytokines described in aspect 1, e.g. selected from IL-7, IL-15, IL-21, IL-12, GM-CSF, TNF , CXCL9, CXCL10 and interferon-) refers to one or more (such as 1 to 10, e.g. 1 to 5) amino acid substitutions, deletions or additions.

In one embodiment, the modification is one or more (such as 1 to 10, e.g. 1 to 5) amino acid substitutions at the N-terminus of the cytokine. Substitutions may be conservative substitutions, for example, as defined in concept 9, concept 29 or aspect 29. In one embodiment, the modification is a deletion. In another embodiment, the modification is an N-terminal deletion, for example, any of the deletions described in concept 9 and aspect 1. In one embodiment, the modification (such as a deletion of 1 to 10 amino acids) is within the final 50 amino acids of the N-terminus of the cytokine, e.g. the IL-2 cytokine. In one embodiment, the modification (such as a deletion of 1 to 10 amino acids) within the final 30 amino acids of the N-terminus of the cytokine, e.g. the IL-2 cytokine. In one embodiment, the modification (such as a deletion of 1 to 10 amino acids) within the final 25 amino acids of the N-terminus of the cytokine, e.g. the IL-2 cytokine. In one embodiment, the modification (such as a deletion of 1 to 10 amino acids) within the final 20 amino acids of the N-terminus of the cytokine, e.g. the IL-2 cytokine. In one embodiment, the modification (such as a deletion of 1 to 10 amino acids) within the final 15 amino acids of the N-terminus of the cytokine, e.g. the IL-2 cytokine. In one embodiment, the modification (such as a deletion of 1 to 10 amino acids) within the final 10 amino acids of the N-terminus of the cytokine, e.g. the IL-2 cytokine.

In one embodiment, the modification is a deletion of 1 to 9 amino acids from within the final 10 amino acids of the N-terminus of the cytokine, such as a deletion of the final 1 to 9 amino acids of the N-terminus of the cytokine. In one embodiment, the modification is a deletion of 1 to 8 amino acids from within the final 10 amino acids of the N-terminus of the cytokine, such as a deletion of the final 1 to 8 amino acids of the N-terminus of the cytokine. In one embodiment, the modification is a deletion of 1 to 7 amino acids from within the final 10 amino acids of the N-terminus of the cytokine, such as a deletion of the final 1 to 7 amino acids of the N-terminus of the cytokine. In one embodiment, the modification is a deletion of 1 to 6 amino acids from within the final 10 amino acids of the N-terminus of the cytokine, such as a deletion of the final 1 to 6 amino acids of the N-terminus of the cytokine. In one embodiment, the modification is a deletion of 1 to 5 amino acids from within the final 10 amino acids of the N-terminus of the cytokine, such as a deletion of the final 1 to 5 amino acids of the N-terminus of the cytokine. In one embodiment, the modification is a deletion of 1 to 4 amino acids from within the final 10 amino acids of the N-terminus of the cytokine, such as a deletion of the final 1 to 4 amino acids of the N-terminus of the cytokine. In one embodiment, the modification is a

deletion of 1 to 3 amino acids from within the final 10 amino acids of the N-terminus of the cytokine, such as a deletion of the final 1 to 3 amino acids of the N-terminus of the cytokine. In one embodiment, the modification is a deletion of 1 or 2 amino acids from within the final 10 amino acids of the N-terminus of the cytokine, such as a deletion of the final 1 or 2 amino acids of the N-terminus of the cytokine. In one embodiment, the modification is a deletion of 1 amino acid from within the final 10 amino acids of the N-terminus of the cytokine, such as a deletion of the final amino acid of the N-terminus of the cytokine. In a particular embodiment, the cytokine is an IL-2 cytokine, such as a human IL-2 cytokine.

In one embodiment, the deletion is of the 9th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. In one embodiment, the deletion is of the 8th and 9th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. In one embodiment, the deletion is of the 7th, 8th and 9th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. In one embodiment, the deletion is of the 6th to 9th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. In one embodiment, the deletion is of the 4th to 9th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. In one embodiment, the deletion is of the 3rd to 9th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. In one embodiment, the deletion is of the 2nd to 9th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. In one embodiment, the deletion is of the 2nd to 6th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. In one embodiment, the deletion is of the 3rd to 7th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. In one embodiment, the deletion is of the 4th to 8th amino acid from the N-terminus of the cytokine, e.g. the IL-2 cytokine, for example the human IL-2 cytokine. Any of the deletions described in Aspect 1 hereinabove may be applied to the non-IL-2 cytokines of this aspect.

Aspect 42a. A variant hIL-2 comprising an N-terminal modification of any of the aspects or features of aspect 42. In one embodiment of aspect 42a, the variant hIL-2 is a purified variant hIL-2. In another embodiment of aspect 42a, the variant hIL-2 is an isolated and purified variant hIL-2.

Aspect 42b. A variant cytokine selected from IL-7, IL-15, IL-21, IL-12, GM-CSF, TNF , CXCL9, CXCL10 and interferon- comprising an N-terminal modification of any of the aspects or features of aspect 42. In one embodiment of aspect 42a, the variant cytokine is a purified variant cytokine. In another embodiment of aspect 42a, the variant cytokine is an isolated and purified variant cytokine.

Aspect 43. An immunocytokine according to aspect 40 or aspect 42, wherein the hIL-2 comprises a variant IL-2 comprising an N-terminal sequence selected from Seq ID No:303 to 323.

Aspect 43a. A variant hIL-2 comprising an N-terminal sequence selected from Seq ID No:303 to 323.

In one embodiment of aspect 43a, the variant hIL-2 is a purified variant hIL-2. In another embodiment of aspect 43a, the variant hIL-2 is an isolated and purified variant hIL-2. In one embodiment, the variant hIL-2 comprises (or consists) of an N-term terminal sequence selected from Seq ID No:303 to 323 directly fused to an IL-2 sequence selected from Seq ID No:324, 517 and 518.

Aspect 44. An immunocytokine according to any one of aspects 40, 42 or 43 wherein the hIL-2 variant comprises one or more (such as 1 to 5, e.g. one or two) mutations independently selected from the following:

1) D20 (such as D20T);
2) R38 (such as R38W, R38A or R38Q);
3) F42 (such as F42A or F42K);
4) Y45 (such as Y45A);
5) E62 (such as E62A);
6) N88 (such as N88R);
7) C125 (such as C125S);
8) Q126 (such as Q126W); or
9) R38 and F42 (such as R38W and F42K or R38A and F42A);

wherein the residue numbering is defined with reference to the human wild-type IL-2 sequence, Seq ID No:301.

Aspect 44a. A variant hIL-2 according to any one of aspects 42a or 43a wherein the hIL-2 variant comprises one or more (such as 1 to 5, e.g. one or two) mutations independently selected from the following:

1) D20 (such as D20T);
2) R38 (such as R38W, R38A or R38Q);
3) F42 (such as F42A or F42K);
4) Y45 (such as Y45A);
5) E62 (such as E62A);
6) N88 (such as N88R);
7) C125 (such as C125S);
8) Q126 (such as Q126W); or
9) R38 and F42 (such as R38W and F42K or R38A and F42A);

wherein the residue numbering is defined with reference to the human wild-type IL-2 sequence, Seq ID No:301.

In one embodiment, the variant hIL-2 comprises (or consists) of an R38 (such as R38W, R38A or R38Q, e.g. R38A) mutation. In one embodiment, the variant hIL-2 comprises (or consists) of an F42 (such as F42A or F42K, e.g. F42A) mutation. In one embodiment, the variant hIL-2 comprises (or

consists) of a Y45 (such as Y45A) mutation. In one embodiment, the variant hIL-2 comprises (or consists) of an E62 (such as E62A) mutation.

In one embodiment, the variant hIL-2 comprises (or consists) of an R38 (such as R38W, R38A or R38Q, e.g. R38A) mutation and an F42 (such as F42A or F42K, e.g. F42A) mutation. In one embodiment, the variant hIL-2 comprises (or consists) of an R38 (such as R38W, R38A or R38Q, e.g. R38A) and a Y45 (such as Y45A) mutation. In one embodiment, the variant hIL-2 comprises (or consists) of an R38 (such as R38W, R38A or R38Q, e.g. R38A) mutation and an E62 (such as E62A). In one embodiment, the variant hIL-2 comprises (or consists) of a Y45 (such as Y45A) mutation and an E62 (such as E62A). In one embodiment, the variant hIL-2 comprises (or consists) of an F42 (such as F42A or F42K, e.g. F42A) mutation and an E62 (such as E62A) mutation. In one embodiment, the variant hIL-2 comprises (or consists) of an F42 (such as F42A or F42K, e.g. F42A) mutation and a Y45 (such as Y45A) mutation.

In one embodiment, the variant hIL-2 comprises (or consists) of an R38 (such as R38W, R38A or R38Q, e.g. R38A) mutation, an F42 (such as F42A or F42K, e.g. F42A) mutation and a Y45 (such as Y45A) mutation. In one embodiment, the variant hIL-2 comprises (or consists) of an R38 (such as R38W, R38A or R38Q, e.g. R38A) mutation, an F42 (such as F42A or F42K, e.g. F42A) mutation and an E62 (such as E62A) mutation. In one embodiment, the variant hIL-2 comprises (or consists) of an R38 (such as R38W, R38A or R38Q, e.g. R38A) mutation, a Y45 (such as Y45A) mutation and an E62 (such as E62A) mutation.

In one embodiment, the variant hIL-2 comprises (or consists) of an R38 (such as R38W, R38A or R38Q, e.g. R38A) mutation, an F42 (such as F42A or F42K, e.g. F42A) mutation, a Y45 (such as Y45A) mutation and an E62 (such as E62A) mutation. In one embodiment, the variant hIL-2 comprises (or consists) of an R38A, F42A, Y45A and an E62A mutation.

Other hIL-2 mutations are known to those skilled in the art. In one embodiment, the hIL-2 mutations are those described in WO2012/062228 (see claims 2 to 7, incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO1999/60128 (see claims 6, 7, 8, 10, 11 and 12 incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO1993/20849 (see claims 4 and 5 incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO2003/015697 (see claims 7 and 10 incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO2005/007121 (see claims 9 to 14 incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO2005/086798 (see claims 5 to 10 incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO2005/086751 (see claims 5 to 9 incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO2009/061853 (see claim 5 incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO2012/088446 (see claims 3 to 8 and 11 to 13 incorporated herein by reference). In one embodiment, the hIL-2 mutations are those

described in WO2012/107417 (see claims 2, 4, 6 and 9, incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO2012/119093 (see claims 1 to 7, incorporated herein by reference). In one embodiment, the hIL-2 mutations are those described in WO2015/164815 (see claims 3 to 19, incorporated herein by reference).

In these aspects, where the residue numbering is defined with reference to the human wild-type IL-2 sequence, if, for example, there is a single amino acid deletion from the N-terminus of the cytokine, and the claim described an N88 amino acid mutation, then, for the variant IL-2 having the single amino acid deletion, the N will in fact be at position 87. If the cytokine has 3 amino acids deleted from the N-terminus, and the mutation is an F42A mutation, then the position to be mutated, will in fact be F39 in the variant sequence.

Aspect 45. An immunocytokine according to aspect 40, wherein the hIL-2 comprises a variant IL-2 consists of an N-terminal sequence selected from Seq ID No:242 to 262 fused to the amino acid sequence of Seq ID No:324.

In one embodiment, the variant hIL-2 comprises (or consists) of an N-terminal sequence selected from Seq ID No:303 to 323 fused to the amino acid sequence selected from Seq ID No:324, 517 and 518.

In one embodiment, the immunocytokine is 1D05 D1-9 ICK. In one embodiment, the immunocytokine is 1D05 D1-9. In one embodiment, the immunocytokine is 1D05 D9-2 ICK. In one embodiment, the immunocytokine is 1D05 D9-7 ICK.

Aspect 45a. A variant hIL-2 comprising an N-terminal sequence selected from Seq ID No:303 to 323 fused to the amino acids sequence of Seq ID No:324.

In one embodiment of aspect 45a, the variant hIL-2 is a purified variant hIL-2. In another embodiment of aspect 44a, the variant hIL-2 is an isolated and purified variant hIL-2.

Aspect 46. An immunocytokine according to any preceding aspect, wherein the IL-2 cytokine binds to) IL-2 receptor with a potency less than free IL-2, for example with an EC_{50} of greater than 20 pM, greater than 50 pM or greater than 100 pM, e.g. when measured in a cell-based proliferative assay.

Free IL-2 has a potency of approximately 10pM against the (high affinity) receptor in a cell-based proliferative assay. As used herein, EC_{50} refers to the effective concentration to give 50% of maximal activation of the IL2R. The higher the EC_{50}, the less potent the substance is, thus a substance having an EC_{50} of 1pM is more potent than a substance with an EC_{50} of 1nM. The sequences of the - -chain and -chain are provided in Seq ID Nos:327, 328 and 329 respectively.

In one embodiment, the IL-2 cytokine has an EC_{50} in the range of 5pM to 20pM. In one embodiment, the EC_{50} is in the range of 5pM to 1nM. In one embodiment, the EC_{50} is in the range of 5pM to 750pM, 5pM to 500pM, 5pM to 250pM or 5pm to 100pM, e.g. 5pM to 50pM.

In one embodiment, the EC_{50} is in the range of 10pM to 1nM. In one embodiment, the EC_{50} is in the range of 10pM to 750pM, 10pM to 500pM, 10pM to 250pM or 10pm to 100pM, e.g. 10pM to 50pM, or 10pM to 30pM.

In one embodiment, the EC_{50} is in the range of 20pM to 1nM. In one embodiment, the EC_{50} is in the range of 20pM to 750pM, 20pM to 500pM, 20pM to 250pM or 20pm to 100pM, e.g. 20pM to 50pM.

In another embodiment, the IL-2 cytokine has an EC_{50} in the range of 50pM to 1nM. In one embodiment, the EC_{50} is in the range of 50pM to 750pM, 50pM to 500pM, 50pM to 250pM or 50pm to 100pM, e.g. 50pM to 75pM. In another embodiment, the IL-2 cytokine has an EC_{50} in the range of 100pM to 1nM. In one embodiment, the EC_{50} is in the range of 100pM to 800pM, 100pM to 700pM, 100pM to 600pM or 100pm to 500pM, e.g. 100pM to 400pM. In another embodiment, the IL-2 cytokine has an EC_{50} in the range of 100pm to 300pM. In another embodiment, the IL-2 cytokine has an EC_{50} in the range of 100pm to 200pM.

In another embodiment, the EC_{50} is greater than 5pM. In another embodiment, the EC_{50} is greater than 10pM. In another embodiment, the EC_{50} is greater than 20pM. In another embodiment, the EC_{50} is greater than 30pM, greater than 40pM, greater than 50pM, greater than 60pM or greater than 70pM. In another embodiment, the EC_{50} is greater than 100pM, greater than 125pM, greater than 150pM, greater than 175pM or greater than 200pM. In another embodiment, the EC_{50} is greater than 250pM, greater than 300pM, greater than 350pM, greater than 400pM. In another embodiment, the EC_{50} is greater than 500pM, greater than 600pM, greater than 700pM or greater than 800pM.

In one embodiment, the EC_{50} is less than 5nM. In one embodiment, the EC_{50} is less than 1nM. In one embodiment, the EC_{50} is less than 800pM. In one embodiment, the EC_{50} is less than 700pM. In one embodiment, the EC_{50} is less than 600pM. In one embodiment, the EC_{50} is less than 500pM. In one embodiment, the EC_{50} is less than 400pM. In one embodiment, the EC_{50} is less than 300pM. In one embodiment, the EC_{50} is less than 200pM. In one embodiment, the EC_{50} is less than 100pM. In one embodiment, the EC_{50} is less than 50pM.

The potency of the immunocytokine against the IL-2R may be measured in a cell-based proliferative assay, which are well-known to those skilled in the art and are detailed more in the Examples hereinbelow (see Example 13 and Figure 12).

Aspect 47. An immunocytokine according to any preceding aspect, wherein the IL-2 binds to the) IL-2 receptor with a potency less than free IL-2, for example with an EC_{50} of greater than 1 nM, greater than 5 nM or greater than 10 nM, e.g. when measured in a cell-based proliferative assay.

Free IL-2 has a potency of approximately 100 (intermediate affinity) receptor in a cell-based proliferative assay. As used herein, EC_{50} refers to the effective concentration to give 50% of maximal activation of the IL-2R. The higher the EC_{50}, the less potent the substance is, thus a substance having an EC_{50} of 1pM is more potent than a substance with an EC_{50} of 1nM. The

sequences of the - -chain and -chain are provided in Seq ID Nos:327, 328 and 329 respectively.

In one embodiment, the EC_{50} is in the range of 1 to 100nM. In one embodiment, the EC_{50} is in the range of 10nM to 100nM. In one embodiment, the EC_{50} is in the range of 20nM to 100nM. In another embodiment, the IL-2 cytokine has an EC_{50} in the range of 30nM to 100nM, 40nM to 100nM, 50nM to 100nM. In one embodiment, the EC_{50} is in the range of 50nM to 100nM, 60nM to 100nM, 70nM to 100nM.

In one embodiment, the EC_{50} is in the range of 1 to 50nM. In one embodiment, the EC_{50} is in the range of 10nM to 50nM. In one embodiment, the EC_{50} is in the range of 20nM to 50nM. In another embodiment, the IL-2 cytokine has an EC_{50} in the range of 30nM to 50nM or 40nM to 50nM.

In one embodiment, the EC_{50} is in the range of 1 to 10nM. In one embodiment, the EC_{50} is in the range of 1 to 20nM. In one embodiment, the EC_{50} is in the range of 1 to 30nM. In one embodiment, the EC_{50} is in the range of 1nM to 9nM. In one embodiment, the EC_{50} is in the range of 1nM to 8nM. In another embodiment, the IL-2 cytokine has an EC_{50} in the range of 1nM to 7nM, 1nM to 6nM or 1nM to 5nM.

In another embodiment, the EC_{50} is greater than 0.5nM, greater than 0.6nM, greater than 0.7nM, greater than 0.8nM or greater than 0.9nM. In another embodiment, the EC_{50} is greater than 1nM, greater than 1.25nM, greater than 1.5nM, greater than 1.75nM or greater than 2nM. In another embodiment, the EC_{50} is greater than 2.5nM, greater than 3nM, greater than 3.5nM, greater than 4nM. In another embodiment, the EC_{50} is greater than 5nM, greater than 6nM, greater than 7nM or greater than 8nM. In a particular embodiment, the EC_{50} is greater than 1nM.

In one embodiment, the EC_{50} is less than 10nM. In one embodiment, the EC_{50} is less than 20nM. In one embodiment, the EC_{50} is less than 30nM. In one embodiment, the EC_{50} is less than 40nM. In one embodiment, the EC_{50} is less than 50nM.

In one embodiment, the EC_{50} is less than 100nM. In one embodiment, the EC_{50} is less than 200nM. In one embodiment, the EC_{50} is less than 300nM.

In another embodiment, the EC_{50} is less than 75nM or less than 50nM.

In one embodiment, the IL-2 shows no detectable potency against the β IL-2R in a cell-based proliferative assay.

The potency of the immunocytokine against the β IL-2R may be measured in a cell-based proliferative assay, which are well-known to those skilled in the art and are detailed more in the Examples hereinbelow (see Example 13 and Figure 12).

Aspect 48. An immunocytokine according to any preceding aspect, wherein the IL-2 preferentially) IL-2 receptor over the intermediate affinity (β) IL-2 receptor.

Aspect 49. An immunocytokine according to aspect 48, wherein the ratio of IL-2 potency against the) IL-2 receptor:intermediate affinity) IL-2 receptor is at least 2:1.

In one embodiment, the ratio is at least 3:1. In one embodiment, the ratio is at least 4:1. In one embodiment, the ratio is at least 5:1. In one embodiment, the ratio is at least 7.5:1. In one embodiment, the ratio is at least 10:1. In one embodiment, the ratio is at least 12.5:1. In one embodiment, the ratio is at least 15:1. In one embodiment, the ratio is at least 17.5:1. In one embodiment, the ratio is at least 20:1.

In another embodiment, the ratio is at least 50:1. In another embodiment, the ratio is at least 75:1. In another embodiment, the ratio is at least 100:1. In another embodiment, the ratio is at least 250:1. In another embodiment, the ratio is at least 500:1. In another embodiment, the ratio is at least 750:1. In another embodiment, the ratio is at least 1000:1.

In another embodiment, the ratio is at least 1250:1. In another embodiment, the ratio is at least 1500:1. In another embodiment, the ratio is at least 1750:1. In another embodiment, the ratio is at least 2000:1.

Aspect 50. An immunocytokine according to any preceding aspect, wherein the antigen binding site binds to hPD-L1 with an affinity of less than 500pM (e.g. less than 300pM or less than 200pM), optionally wherein the immunocytokine provides a ratio of the potency of the IL-2 cytokine against the high affinity) receptor: affinity of the anti-PD-L1 antigen binding site against hPD-L1 of at least 2:1.

In one embodiment, the antigen binding site binds to hPD-L1 with an affinity of less than 200pM. In one embodiment, the antigen binding site binds to hPD-L1 with an affinity of less than 100pM, or less than 50pM.

In one embodiment, the antigen binding site binds to hPD-L1 with an affinity of between 50pM and 500pM, or between 75pM and 500pM, or between 100pM and 500pM or between 200pM and 500pM.

In one embodiment, the antigen binding site binds to hPD-L1 with an affinity of between 50pM and 400pM, or between 50pM and 300pM, or between 50pM and 200pM or between 50pM and 100pM.

In one embodiment, the antigen binding site binds to hPD-L1 with an affinity of between 100pM and 500pM, or between 100pM and 400pM, or between 100pM and 300pM.

In one embodiment, the ratio of the potency of the IL-2 cytokine against the high affinity) receptor: affinity of the anti-PD-L1 antigen binding site against hPD-L1 is at least 3:1. In one embodiment, the ratio of the potency of the IL-2 cytokine against the high affinity (αβ) receptor: affinity of the anti-PD-L1 antigen binding site against hPD-L1 is at least 4:1. In one embodiment, the ratio of the potency of the IL-2 cytokine against the high affinity (αβ) receptor: affinity of the anti-PD-L1 antigen binding site against hPD-L1 is at least 5:1. In one embodiment, the ratio of the potency of the IL-2 cytokine against the high affinity (αβ) receptor: affinity of the anti-PD-L1 antigen binding site against hPD-L1 is at least 7:1. In one embodiment, the ratio of the potency of the IL-2 cytokine

against the hi) receptor: affinity of the anti-PD-L1 antigen binding site against hPD-L1 is at least 10:1.

Any of the half-life, K_{ON} rates, K_{OFF} rates, or binding characteristics of the anti-PD-L1 antibodies in concepts 1 to 40 applu to the immunocytokines disclosed herein.

Aspect 50a. An immunocytokine according to any preceding aspect, wherein the antigen binding site binds to mPD-L1 (Seq ID No:325) with an affinity of less than 500nM (e.g. less than 100nM, less than 10nM or less than 1nm).

In one embodiment, the antigen binding site binds to hPD-L1 with an affinity of between 1nM and 500nM, or between 1nM and 250nM, or between 1nM and 100nM, or between 1nM and 50nM.

In one embodiment, the antigen binding site binds to hPD-L1 with an affinity of between 10nM and 500nM, or between 10nM and 250nM, or between 10nM and 100nM, or between 1nM and 50nM, in particular between 10nM and 100nM.

In one embodiment, the antigen binding site binds to hPD-L1 with an affinity of between 100nM and 500nM, or between 100nM and 400nM, or between 100nM and 300nM, or between 100nM and 200nM.

The affinity of the antigen-binding site to hPD-L1 or mPD-L1 may be measured by any technique well-known to those skilled in the art. In one embodiment, the affinity is measured using SPR, the details of which are provided hereinabove.

Aspect 51. An immunocytokine as defined in any preceding aspect for use in treating or preventing a hPD-L1-mediated disease or condition, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, breast cancer, ovarian cancer, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, colorectal cancer (without MSI or microsatellite instability), head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease, diffuse large B-cell lymphoma (for example melanoma, breast cancer, ovarian cancer, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, colorectal cancer (without MSI or microsatellite instability), head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

Aspect 52. Use of an immunocytokine as defined in any one of aspects 1 to 50 in the manufacture of a medicament for administration to a human for treating or preventing a hPD-L1 mediated disease or condition in the human, e.g. wherein the hPD-L1 mediated disease or condition is selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, breast cancer, ovarian cancer, Merkel cell carcinoma, non-small cell lung cancer

(squamous and non-squamous), renal cell cancer, bladder cancer, colorectal cancer (without MSI or microsatellite instability), head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease, diffuse large B-cell lymphoma (for example melanoma, breast cancer, ovarian cancer, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, colorectal cancer (without MSI or microsatellite instability), head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

Aspect 53. A method of treating or preventing a hPD-L1 mediated disease or condition, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, breast cancer, ovarian cancer, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, colorectal cancer (without MSI or microsatellite instability), head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease, diffuse large B-cell lymphoma (for example melanoma, breast cancer, ovarian cancer, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, colorectal cancer (without MSI or microsatellite instability), head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas) in a human, comprising administering to said human a therapeutically effective amount of an immunocytokine as defined in any one of aspects 1 to 50, wherein the hPD-L1 mediated disease or condition is thereby treated or prevented.

In any of aspects 51 to 53, the hPD-L1 mediated disease may be any of those as described herein. In one embodiment, in any of aspects 51 to 53, the hPD-L1 mediated disease is a virally induced cancer, such as cervical cancer and nasopharyngeal cancer, for example cervical cancers caused by HPV infection. In one embodiment, in any of aspects 51 to 53, the hPD-L1 mediated disease is a chronic viral infection. In one embodiment, in any of aspects 51 to 53, the hPD-L1 mediated disease is a neoplastic disease. In one embodiment, in any of aspects 51 to 53, the hPD-L1 mediated disease is a non-neoplastic disease. In one embodiment, in any of aspects 51 to 53, the hPD-L1 mediated disease is a malignant tumour. In one embodiment, in any of aspects 51 to 53, the hPD-L1 mediated disease is a cancer which is known to be responsive to PD-L1 therapy, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma. In one embodiment, in any of aspects 51 to 53, the hPD-L1 mediated disease is a cancer which is a soft tissue sarcoma. In one embodiment, in any of aspects 51 to 53, the hPD-L1 mediated disease is a neurodegenerative disease, disorder or condition, optionally wherein the neurodegenerative disease, disorder or condition is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's

disease, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, corticobasal degeneration, Rett syndrome, a retinal degeneration disorder selected from age-related macular degeneration and retinitis pigmentosa; anterior ischemic optic neuropathy, glaucoma, uveitis, depression, trauma-associated stress or post-traumatic stress disorder, frontotemporal dementia, Lewy body dementias, mild cognitive impairments, posterior cortical atrophy, primary progressive aphasia and progressive supranuclear palsy or aged-related dementia, in particular Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease, and e.g. Alzheimer's disease.

Aspect 54. The immunocytokine according to aspect 51, the use according to aspect 52 or the method according to aspect 53, wherein the hPD-L1-mediated disease or condition is cancer.

Aspect 55. The immunocytokine, the use or the method according to aspect 54, wherein the cancer is selected from melanoma, Merkel cell cancer, non-small cell lung cancer, bladder cancer, Non-Hodgkin's lymphomas, colorectal cancer with microsatellite instability (MSI) or a cancer selected from breast cancer, ovarian cancer, colorectal cancer (without MSI or microsatellite instability), in particular melanoma and renal cell cancer.

In one embodiment, the cancer is a cancer which is known to be responsive to both IL-2 therapy and PD-L1 therapy, such as melanoma and renal cell cancer.

In one embodiment, the cancer is colorectal cancer with microsatellite instability (MSI). In one embodiment, the cancer is breast cancer. In one embodiment, the cancer is ovarian cancer.

Aspect 56. The immunocytokine, use or the method according to any one of aspects 51 to 55, further comprising administering to the human a further therapy, for example a further therapeutic agent, optionally wherein the further therapeutic agent is independently selected from the group consisting of:

A) other immune checkpoint inhibitors (such as anti-TIM-3 antibodies, anti-CTLA-4 antibodies, anti-TIGIT antibodies and anti-LAG-3 antibodies);
B) immune stimulators (such as anti-OX40 antibodies, anti-GITR antibodies, anti-CD137 antibodies, anti-ICOS antibodies and anti-CD40 antibodies);
C) chemokine receptor antagonists (such as CXCR4, CCR4 and CXCR2);
D) targeted kinase inhibitors (such as CSF-1R or VEGFR inhibitors);
E) angiogenesis inhibitors (such as anti-VEGF-A or Delta-like Ligand-4);
F) immune stimulating peptides or chemokines (such as CXCL9 or CXCL10);
G) cytokines (such as IL-15 and IL-21);
H) bispecific T-cell engagers (BiTEs) having at least one specificity against CD3 (e.g. CD3/CD19 BiTE);
I) other bi-specific molecules (for example IL-15-containing molecules targeted towards tumour associated antigens, for example Epidermal growth factor receptors such as

EGFR, Her-2, New York Esophageal Cancer-1 (NY-ESO-1), GD2, EpCAM or Melanoma Associated Antigen-3 (MAGE-A3));

J) oncolytic viruses (such as HSV virus (optionally which secretes GMCSF), Newcastle disease virus and Vaccinia virus);

K) vaccination with tumour associated antigens (such as New York Esophageal Cancer-1 [NY-ESO-1], Melanoma Associated Antigen-3 [MAGE-3]);

L) cell-based therapies (such as chimeric Antigen Receptor-T-cells (CAR-T) for example expressing anti-CD19, anti-EpCam or anti-mesothelin);

M) bi-specific NK cell engagers having a specificity against an activating MK receptor such as NKG2D or CD16a; and

N) adoptive transfer of tumour specific T-cells or LAK cells,

or optionally wherein the further therapy is chemotherapy, radiotherapy and surgical removal of tumours.

Radiotherapy may be single dose or in fractionated doses, either delivered to affected tissues directly or to the whole body.

In this aspect, any of the features and embodiments of concept 46 apply .

In this aspect, the bispecific molecules include "bispecific antibodies" and antibody fusion proteins, including those formats and molecules described in concepts 37 to 40.

The antibodies may be any of the sequences or antibodies described in arrangement 5, 5a or detailed in Aspect 1a.

Aspect 57. A pharmaceutical composition comprising an immunocytokine as defined in any one of aspects 1 to 50 and a pharmaceutically acceptable excipient, diluent or carrier and optionally further comprising a further therapeutic agent independently selected from the group consisting of:

A) other immune checkpoint inhibitors (such as anti-TIM-3 antibodies, anti-CTLA-4 antibodies, anti-TIGIT antibodies and anti-LAG-3 antibodies);

B) immune stimulators (such as anti-OX40 antibodies, anti-GITR antibodies, anti-CD137 antibodies, anti-ICOS antibodies and anti-CD40 antibodies);

C) chemokine receptor antagonists (such as CXCR4, CCR4 and CXCR2);

D) targeted kinase inhibitors (such as CSF-1R or VEGFR inhibitors);

E) angiogenesis inhibitors (such as anti-VEGF-A or Delta-like Ligand-4);

F) immune stimulating peptides or chemokines (such as CXCL9 or CXCL10);

G) cytokines (such as IL-15 and IL-21);

H) bispecific T-cell engagers (BiTEs) having at least one specificity against CD3 (e.g. CD3/CD19 BiTE);

I) other bi-specific molecules (for example IL-15-containing molecules targeted towards tumour associated antigens, for example Epidermal growth factor receptors such as

EGFR, Her-2, New York Esophageal Cancer-1 (NY-ESO-1), GD2, EpCAM or Melanoma Associated Antigen-3 (MAGE-A3));

J) oncolytic viruses (such as HSV virus (optionally which secretes GMCSF), Newcastle disease virus and Vaccinia virus);

K) vaccination with tumour associated antigens (such as New York Esophageal Cancer-1 [NY-ESO-1], Melanoma Associated Antigen-3 [MAGE-3]);

L) cell-based therapies (such as chimeric Antigen Receptor-T-cells (CAR-T) for example expressing anti-CD19, anti-EpCam or anti-mesothelin);

M) bi-specific NK cell engagers having a specificity against an activating MK receptor such as NKG2D or CD16a; and

N) adoptive transfer of tumour specific T-cells or LAK cells.

In one embodiment, the further therapeutic agent is administered sequentially or simultaneously with the immunocytokine.

In this aspect, any of the features and embodiments of concept 48 apply .

In this aspect, the bispecific molecules include "bispecific antibodies" and antibody fusion proteins, including those formats and molecules described in concepts 37 to 40.

The antibodies may be any of the sequences or antibodies described in arrangement 5, 5a or detailed in Aspect 1a.

Aspect 58. A pharmaceutical composition according to aspect 57, or a kit comprising a pharmaceutical composition as defined in aspect 57, wherein the composition is for treating and/or preventing a hPD-L1 mediated disease or condition, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, breast cancer, ovarian cancer, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, colorectal cancer (without MSI or microsatellite instability), head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease, diffuse large B-cell lymphoma (for example melanoma, breast cancer, ovarian cancer, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, colorectal cancer (without MSI or microsatellite instability), head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

Aspect 59. A pharmaceutical composition according to aspect 57 or aspect 58 in combination with, or kit according to aspect 58 comprising a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the immunocytokine.

Aspect 60. A method of treating a proliferative disease in an animal (e.g. a human), comprising administering an effective amount of an immunocytokine as defined in any one of aspects 1 to 50 to said patient.

Proliferative diseases may be any as described elsewhere herein.

Aspect 61. A nucleic acid that encodes a heavy chain and/or a light chain of an immunocytokine as defined in any one of aspects 1 to 50.

In one embodiment, the nucleic acid encodes a light chain of an immunocytokine as defined in any one of aspects 1 to 50.

Aspect 62. A vector comprising the nucleic acid as defined in aspect 61; optionally wherein the vector is a CHO or HEK293 vector.

Aspect 63. A host comprising the nucleic acid as defined in aspect 61 or the vector as defined in aspect 62.

4. ICOS antibodies

ICOS antibodies are provided herein. The ICOS antibodies may be any of those described in GB patent application 1620414.1 (filed 1st December 2016), the sequences of the anti-ICOS antibodies disclosed therein are incorporated herein by reference.

STIM001 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:366, comprising the CDRH1 amino acid sequence of Seq ID No:363, the CDRH2 amino acid sequence of Seq ID No:364, and the CDRH3 amino acid sequence of Seq ID No:365. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:367. STIM001 has a light chain variable region (V_L) amino acid sequence of Seq ID No:373, comprising the CDRL1 amino acid sequence of Seq ID No:370, the CDRL2 amino acid sequence of Seq ID No:371, and the CDRL3 amino acid sequence of Seq ID No:372. The light chain nucleic acid sequence of the V_L domain is Seq ID No:374. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:368 (heavy chain nucleic acid sequence Seq ID No:369). A full length light chain amino acid sequence is Seq ID No:375 (light chain nucleic acid sequence Seq ID No:376).

STIM002 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:380, comprising the CDRH1 amino acid sequence of Seq ID No:377, the CDRH2 amino acid sequence of Seq ID No:378, and the CDRH3 amino acid sequence of Seq ID No:379. The heavy chain nucleic acid

sequence of the V_H domain is Seq ID No:381. STIM002 has a light chain variable region (V_L) amino acid sequence of Seq ID No:387, comprising the CDRL1 amino acid sequence of Seq ID No:384, the CDRL2 amino acid sequence of Seq ID No:385, and the CDRL3 amino acid sequence of Seq ID No:386. The light chain nucleic acid sequence of the V_L domain is Seq ID No:388 or Seq ID No:519. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:382 (heavy chain nucleic acid sequence Seq ID No:383). A full length light chain amino acid sequence is Seq ID No:389 (light chain nucleic acid sequence Seq ID No:390 or or Seq ID No:520).

STIM002-B has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:394, comprising the CDRH1 amino acid sequence of Seq ID No:391, the CDRH2 amino acid sequence of Seq ID No:392, and the CDRH3 amino acid sequence of Seq ID No:393. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:395. STIM002-B has a light chain variable region (V_L) amino acid sequence of Seq ID No:401, comprising the CDRL1 amino acid sequence of Seq ID No:398, the CDRL2 amino acid sequence of Seq ID No:399, and the CDRL3 amino acid sequence of Seq ID No:400. The light chain nucleic acid sequence of the V_L domain is Seq ID No:402. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:396 (heavy chain nucleic acid sequence Seq ID No:397). A full length light chain amino acid sequence is Seq ID No:403 (light chain nucleic acid sequence Seq ID No:404).

STIM003 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:408, comprising the CDRH1 amino acid sequence of Seq ID No:405, the CDRH2 amino acid sequence of Seq ID No:406, and the CDRH3 amino acid sequence of Seq ID No:407. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:409 or Seq ID No:521. STIM003 has a light chain variable region (V_L) amino acid sequence of Seq ID No:415, comprising the CDRL1 amino acid sequence of Seq ID No:412, the CDRL2 amino acid sequence of Seq ID No:413, and the CDRL3 amino acid sequence of Seq ID No:414. The light chain nucleic acid sequence of the V_L domain is Seq ID No:4416. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID

No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:410 (heavy chain nucleic acid sequence Seq ID No:411 or Seq ID No:522). A full length light chain amino acid sequence is Seq ID No:417 (light chain nucleic acid sequence Seq ID No:418).

STIM004 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:422, comprising the CDRH1 amino acid sequence of Seq ID No:419, the CDRH2 amino acid sequence of Seq ID No:420, and the CDRH3 amino acid sequence of Seq ID No:421. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:423. STIM004 has a light chain variable region (V_L) amino acid sequence of Seq ID No:429, comprising the CDRL1 amino acid sequence of Seq ID No:426, the CDRL2 amino acid sequence of Seq ID No:427, and the CDRL3 amino acid sequence of Seq ID No:428. The light chain nucleic acid sequence of the V_L domain is Seq ID No:430 or Seq ID No:431. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:424 (heavy chain nucleic acid sequence Seq ID No:425). A full length light chain amino acid sequence is Seq ID No:432 (light chain nucleic acid sequence Seq ID No:433 or Seq ID no: 434).

STIM005 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:438, comprising the CDRH1 amino acid sequence of Seq ID No:435, the CDRH2 amino acid sequence of Seq ID No:436, and the CDRH3 amino acid sequence of Seq ID No:437. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:439. STIM005 has a light chain variable region (V_L) amino acid sequence of Seq ID No:445, comprising the CDRL1 amino acid sequence of Seq ID No:442, the CDRL2 amino acid sequence of Seq ID No:443, and the CDRL3 amino acid sequence of Seq ID No:444. The light chain nucleic acid sequence of the V_L domain is Seq ID No:446. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:440 (heavy chain nucleic acid sequence Seq ID No:441). A full length light chain amino acid sequence is Seq ID No:447 (light chain nucleic acid sequence Seq ID No:448).

STIM006 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:452, comprising the CDRH1 amino acid sequence of Seq ID No:449, the CDRH2 amino acid sequence of

Seq ID No:450, and the CDRH3 amino acid sequence of Seq ID No:451. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:453. STIM006 has a light chain variable region (V_L) amino acid sequence of Seq ID No:459, comprising the CDRL1 amino acid sequence of Seq ID No:456, the CDRL2 amino acid sequence of Seq ID No:457, and the CDRL3 amino acid sequence of Seq ID No:458. The light chain nucleic acid sequence of the V_L domain is Seq ID No:460. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:454 (heavy chain nucleic acid sequence Seq ID No:455). A full length light chain amino acid sequence is Seq ID No:461 (light chain nucleic acid sequence Seq ID No:462).

STIM007 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:466, comprising the CDRH1 amino acid sequence of Seq ID No:463, the CDRH2 amino acid sequence of Seq ID No:464, and the CDRH3 amino acid sequence of Seq ID No:465. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:467. STIM007 has a light chain variable region (V_L) amino acid sequence of Seq ID No:473, comprising the CDRL1 amino acid sequence of Seq ID No:470, the CDRL2 amino acid sequence of Seq ID No:471, and the CDRL3 amino acid sequence of Seq ID No:472. The light chain nucleic acid sequence of the V_L domain is Seq ID No:474. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:468 (heavy chain nucleic acid sequence Seq ID No:469). A full length light chain amino acid sequence is Seq ID No:475 (light chain nucleic acid sequence Seq ID No:476).

STIM008 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:480, comprising the CDRH1 amino acid sequence of Seq ID No:477, the CDRH2 amino acid sequence of Seq ID No:478, and the CDRH3 amino acid sequence of Seq ID No:479. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:481. STIM008 has a light chain variable region (V_L) amino acid sequence of Seq ID No:487, comprising the CDRL1 amino acid sequence of Seq ID No:484, the CDRL2 amino acid sequence of Seq ID No:485, and the CDRL3 amino acid sequence of Seq ID No:486. The light chain nucleic acid sequence of the V_L domain is Seq ID No:488. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID

No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:482 (heavy chain nucleic acid sequence Seq ID No:483). A full length light chain amino acid sequence is Seq ID No:489 (light chain nucleic acid sequence Seq ID No:490).

STIM009 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:494, comprising the CDRH1 amino acid sequence of Seq ID No:491, the CDRH2 amino acid sequence of Seq ID No:492, and the CDRH3 amino acid sequence of Seq ID No:493. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:495. STIM009 has a light chain variable region (V_L) amino acid sequence of Seq ID No:501, comprising the CDRL1 amino acid sequence of Seq ID No:498, the CDRL2 amino acid sequence of Seq ID No:499, and the CDRL3 amino acid sequence of Seq ID No:500. The light chain nucleic acid sequence of the V_L domain is Seq ID No:502. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:496 (heavy chain nucleic acid sequence Seq ID No:497). A full length light chain amino acid sequence is Seq ID No:503 (light chain nucleic acid sequence Seq ID No:504).

Antibodies STIM001-009 are described in more detail in GB patent application 1620414.1 (filed 1st December 2016), the contents of which are incorporated herein by reference. ICOS antibodies may also be described as in the following numbered sentences below:

Sentence 1. An isolated antibody that binds the extracellular domain of human and/or mouse ICOS, comprising:

an antibody V_H domain comprising complementarity determining regions (CDRs) HCDR1, HCDR2 and HCDR3, and

an antibody V_L domain comprising complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein

HCDR1 is the HCDR1 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that HCDR1 with 1, 2, 3, 4 or 5 amino acid alterations,

HCDR2 is the HCDR2 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that HCDR2 with 1, 2, 3, 4 or 5 amino acid alterations, and/or

HCDR3 is the HCDR3 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprises that HCDR3 with 1, 2, 3, 4 or 5 amino acid alterations.

Sentence 2. An antibody according to sentence 1, wherein the antibody heavy chain CDRs are those of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 heavy chain CDRs with 1, 2, 3, 4 or 5 amino acid alterations.

Sentence 3. An antibody according to sentence 2, wherein the antibody V_H domain has the heavy chain CDRs of STIM003.

Sentence 4. An isolated antibody that binds the extracellular domain of human and/or mouse ICOS, comprising:

an antibody V_H domain comprising complementarity determining regions HCDR1, HCDR2 and HCDR3, and

an antibody V_L domain comprising complementarity determining regions LCDR1, LCDR2 and LCDR3,

wherein LCDR1 is the LCDR1 of STIM001, STIM002, STIM002-B, STIM003, STIM004 STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that LCDR1 with 1, 2, 3, 4 or 5 amino acid alterations,

LCDR2 is the LCDR2 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that LCDR2 with 1, 2, 3, 4 or 5 amino acid alterations, and/or

LCDR3 is the LCDR3 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprises that LCDR3 with 1, 2, 3, 4 or 5 amino acid alterations.

Sentence 5. An antibody according to any preceding sentence, wherein the antibody light chain CDRs are those of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 light chain CDRs with 1, 2, 3, 4 or 5 amino acid alterations.

Sentence 6. An antibody according to sentence 5, wherein the antibody V_L domain has the light chain CDRs of STIM003.

Sentence 7. An antibody according to any of the preceding sentences, comprising V_H and/or V_L domain framework regions of human germline gene segment sequences.

Sentence 8. An antibody according to any of the preceding sentences, comprising a V_H domain which

(i) is derived from recombination of a human heavy chain V gene segment, a human heavy chain D gene segment and a human heavy chain J gene segment, wherein

the V segment is IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10);

the D gene segment is IGHD6-19 (e.g., IGHD6-19*01), IGHD3-10 (e.g., IGHD3-10*01) or IGHD3-9 (e.g., IGHD3-9*01); and/or

the J gene segment is IGHJ6 (e.g., IGHJ6*02), IGHJ4 (e.g., IGHJ4*02) or IGHJ3 (e.g., IGHJ3*02), or

(ii) comprises framework regions FR1, FR2, FR3 and FR4, wherein

FR1 aligns with human germline V gene segment IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR2 aligns with human germline V gene segment IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR3 aligns with human germline V gene segment IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10), optionally with 1, 2, 3, 4 or 5 amino acid alterations, and/or

FR4 aligns with human germline J gene segment IGJH6 (e.g., JH6*02), IGJH4 (e.g., JH4*02) or IGJH3 (e.g., JH3*02), optionally with 1, 2, 3, 4 or 5 amino acid alterations.

Sentence 9. An antibody according to any of the preceding sentences, comprising an antibody V_L domain which

(i) is derived from recombination of a human light chain V gene segment and a human light chain J gene segment, wherein

the V segment is IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), and/or

the J gene segment is IGKJ4 (e.g., IGKJ4*01), IGKJ2 (e.g., IGKJ2*04), IGLJ3 (e.g., IGKJ3*01) or IGKJ1 (e.g., IGKJ1*01); or

(ii) comprises framework regions FR1, FR2, FR3 and FR4, wherein

FR1 aligns with human germline V gene segment IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR2 aligns with human germline V gene segment IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR3 aligns with human germline V gene segment IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations, and/or

FR4 aligns with human germline J gene segment IGKJ4 (e.g., IGKJ4*01), IGKJ2 (e.g., IGKJ2*04), IGKJ3 (e.g., IGKJ3*01) or IGKJ1 (e.g., IGKJ1*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations.

Sentence 10. An antibody according to any of the preceding sentences, comprising an antibody VH domain which is the V_H domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VH domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009.

Sentence11. An antibody according to any of the preceding sentences, comprising an antibody VL domain which is the V_L domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VL domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009.

Sentence 12. An antibody according to sentence 11, comprising

an antibody V_H domain which is selected from the VH domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VH domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, and

an antibody V_L domain which is the V_L domain of said selected antibody, or which has an amino acid sequence at least 90 % identical to the antibody V_L domain sequence of said selected antibody.

Sentence 13. An antibody according to sentence 12, comprising the STIM003 V_H domain and the STIM003 V_L domain.

Sentence 14. An antibody according to any of the preceding sentences, comprising an antibody constant region.

Sentence 15. An antibody according to sentence 14, wherein the constant region comprises a human heavy and/or light chain constant region.

Sentence 16. An antibody according to sentence 14 or sentence 15, wherein the constant region is Fc effector positive.

Sentence 17. An antibody according to sentence 16, comprising an Fc region that has enhanced ADCC, ADCP and/or CDC function compared with a native human Fc region.

Sentence 18. An antibody according to any of sentences 14 to 17, wherein the antibody is an IgG1.

Sentence 19. An antibody according to sentence 17 or sentence 18, wherein the antibody is afucosylated.

Sentence 20. An antibody according to any of the preceding sentences which is conjugated to a cytotoxic drug or pro-drug.

Sentence 21. An antibody according to any of the preceding sentences, which is a multispecific antibody.

Sentence 22. An isolated antibody that competes for binding to human ICOS with a human IgG1 antibody comprising the heavy and light chain complementarity determining regions of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009.

Sentence 23. An isolated antibody that binds the extracellular domain of human and mouse ICOS with an affinity (KD) of less than 50 nM as determined by surface plasmon resonance.

Sentence 24. An antibody according to sentence 23, wherein the antibody binds the extracellular domain of human and mouse ICOS with an affinity (KD) of less than 5 nM as determined by surface plasmon resonance.

Sentence 25. An antibody according to sentence 23 or sentence 24, wherein the KD of binding the extracellular domain of human ICOS is within 10-fold of the KD of binding the extracellular domain of mouse ICOS.

Sentence 26. A composition comprising an isolated antibody according to any of the preceding sentences and a pharmaceutically acceptable excipient.

Sentence 27. A composition comprising isolated nucleic acid encoding an antibody according to any of sentences 1 to 25 and a pharmaceutically acceptable excipient.

Sentence 28. A method of depleting regulatory T-cells and/or increasing effector T-cell response in a patient comprising administering a composition according to sentence 26 to the patient.

Sentence 29. A method of treating a disease or condition amenable to therapy by depleting regulatory T-cells and/or increasing effector T-cell response in a patient, the method comprising administering a composition according to sentence 26 to the patient.

Sentence 30. A composition according to sentence 26 for use in a method of treatment of the human body by therapy.

Sentence 31. A composition for use according to sentence 30, for use in depleting regulatory T-cells and/or increasing effector T-cell response in a patient.

Sentence 32. A composition for use according to sentence 30, for use in treating a disease or condition amenable to therapy by depleting regulatory T-cells and/or increasing effector T-cell response in a patient.

Sentence 33. A method according to sentence 29, or a composition for use according to sentence 32, wherein the disease is a cancer or a solid tumour.

Sentence 34. A method or a composition for use according to any of sentences 29 to 33, wherein the method comprises administering the antibody and another therapeutic agent to the patient.

Sentence 35. A method or composition for use according to sentence 34, wherein the therapeutic agent is an anti-PDL1 antibody.

Sentence 36. A method or composition for use according to sentence 35, wherein the anti-ICOS antibody and the anti-PDL1 antibody are each able to mediate ADCC, ADCP and/or CDC.

Sentence 37. A method or composition for use according to sentence 35, wherein the anti-ICOS antibody is a human IgG1 antibody and the anti-PDL1 antibody is a human IgG1 antibody.

Sentence 38. A method or composition for use according to sentence 34, wherein the other therapeutic agent is IL-2.

Sentence 39. A method or composition for use according to any of sentences 34 to 38, wherein the method comprises administering the anti-ICOS antibody after administering the other therapeutic agent.

Sentence 40. A method or a composition for use according to any of sentences 28 to 39, wherein

the anti-ICOS antibody is conjugated to a pro-drug, and wherein

the method or use comprises

administering the anti-ICOS antibody to a patient and

selectively activating the pro-drug at a target tissue site.

Sentence 41. A method or a composition for use according to sentence 40, wherein the patient has a solid tumour and the method comprises selectively activating the pro-drug in the tumour.

Sentence 42. A method or a composition for use according to sentence 40 or sentence 41, comprising selectively activating the pro-drug through photoactivation.

Sentence 43. Combination of anti-ICOS human IgG1 antibody and anti-PDL1 human IgG1 antibody for use in a method of treating cancer.

Sentence 44. Combination according to sentence 43, wherein the anti-ICOS antibody and the anti-PDL1 antibody are provided in separate compositions for administration.

Sentence 45. A method or composition for use according to sentence 37, or a combination according to sentence 43 or sentence 44, wherein the human IgG1 constant region has a wild type amino acid sequence shown in the appended sequence listing.

Sentence 46. Anti-ICOS antibody for use in a method of reducing or reversing a surge in ICOS-positive regulatory T-cells in a patient, wherein the surge results from treatment of the patient with another therapeutic agent.

Sentence 47. A method of treating a patient, the method comprising reducing or reversing a surge in ICOS-positive regulatory T-cells in the patient, wherein the surge results from treatment of the patient with another therapeutic agent.

Sentence 48. Anti-ICOS antibody for use in a method of treating a patient, the method comprising comprising administering the anti-ICOS antibody to a patient who has an increased level of ICOS-positive regulatory T-cells following treatment with another therapeutic agent.

Sentence 49. A method of treating a patient, the method comprising administering an anti-ICOS antibody to a patient who has an increased level of ICOS-positive regulatory T-cells following treatment with another therapeutic agent.

Sentence 50. An anti-ICOS antibody for use according to sentence 46 or sentence 48, or a method according to sentence 47 or sentence 49, wherein the method comprises administering a therapeutic agent to the patient, determining that the patient has an increased level of ICOS-positive regulatory T-cells following the treatment with said agent, and administering an anti-ICOS antibody to the patient to reduce the level of regulatory T-cells.

Sentence 51. An anti-ICOS antibody for use or a method according to any of sentences 46 to 50, wherein the therapeutic agent is IL-2 or an immunomodulatory antibody (e.g., anti-PDL-1, anti-PD-1 or anti-CTLA-4).

Sentence 52. An anti-ICOS antibody for use or a method according to any of sentences 46 to 51, wherein the method comprises treating a tumour, e.g., melanoma, such as metastatic melanoma.

Sentence 53. Anti-ICOS antibody for use in a method of treating cancer in a patient by in vivo vaccination of the patient against their cancer cells, the method comprising

treating the patient with a therapy that causes immunological cell death of the cancer cells, resulting in presentation of antigen to antigen-specific effector T-cells, and

administering an anti-ICOS antibody to the patient, wherein the anti-ICOS antibody enhances the antigen-specific effector T-cell response.

Sentence 54. A method of treating cancer in a patient by in vivo vaccination of the patient against their cancer cells, the method comprising

treating the patient with a therapy that causes immunological cell death of the cancer cells, resulting in presentation of antigen to antigen-specific effector T-cells, and

administering an anti-ICOS antibody to the patient, wherein the anti-ICOS antibody enhances the antigen-specific effector T-cell response.

Sentence 55. A method of treating cancer in a patient by in vivo vaccination of the patient against their cancer cells, the method comprising administering an anti-ICOS antibody to the patient, wherein

the patient is one who has been previously treated with a therapy that causes immunological cell death of the cancer cells, resulting in presentation of antigen to antigen-specific effector T-cells, and wherein

the anti-ICOS antibody enhances the antigen-specific effector T-cell response.

Sentence 56. Anti-ICOS antibody for use or a method according to any of sentences 53 to 55, wherein the therapy that causes immunological cell death is radiation of the cancer cells, administration of a chemotherapeutic agent and/or administration of an antibody directed to a tumour-associated antigen.

Sentence 57. Anti-ICOS antibody for use or a method according to sentence 56, wherein the chemotherapeutic agent is oxaliplatin.

Sentence 58. Anti-ICOS antibody for use or a method according to sentence 56, wherein the tumour-associated antigen is HER2 or CD20.

Sentence 59. Anti-ICOS antibody for use in a method of vaccinating a patient, the method comprising administering the antibody and a vaccine composition to the patient.

Sentence 60. A method of vaccinating a patient, the method comprising administering an anti-ICOS antibody and a vaccine composition to the patient.

Sentence 61. Anti-ICOS antibody for use according to sentence 59, or a method according to sentence 60, wherein the vaccine composition is a vaccine against hepatitis B, malaria or HIV.

Sentence 62. Anti-ICOS antibody for use in a method of treating a cancer in a patient, wherein the cancer is or has been characterised as being positive for expression of ICOS ligand and/or FOXP3.

Sentence 63. A method of treating a cancer in a patient, wherein the cancer is or has been characterised as being positive for expression of ICOS ligand and/or FOXP3, the method comprising administering an anti-ICOS antibody to the patient.

Sentence 64. Anti-ICOS antibody for use according to sentence 62, or a method according to sentence 63, wherein the method comprises:

testing a sample from a patient to determine that the cancer expresses ICOS ligand and/or FOXP3;

selecting the patient for treatment with the anti-ICOS antibody; and

administering the anti-ICOS antibody to the patient.

Sentence 65. Anti-ICOS antibody for use according to sentence 62, or a method according to sentence 63, wherein the method comprises administering an anti-ICOS antibody to a patient from whom a test sample has indicated that the cancer is positive for expression of ICOS ligand and/or FOXP3.

Sentence 66. Anti-ICOS antibody for use or a method according to sentence 64 or sentence 65, wherein the sample is biopsy sample of a solid tumour.

Sentence 67. Anti-ICOS antibody for use in a method of treating a cancer in a patient, wherein the cancer is or has been characterised as being refractory to treatment with an immunooncology drug, e.g., anti-CTLA-4 antibody, anti-PD1 antibody, anti-PD-L1 antibody, anti-CD137 antibody or anti-GITR antibody.

Sentence 68. A method of treating a cancer in a patient, wherein the cancer is or has been characterised as being refractory to treatment with an immunooncology drug, e.g., anti-CTLA-4 antibody, anti-PD1 antibody, anti-PD-L1 antibody, anti-CD137 antibody or anti-GITR antibody, the method comprising administering an anti-ICOS antibody to the patient.

Sentence 69. Anti-ICOS antibody for use according to sentence 67 or a method according to sentence 68, wherein the method comprises:

treating the patient with the immunooncology drug;

determining that the cancer is not responsive to the drug;

selecting the patient for treatment with the anti-ICOS antibody; and

administering the anti-ICOS antibody to the patient.

Sentence 70. Anti-ICOS antibody for use according to sentence 67, or a method according to sentence 68, wherein the method comprises administering an anti-ICOS antibody to a patient whose cancer was not responsive to prior treatment with the immunooncology drug.

Sentence 71. Anti-ICOS antibody for use or a method according to any of sentences 62 to 70, wherein the cancer is a tumour derived from cells that have acquired ability to express ICOS ligand.

Sentence 72. Anti-ICOS antibody for use or a method according to sentence 71, wherein the cancer is melanoma.

Sentence 73. Anti-ICOS antibody for use or a method according to any of sentences 62 to 70, wherein the cancer is derived from an antigen-presenting cell, such as a B lymphocyte (e.g., B cell lymphoma, such as diffused large B cell lymphoma) or a T lymphocyte.

Sentence 74. Anti-ICOS antibody for use or a method according to any of sentences 62 to 70, wherein the cancer is resistant to treatment with an anti-CD20 antibody.

Sentence 75. Anti-ICOS antibody for use or a method according to sentence 74, wherein the cancer is B cell lymphoma.

Sentence 76. Anti-ICOS antibody for use or a method according to sentence 75, wherein the anti-CD20 antibody is rituximab.

Sentence 77. Anti-ICOS antibody for use or a method according to any of sentences 74 to 76, wherein the method comprises treating the patient with the anti-CD20 antibody;

determining that the cancer is not responsive to the anti-CD20 antibody;

testing a sample from a patient to determine that the cancer expresses ICOS ligand;

selecting the patient for treatment with the anti-ICOS antibody; and

administering the anti-ICOS antibody to the patient.

Sentence 78. Anti-ICOS antibody for use or a method according to any of sentences 74 to 76, wherein the method comprises administering an anti-ICOS antibody to a patient whose cancer was not responsive to prior treatment with anti-CD20 antibody.

Sentence 79. Anti-ICOS antibody for use or a method according to any of sentences 52 to 78, wherein the cancer is a solid tumour.

Sentence 80. Anti-ICOS antibody for use or a method according to any of sentences 52 to 78, wherein the cancer is a haemotological liquid tumour.

Sentence 81. Anti-ICOS antibody for use or a method according to sentence 79 or 80, wherein the tumour is high in regulatory T-cells.

Sentence 82. Anti-ICOS antibody for use or a method according to any of sentences 43 to 81, wherein the anti-ICOS antibody is as defined in any of sentences 1 to 25 or is provided in a composition according to sentence 26.

Sentence 83. A transgenic non-human mammal having a genome comprising a human or humanised immunoglobulin locus encoding human variable region gene segments, wherein the mammal does not express ICOS.

Sentence 84. A method of producing an antibody that binds the extracellular domain of human and non-human ICOS, comprising

(a) immunising a mammal according to sentence 83 with human ICOS antigen;

(b) isolating antibodies generated by the mammal;

(c) testing the antibodies for ability to bind human ICOS and non-human ICOS; and

(d) selecting one or more antibodies that binds both human and non-human ICOS.

Sentence 85. A method according to sentence 84, comprising immunising the mammal with cells expressing human ICOS.

Sentence 86. A method according to sentence 84 or sentence 85, comprising

(c) testing the antibodies for ability to bind human ICOS and non-human ICOS using surface plasmon resonance and determining binding affinities; and

(d) selecting one or more antibodies for which the KD of binding to human ICOS is less than 50 nM and the KD of binding to non-human ICOS is less than 500 nM.

Sentence 87. A method according to sentence 86, comprising

(d) selecting one or more antibodies for which the KD of binding to human ICOS is less than 10 nM and the KD of binding to non-human ICOS is less than 100 nM.

Sentence 88. A method according to any of sentences 84 to 87, comprising

(c) testing the antibodies for ability to bind human ICOS and non-human ICOS using surface plasmon resonance and determining binding affinities; and

(d) selecting one or more antibodies for which the KD of binding to human ICOS is within 10-fold of the KD of binding to non-human ICOS.

Sentence 89. A method according to sentence 88, comprising

(d) selecting one or more antibodies for which the KD of binding to human ICOS is within 5-fold of the KD of binding to non-human ICOS.

Sentence 90. A method according to any of sentences 84 to 89, comprising testing the antibodies for ability to bind non-human ICOS from the same species as the mammal.

Sentence 91. A method according to any of sentences 84 to 90, comprising testing the antibodies for ability to bind non-human ICOS from a different species as the mammal.

Sentence 92. A method according to any of sentences 84 to 91, wherein the mammal is a mouse or a rat.

Sentence 93. A method according to any of sentences 84 to 92, wherein the non-human ICOS is mouse ICOS or rat ICOS.

Sentence 94. A method according to any of sentences 84 to 93, wherein the human or humanised immunoglobulin locus comprises human variable region gene segments upstream of an endogenous constant region.

Sentence 95. A method according to sentence 94, comprising

(a) immunising a mammal according to sentence 83 with human ICOS antigen, wherein the mammal is a mouse;

(b) isolating antibodies generated by the mouse;

(c) testing the antibodies for ability to bind human ICOS and mouse ICOS; and

(d) selecting one or more antibodies that binds both human and mouse ICOS.

Sentence 96. A method according to any of sentences 84 to 95, comprising isolating nucleic acid encoding an antibody heavy chain variable domain and/or an antibody light chain variable domain.

Sentence 97. A method according to any of sentences 84 to 96, wherein the mammal generates antibodies through recombination of human variable region gene segments and an endogenous constant region.

Sentence 98. A method according to sentence 96 or sentence 97, comprising conjugating the nucleic acid encoding the heavy and/or light chain variable domain to a nucleotide sequence encoding a human heavy chain constant region and/or human light chain constant region respectively.

Sentence 99. A method according to any of sentences 96 to 98, comprising introducing the nucleic acid into a host cell.

Sentence 100. A method according to sentence 99, comprising culturing the host cell under conditions for expression of the antibody, or of the antibody heavy and/or light chain variable domain.

Sentence 101. An antibody, or antibody heavy and/or light chain variable domain, produced by the method according to any of sentences 84 to 100.

Sentence 102. A method of selecting an antibody that binds ICOS, optionally for selecting an ICOS agonist antibody, the assay comprising:

providing an array of antibodies immobilised (attached or adhered) to a substrate in a test well;

adding ICOS-expressing cells (e.g., activated primary T-cells, or MJ cells) to the test well;

observing morphology of the cells;

detecting shape change in the cells from rounded to flattened against the substrate within the well; wherein the shape change indicates that the antibody is an antibody that binds ICOS, optionally an ICOS agonist antibody;

selecting the antibody from the test well;

expressing nucleic acid encoding the CDRs of the selected antibody; and

formulating the antibody into a composition comprising one or more additional components.

Alternative sentences describing anti-ICOS antibodies are described below:

Sentence 1a. An antibody or a fragment thereof which specifically binds to human ICOS (hICOS) (SEQ ID NO: 508, 507 and/or 506), and:

a) competes for binding to said hICOS with the antibody STIM001, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:365, or the CDRH3 sequence of SEQ ID NO:365 comprising 3, 2 or 1 amino acid substitution(s);

b) competes for binding to said hICOS with the antibody STIM002, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:379, or the CDRH3 sequence of SEQ ID NO:379 comprising 3, 2 or 1 amino acid substitution(s);

c) competes for binding to said hICOS with the antibody STIM002-B, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:393, or the CDRH3 sequence of SEQ ID NO:393 comprising 3, 2 or 1 amino acid substitution(s);

d) competes for binding to said hICOS with the antibody STIM003, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:407, or the CDRH3 sequence of SEQ ID NO:407 comprising 3, 2 or 1 amino acid substitution(s);

e) competes for binding to said hICOS with the antibody STIM004, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:421, or the CDRH3 sequence of SEQ ID NO:421 comprising 3, 2 or 1 amino acid substitution(s);

f) competes for binding to said hICOS with the antibody STIM005, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:437, or the CDRH3 sequence of SEQ ID NO:437 comprising 3, 2 or 1 amino acid substitution(s);

g) competes for binding to said hICOS with the antibody STIM006, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:451, or the CDRH3 sequence of SEQ ID NO:451 comprising 3, 2 or 1 amino acid substitution(s);

h) competes for binding to said hICOS with the antibody STIM007, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:465, or the CDRH3 sequence of SEQ ID NO:465 comprising 3, 2 or 1 amino acid substitution(s);

i) competes for binding to said hICOS with the antibody STIM008, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:479, or the CDRH3 sequence of SEQ ID NO:479 comprising 3, 2 or 1 amino acid substitution(s); or

j) competes for binding to said hICOS with the antibody STIM009, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:493, or the CDRH3 sequence of SEQ ID NO:493 comprising 3, 2 or 1 amino acid substitution(s).

Sentence 2a. The antibody or a fragment thereof according to sentence 1a, wherein the V_H domain comprises the CDRH1 sequence of:

a) SEQ ID NO:363, or the CDRH1 sequence of SEQ ID NO:363 comprising 1 amino acid substitution;

b) SEQ ID NO:377, or the CDRH1 sequence of SEQ ID NO:377 comprising 1 amino acid substitution;

c) SEQ ID NO:391, or the CDRH1 sequence of SEQ ID NO:391 comprising 1 amino acid substitution;

d) SEQ ID NO:405, or the CDRH1 sequence of SEQ ID NO:405 comprising 1 amino acid substitution;

e) SEQ ID NO:419, or the CDRH1 sequence of SEQ ID NO:419 comprising 1 amino acid substitution;

f) SEQ ID NO:435, or the CDRH1 sequence of SEQ ID NO:435 comprising 1 amino acid substitution;

g) SEQ ID NO:449, or the CDRH1 sequence of SEQ ID NO:449 comprising 1 amino acid substitution;

h) SEQ ID NO:463, or the CDRH1 sequence of SEQ ID NO:463 comprising 1 amino acid substitution; or

i) SEQ ID NO:477, or the CDRH1 sequence of SEQ ID NO:477 comprising 1 amino acid substitution.

j) SEQ ID NO:491, or the CDRH1 sequence of SEQ ID NO:491 comprising 1 amino acid substitution.

Sentence 3a. The antibody or a fragment thereof according to sentence 1a or sentence 2a, wherein the V_H domain comprises the CDRH2 sequence of:

a) SEQ ID NO:364, or the CDRH2 sequence of SEQ ID NO:364 comprising 2 or 1 amino acid substitution(s);

b) SEQ ID NO:378, or the CDRH2 sequence of SEQ ID NO:378 comprising 2 or 1 amino acid substitution(s);

c) SEQ ID NO:392, or the CDRH2 sequence of SEQ ID NO:392 comprising 2 or 1 amino acid substitution(s);

d) SEQ ID NO:406, or the CDRH2 sequence of SEQ ID NO:406 comprising 2 or 1 amino acid substitution(s);

e) SEQ ID NO:420, or the CDRH2 sequence of SEQ ID NO:420 comprising 2 or 1 amino acid substitution(s);

f) SEQ ID NO:436, or the CDRH2 sequence of SEQ ID NO:436 comprising 2 or 1 amino acid substitution(s);

g) SEQ ID NO:450, or the CDRH2 sequence of SEQ ID NO:450 comprising 2 or 1 amino acid substitution(s);

h) SEQ ID NO:464, or the CDRH2 sequence of SEQ ID NO:464 comprising 2 or 1 amino acid substitution(s);

i) SEQ ID NO:478, or the CDRH2 sequence of SEQ ID NO:478 comprising 2 or 1 amino acid substitution(s); or

j) SEQ ID NO:492, or the CDRH2 sequence of SEQ ID NO:492 comprising 2 or 1 amino acid substitution(s).

Sentence 4a. The antibody or a fragment thereof according to any preceding sentence, wherein the V_H domain comprises:

a) an amino acid sequence of SEQ ID NO:366, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:366;

b) an amino acid sequence of SEQ ID NO:380, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:380;

c) an amino acid sequence of SEQ ID NO:394, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:394;

d) an amino acid sequence of SEQ ID NO:408, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:408;

e) an amino acid sequence of SEQ ID NO:422, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:422;

f) an amino acid sequence of SEQ ID NO:438, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:438;

g) an amino acid sequence of SEQ ID NO:452, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:452;

h) an amino acid sequence of SEQ ID NO:466, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:466;

i) an amino acid sequence of SEQ ID NO:480, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:480; or

j) an amino acid sequence of SEQ ID NO:494, or a heavy chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:494.

Sentence 5a. The antibody or fragment according to any preceding sentence comprising first and second copies of said V_H domain.

Sentence 6a. The antibody or a fragment thereof according to any preceding sentence comprising a V_L domain, which comprises the CDRL1 sequence of:

a) SEQ ID NO:370, or the CDRL1 sequence of SEQ ID NO:370 comprising one amino acid substitution;

b) SEQ ID NO:384, or the CDRL1 sequence of SEQ ID NO:384 comprising one amino acid substitution;

c) SEQ ID NO:398, or the CDRL1 sequence of SEQ ID NO:398 comprising one amino acid substitution;

d) SEQ ID NO:412, or the CDRL1 sequence of SEQ ID NO:412 comprising one amino acid substitution;

e) SEQ ID NO:426, or the CDRL1 sequence of SEQ ID NO:426 comprising one amino acid substitution;

f) SEQ ID NO:442, or the CDRL1 sequence of SEQ ID NO:442 comprising one amino acid substitution;

g) SEQ ID NO:456, or the CDRL1 sequence of SEQ ID NO:456 comprising one amino acid substitution;

h) SEQ ID NO:470, or the CDRL1 sequence of SEQ ID NO:470 comprising one amino acid substitution; or

i) SEQ ID NO:484, or the CDRL1 sequence of SEQ ID NO:484 comprising one amino acid substitution.

j) SEQ ID NO:498, or the CDRL1 sequence of SEQ ID NO:498 comprising one amino acid substitution.

Sentence 7a. The antibody or a fragment thereof according to any preceding sentence comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of:

a) SEQ ID NO:371, or the CDRL2 sequence of SEQ ID NO:371 comprising 1 amino acid substitution;

b) SEQ ID NO:385, or the CDRL2 sequence of SEQ ID NO:385 comprising 1 amino acid substitution;

c) SEQ ID NO:399, or the CDRL2 sequence of SEQ ID NO:399 comprising 1 amino acid substitution;

d) SEQ ID NO:413, or the CDRL2 sequence of SEQ ID NO:413 comprising 1 amino acid substitution;

e) SEQ ID NO:427, or the CDRL2 sequence of SEQ ID NO:427 comprising 1 amino acid substitution;

f) SEQ ID NO:443, or the CDRL2 sequence of SEQ ID NO:443 comprising 1 amino acid substitution;

g) SEQ ID NO:457, or the CDRL2 sequence of SEQ ID NO:457 comprising 1 amino acid substitution;

h) SEQ ID NO:471, or the CDRL2 sequence of SEQ ID NO:471 comprising 1 amino acid substitution;

i) SEQ ID NO:485, or the CDRL2 sequence of SEQ ID NO:485 comprising 1 amino acid substitution; or

j) SEQ ID NO:499, or the CDRL2 sequence of SEQ ID NO:499 comprising 1 amino acid substitution.

Sentence 8a. The antibody or a fragment thereof according to any preceding sentence comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of:

a) SEQ ID NO:372, or the CDRL3 sequence of SEQ ID NO:372 comprising 2 or 1 amino acid substitution(s);

b) SEQ ID NO:386, or the CDRL3 sequence of SEQ ID NO:386 comprising 2 or 1 amino acid substitution(s);

c) SEQ ID NO:400, or the CDRL3 sequence of SEQ ID NO:400 comprising 2 or 1 amino acid substitution(s);

d) SEQ ID NO:414, or the CDRL3 sequence of SEQ ID NO:414 comprising 2 or 1 amino acid substitution(s);

e) SEQ ID NO:428, or the CDRL3 sequence of SEQ ID NO:428 comprising 2 or 1 amino acid substitution(s);

f) SEQ ID NO:444, or the CDRL3 sequence of SEQ ID NO:444 comprising 2 or 1 amino acid substitution(s);

g) SEQ ID NO:458, or the CDRL3 sequence of SEQ ID NO:458 comprising 2 or 1 amino acid substitution(s);

h) SEQ ID NO:472, or the CDRL3 sequence of SEQ ID NO:472 comprising 2 or 1 amino acid substitution(s);

i) SEQ ID NO:486, or the CDRL3 sequence of SEQ ID NO:486 comprising 2 or 1 amino acid substitution(s); or

j) SEQ ID NO:500, or the CDRL3 sequence of SEQ ID NO:500 comprising 2 or 1 amino acid substitution(s).

Sentence 9a. The antibody or a fragment thereof according to any preceding sentence, comprising a or said V_L domain, wherein the V_L domain comprises an amino acid sequence of:

a) SEQ ID NO:373, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:373;

b) SEQ ID NO:387, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:387;

c) SEQ ID NO:401, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:401;

d) SEQ ID NO:415, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:415;

e) SEQ ID NO:429, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:429;

f) SEQ ID NO:445, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:445;

g) SEQ ID NO:459, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:459;

h) SEQ ID NO:473, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:473;

i) SEQ ID NO:487, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:487; or

j) SEQ ID NO:501, or a light chain variable domain amino acid sequence that is at least 98% identical to SEQ ID NO:501.

Sentence 10a. The antibody or fragment according to any one of sentences 6a to 9a, comprising first and second copies of the a or said V_L domain.

Sentence 11. The antibody or fragment according to any preceding sentence, wherein the amino acid substitutions are conservative amino acid substitutions, optionally wherein the conservative substitutions are from one of six groups (each group containing amino acids that are conservative substitutions for one another) selected from:

1) Alanine (A), Serine (S), Threonine (T);

2) Aspartic acid (D), Glutamic acid (E);

3) Asparagine (N), Glutamine (Q);

4) Arginine (R), Lysine (K);

5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and

6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

Sentence 12a. An antibody or fragment thereof which specifically binds to an epitope that is:

a) Identical to an epitope to which the antibody STIM001 specifically binds;

b) Identical to an epitope to which the antibody STIM002 specifically binds;

c) Identical to an epitope to which the antibody STIM002-B specifically binds;

d) Identical to an epitope to which the antibody STIM003 specifically binds;

e) Identical to an epitope to which the antibody STIM004 specifically binds;

f) Identical to an epitope to which the antibody STIM005 specifically binds;

g) Identical to an epitope to which the antibody STIM006 specifically binds;

h) Identical to an epitope to which the antibody STIM007 specifically binds;

i) Identical to an epitope to which the antibody STIM008 specifically binds; or

j) Identical to an epitope to which the antibody STIM009 specifically binds.

Sentence 13a. The antibody or fragment according to sentence 12a, wherein the epitope is identified by unrelated amino acid scanning, or by X-ray crystallography.

Sentence 14a. The antibody or fragment according to sentence 13a, wherein the contact residues of the epitope are defined by a reduction in affinity of at least 10-fold in an unrelated amino acid scan, e.g. an alanine scan as determined by SPR.

Sentence 15a. An antibody or fragment thereof which:

a) Competes for binding to hICOS with the antibody STIM001;

b) Competes for binding to hICOS with the antibody STIM002;

c) Competes for binding to hICOS with the antibody STIM002-B;

d) Competes for binding to hICOS with the antibody STIM003;

e) Competes for binding to hICOS with the antibody STIM004;

f) Competes for binding to hICOS with the antibody STIM005;

g) Competes for binding to hICOS with the antibody STIM006;

h) Competes for binding to hICOS with the antibody STIM007;

i) Competes for binding to hICOS with the antibody STIM008; or

j) Competes for binding to hICOS with the antibody STIM009.

Sentence 16a. The antibody or fragment according to any preceding sentence which specifically binds to cynomolgus ICOS (Seq ID No:513, Seq ID NO: 513 or Seq ID No: 514) and/or mouse ICOS (Seq ID No:510, Seq ID No:511 or Seq ID No:512).

Sentence 17a. The antibody or fragment according to any preceding sentence which specifically binds to a hICOS isoform or natural variant, a mouse ICOS isoform or natural variant and/or a cynomolgus ICOS isoform or natural variant.

Sentence 18a. The antibody or fragment according to sentence 17a, wherein the hICOS isoform comprises an amino acid sequence as defined by Seq ID no:509.

Sentence 19a. The antibody or fragment according to any preceding sentence, wherein the antibody or fragment comprises a constant region, such as a human constant region, for example an effector-null human constant region, e.g. an IgG4 constant region or an IgG1 constant region, optionally wherein the constant region is IgG4-PE (Seq ID No:199), or a disabled IgG1 (Seq ID No:205).

Sentence 20a. The antibody or fragment according to sentence 19a, wherein the constant region is a murine constant region.

Sentence 21a. The antibody or fragment according to sentence 19a or sentence 20a, wherein the constant region has CDC and/or ADCC activity.

5. Anti-ICOS bispecific antibodies

As previously described, the PD-L1 antibodies as provided herein, may be formatted as a multispecific (e.g. bispecific) antibody, as disclosed hereinabove in concepts 37 to 40. In one embodiment disclosed therein, the PD-L1 antibodies as disclosed herein may be formatted in a bispecific antibody which has specificity for both PD-L1 (e.g. human PD-L1) and for ICOS (e.g. an agonist to ICOS, such as human ICOS).

Thus, there is provided a multispecific (e.g. bispecific antibody or a dual-binding antibody) which has specificity for PD-L1 (e.g. human PD-L1) and ICOS (e.g. human ICOS). In one embodiment the multispecific (e.g. bispecific or dual-binding) antibody has agonistic activity against ICOS (e.g. human ICOS).

Various ICOS-containing mutispecific antibodies are described in the arrangments below:

Arrangement 1. A multispecific antibody (e.g. bispecific antibody or a dual-binding antibody) which binds (and optionally has specificity for) ICOS (e.g. human ICOS) and another target antigen.

In one embodiment, there is provided a bispecific antibody or a dual-binding antibody which binds ICOS (e.g. human ICOS) and another target antigen. In one embodiment, there is provided a

bispecific antibody or a dual-binding antibody which has specificity for ICOS (e.g. human ICOS) and another target antigen. In one embodiment, there is provided a bispecific antibody antibody which binds ICOS (e.g. human ICOS) and another target antigen, and wherein the bispecific antibody format is a mAb^2. In one embodiment, there is provided a bispecific antibody antibody which binds ICOS (e.g. human ICOS) and another target antigen, and wherein the bispecific antibody format is a mAb^2, and the binding to another target antigen is provided by a modified constant region (i.e. an Fcab). In one embodiment, there is provided a bispecific antibody antibody which binds ICOS (e.g. human ICOS) and another target antigen which is PD-L1 (e.g. human PD-L1), and wherein the bispecific antibody format is a mAb2, and the binding to ICOS is provided by a modified constant region (i.e. an Fcab). In one embodiment, there is provided a bispecific antibody antibody which binds ICOS (e.g. human ICOS) and another target antigen which is PD-L1 (e.g. human PD-L1), and wherein the bispecific antibody format is a mAb2, and the binding to ICOS is provided by a modified constant region (i.e. an Fcab) and the binding to PD-L1 is provided by any of the antibodies described in concepts 1 to 70, or by any of the PD-L1 antibodies described in arrangement 5 or 5a below. In one embodiment, there is provided a bispecific antibody antibody which binds ICOS (e.g. human ICOS) and another target antigen which is PD-L1 (e.g. human PD-L1), and wherein the bispecific antibody format is a mAb^2, and the binding to PD-L1 is provided by a modified constant region (i.e. an Fcab). In one embodiment, there is provided a bispecific antibody antibody which binds ICOS (e.g. human ICOS) and another target antigen which is PD-L1 (e.g. human PD-L1), and wherein the bispecific antibody format is a mAb^2, and the binding to PD-L1 is provided by a modified constant region (i.e. an Fcab) and the binding to ICOS is provided by any of the antibodies described in sentences 1 to 102 or sentences 1a to 21a.

In one embodiment, the multispecific (e.g. bispecific or dual-binding) antibody has agonistic activity against ICOS (e.g. human ICOS). The another target antigen may be any of the target antigens specified in concept 39. In one embodiment, the another target antigen is an immune checkpoint inhibitor, such as PD-1, PD-L1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. PD-L1, TIGIT, CTLA-4, TIM-3 and LAG-3. In one embodiment, the another target antigen is an immune modulator, such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRP , CXCL9, CXCL10 and CD155, e.g. GARP, SIRP , CXCR4, BTLA, hVEM and CSF1R. In one embodiment, the another target antigen is an immune activator, such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies), CD27 and CD3, or CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies) and CD3, for example CD137, GITR and OX40). In one embodiment, the another target antigen is PD-L1. In one embodiment, the another target antigen is CTLA-4. In one embodiment, the another target antigen is TIGIT. In one embodiment, the another target antigen is TIM-3. In one embodiment, the another target antigen is LAG-3. In one embodiment, the another target antigen is GITR. In one embodiment, the another target antigen is VISTA. In one embodiment, the another target antigen is CD137. In one embodiment, the another target antigen is SIRPα. In one embodiment, the another target antigen is CXCL10. In one embodiment, the another target antigen

is CD155. In one embodiment, the another target antigen is CD40. The antibodies against these another target antigens may be any of those described in aspect 1a hereinabove.

The format of the multispecific, bispecific or dual-binding antibody may be any of the formats disclosed herein, for example as set out in concepts 37 to 40. In particular, the binding and/or specificity for ICOS may be provided by a non-immunoglobulin format, for example, a T-cell receptor binding domain; an immunoglobulin superfamily domain; an agnathan variable lymphocyte receptor; a fibronectin domain (e.g., an Adnectin™); an antibody constant domain (e.g., a CH3 domain, e.g., a CH2 and/or CH3 of an Fcab™) wherein the constant domain is not a functional CH1 domain; an scFv; an (scFv)2; an sc-diabody; an scFab; a centyrin and an epitope binding domain derived from a scaffold selected from CTLA-4 (Evibody™); a lipocalin domain; Protein A such as Z-domain of Protein A (e.g., an Affibody™ or SpA); an A-domain (e.g., an Avimer™ or Maxibody™); a heat shock protein (such as and epitope binding domain derived from GroEI and GroES); a transferrin domain (e.g., a trans-body); ankyrin repeat protein (e.g., a DARPin™); peptide aptamer; C-type lectin domain (e.g., Tetranectin™);

- crystallin or human ubiquitin (an affilin); a PDZ domain; scorpion toxin; and a kunitz type domain of a human protease inhibitor. The binding and/or specificity for another target antigen may be provided by an immunoglobulin-dervied antigen-binding protein.

"Specificially binds" has the meaning provided hereinabove. Binding constants, e.g. K_D may be determined as described elsewhere herein, and particular K_Ds of interest are described in arrangment 2 below, and in concept 1 hereinabove (although specified for PD-L1 binding, the values of K_D may be equally applied to anti-ICOS binding).

Arrangement 2. A multispecific antibody according to arrangement 1, wherein the ICOS is human ICOS.

Sequences of human ICOS are provided in Seq ID Nos:506, 507 and 508. In one embodiment, the multispecific antibody is specific for wild type human ICOS. In another embodiment, the multispecific antibody is cross-reactive to an isoform or natural variant of hICOS, for example the isoform of Seq ID No:509. Other isoforms and natural variants are well known to those skilled in the art. In another embodiment, the multispecific antibody is specific for the isoform or natural variant (e.g. the ICOS isoform having the amino acid sequence of Seq ID No:509) over wild type hICOS.

One way to quantify the extent of species cross-reactivity of an antibody, e.g. a multispecific, bispecific or dual-binding antibody is as the fold-difference in its affinity for antigen compared with a different antigen (e.g. fold difference in affinity for human ICOS vs mouse ICOS or fold difference in affinity for wild-type hICOS vs an isoform of hICOS). Affinity may be quantified as K_D, referring to the equilibrium dissociation constant of the antibody-antigen reaction as determined by SPR (optionally with the antibody in Fab format as described elsewhere herein). A species or isoform cross-reactive anti-ICOS antibody may have a fold-difference in affinity for binding human and mouse ICOS that is 30-fold or less, 25-fold or less, 20-fold or less, 15-fold or less, 10-fold or less or 5-fold or less. To put it another way, the K_D of binding the extracellular domain of hICOS may be within 30-fold, 25-fold,

20-fold, 15-fold, 10-fold or 5-fold of the K_D of binding the extracellular domain of mouse ICOS. Antibodies can also be considered cross-reactive if the K_D for binding antigen of both species meets a threshold value, e.g., if the K_D of binding hICOS and the K_D of binding mouse ICOS are both 10 mM or less, preferably 5 mM or less, more preferably 1 mM or less. The K_D may be 10 nM or less, 5 nM or less, 2 nM or less, or 1 nM or less. The KD may be 0.9 nM or less, 0.8 nM or less, 0.7 nM or less, 0.6 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, or 0.1 nM or less.

An alternative measure of cross-reactivity for binding hICOS and mouse ICOS, or WT hICOS and an isoform of hICOS is the ability of an antibody to neutralise ICOS ligand binding to ICOS receptor, such as in an HTRF assay (as described elsewhere herein). Examples of species cross-reactive antibodies are provided herein, including STIM001, STIM002, STIM002-B, STIM003, STIM005 and STIM006, each of which was confirmed as neutralising binding of human B7-H2 (ICOS ligand) to hICOS and neutralising binding of mouse B7-H2 to mouse ICOS in an HTRF assay. Any of these antibodies or their variants may be selected when an antibody cross-reactive for human and mouse ICOS is desired. A species cross-reactive anti-ICOS antibody may have an IC_{50} for inhibiting binding of hICOS to human ICOS receptor that is within 25-fold, 20-fold, 15-fold, 10-fold or 5-fold of the IC50 for inhibiting mouse ICOS to mouse ICOS receptor as determined in an HTRF assay. Antibodies can also be considered cross-reactive if the IC_{50} for inhibiting binding of hICOS to human ICOS receptor and the IC_{50} for inhibiting binding of mouse ICOS to mouse ICOS receptor are both 1 mM or less, preferably 0.5 mM or less, e.g., 30 nM or less, 20 nM or less, 10 nM or less. The IC_{50}s may be 5 nM or less, 4 nM or less, 3 nM or less or 2 nM or less. In some cases, the IC_{50}s will be at least 0.1 nM, at least 0.5 nM or at least 1 nM.

Affinities may also be as disclosed in concept 27 hereinabove.

Arrangement 3. A multispecific antibody according to arrangment 2, which comprises a V_H domain comprising a CDRH1, a CDRH2 and a CDRH3 which V_H domain binds (and optionally has specificity for) hICOS.

In one embodiment, the multispecific antibody comprises at least one V_H domain which binds to hICOS. For example, the multispecific antibody may comprise a single-chain Fv (scFv), single-chain antibody, a single domain antibody or a domain antibody compsiting only the V_H region which binds to (and optionally has specificity for) hICOS.

Arrangement 4. A multispecific antibody according to arrangement 2 or arrangement 3, which comprises a V_L domain comprising a CDRL1, a CDRL2 and a CDRL3, which V_L domain binds (and optionally has specificity for) hICOS.

In one embodiment, the multispecific antibody comprises at least one V_L domain which binds to hICOS. For example, the multispecific antibody may comprise a single-chain Fv (scFv), single-chain antibody, a single domain antibody or a domain antibody compsiting only the V_L region which binds to (and optionally has specificity for) hICOS.

In another embodiment, the multispecific antibody comprises a paired V_H and V_L domain, including, but not limited to, an intact or full-length antibody, a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment or a Fv fragment.

Arrangement 5. A multispecific antibody according to arrangement 3 or 4, wherein the V_H and/or V_L domain is any of V_H and/or V_L domains:

a. of the antibody 7F12, 37A10, 35A9, 36E10, 16G10, 37A10S713, 37A10S714, 37A10S715, 37A10S716, 37A10S717, 37A10S718, 16G10S71, 16G10S72, 16G10S73, 16G10S83, 35A9S79, 35A9S710, 35A9S89 or any other antibody described in WO2016/154177 and US2016/0304610;
b. of the antibody 422.2, H2L5, or any other antibody described in WO2016/120789 and US2016/0215059;
c. of the antibody 314-8, the antibody produced from hybridoma CNCM I-4180, or any other antibody described in WO2014/033327 and US2015/0239978;
d. of the antibody Icos145-1, the antibody produced by hybridoma CNCM I-4179, or any other antibody described in WO2012/131004, US9,376,493 and US2016/0264666;
e. of the antibody JMAb 136, "136", or any other antibody described in WO2010/056804;
f. of the antibody MIC-944, 9F3 or any other antibody described in WO99/15553, US7,259,247, US7,132,099, US7,125,551, US7,306,800, US7,722,872, WO05/103086, US8.318.905 and US8,916,155;
g. of any JMAb antibody, e.g., any of JMAb-124, JMAb-126, JMAb-127, JMAb-128, JMAb-135, JMAb-136, JMAb-137, JMAb-138, JMAb-139, JMAb-140, JMAb-141, e.g., JMAb136, or any other antibody described in WO98/3821, US7,932,358B2, US2002/156242, US7,030,225, US7,045,615, US7,279,560, US7,226,909, US7,196,175, US7,932,358, US8,389,690, WO02/070010, US7,438,905, US7,438,905, WO01/87981, US6,803,039, US7,166,283, US7,988,965, WO01/15732, US7,465,445 and US7,998,478;
h. of the antibody 17G9 or any other antibody described in WO2014/08911;
i. of any antibody described in WO2012/174338;
j. of any antibody described in US2016/0145344;
k. of any antibody described in WO2011/020024, US2016/002336, US2016/024211 and US8,840,889;
l. of any antibody described in US8,497,244;
m. of the antibody known as GSK3359609;
n. of the antibody known as JTX-2011; or
o. of antibody clone ISA-3 (eBioscience), clone SP98 (Novus Biologicals), clone 1 G1 , clone 3G4 (Abnova Corporation), clone 669222 (R&D Systems), clone TQ09 (Creative Diagnostics), or clone C398.4A (BioLegend).

Arrangement 5a. A multispecific antibody according to any preceding arrangement, which comprises the CDRH1, CDRH2, CDR3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L region:

a. of the antibody 7F12, 37A10, 35A9, 36E10, 16G10, 37A10S713, 37A10S714, 37A10S715, 37A10S716, 37A10S717, 37A10S718, 16G10S71, 16G10S72, 16G10S73, 16G10S83, 35A9S79, 35A9S710, 35A9S89 or any other antibody described in WO2016/154177 and US2016/0304610;
b. of the antibody 422.2, H2L5, or any other antibody described in WO2016/120789 and US2016/0215059;
c. of the antibody 314-8, the antibody produced from hybridoma CNCM I-4180, or any other antibody described in WO2014/033327 and US2015/0239978;
d. of the antibody Icos145-1, the antibody produced by hybridoma CNCM I-4179, or any other antibody described in WO2012/131004, US9,376,493 and US2016/0264666;
e. of the antibody JMAb 136, "136", or any other antibody described in WO2010/056804;
f. of the antibody MIC-944, 9F3 or any other antibody described in WO99/15553, US7,259,247, US7,132,099, US7,125,551, US7,306,800, US7,722,872, WO05/103086, US8.318.905 and US8,916,155;
g. of any JMAb antibody, e.g., any of JMAb-124, JMAb-126, JMAb-127, JMAb-128, JMAb-135, JMAb-136, JMAb-137, JMAb-138, JMAb-139, JMAb-140, JMAb-141, e.g., JMAb136, or any other antibodye described in WO98/3821, US7,932,358B2, US2002/156242, US7,030,225, US7,045,615, US7,279,560, US7,226,909, US7,196,175, US7,932,358, US8,389,690, WO02/070010, US7,438,905, US7,438,905, WO01/87981, US6,803,039, US7,166,283, US7,988,965, WO01/15732, US7,465,445 and US7,998,478;
h. of the antibody 17G9 or any other antibody described in WO2014/08911;
i. of any antibody described in WO2012/174338;
j. of any antibody described in US2016/0145344;
k. of any antibody described in WO2011/020024, US2016/002336, US2016/024211 and US8,840,889;
l. of any antibody described in US8,497,244;
m. of the antibody known as GSK3359609;
n. of the antibody known as JTX-2011; or
o. of antibody clone ISA-3 (eBioscience), clone SP98 (Novus Biologicals), clone 1 G1 , clone 3G4 (Abnova Corporation), clone 669222 (R&D Systems), clone TQ09 (Creative Diagnostics), or clone C398.4A (BioLegend).

Arrangement 6. A multispecific antibody according to arrangement 3 or 4, wherein the V_H and/or V_L domain is any of V_H and/or V_L domains defined in sentences 1 to 102 or sentences 1a to 21a.

In one embodiment, the anti-ICOS V_H and/or V_L is as described in GB patent application 1620414.1 (filed 1st December 2016), the contents of which are incorporated herein by reference.

Arrangement 7. A multispecific antibody according to any preceding arrangement, which has agonistic activity against ICOS.

Agonism can be tested for in an T-cell activation assays, using antibody in soluble form (e.g. in immunoglobulin format or other antibody format comprising two spatially separated antigen-binding sites, e.g., two V_H-V_L pairs), either including or excluding a cross-linking agent, or using antibody (e.g. multispecific antibody) bound to a solid surface to provide a tethered array of antigen-binding sites. Agonism assays may use a hICOS positive T-lymphocyte cell line such as MJ cells (ATCC CRL-8294) as the target T-cell for activation in such assays. One or more measures of T-cell activation can be determined for a test antibody and compared with a reference molecule or a negative control to determine whether there is a statistically significant ($p<0.05$) difference in T-cell activation effected by the test antibody (e.g. multispecific antibody) compared with the reference molecule or the control. One suitable measure of T-cell activation is production of cytokines, e.g., IFNγ, TNFα or IL-2. A skilled person will include suitable controls as appropriate, standardising assay conditions between test antibody and control. A suitable negative control is an antibody in the same format (e.g., isotype control) that does not bind ICOS, e.g., an antibody (e.g. multispecific antibody) specific for an antigen that is not present in the assay system. A significant difference is observed for test antibody relative to a cognate isotype control within the dynamic range of the assay is indicative that the antibody acts as an agonist of the ICOS receptor in that assay.

An agonist antibody may be defined as one which, when tested in a T-cell activation assay:

has a significantly lower EC_{50} for induction of IFNγ production compared with control antibody;

induces significantly higher maximal IFNγ production compared with control antibody;

has a significantly lower EC_{50} for induction of IFNγ production compared with ICOSL-Fc;

induces significantly higher maximal IFNγ production compared with ICOSL-Fc;

has a significantly lower EC_{50} for induction of IFNγ production compared with reference antibody C398.4A; and/or

induces significantly higher maximal IFNγ production compared with reference antibody C398.4A.

A significantly lower or significantly higher value may for example be up to 0.5-fold different, up to 0.75-fold different, up to 2-fold different, up to 3-fold different, up to 4-fold different or up to 5-fold different, compared with the reference or control value.

Thus, in one example, an antibody (e.g. a multispecific antibody) provided herein has a significantly lower, e.g., at least 2-fold lower, EC_{50} for induction of IFNγ in an MJ cell activation assay using the antibody in bead-bound format, compared with control.

The bead-bound assay uses the antibody (e.g. multispecific antibody) (and, for control or reference experiments, the control antibody, reference antibody or ICOSL-Fc) bound to the surface of beads. Magnetic beads may be used, and various kinds are commercially available, e.g., Tosyl-activated DYNABEADS M-450 (DYNAL Inc, 5 Delaware Drive, Lake Success, N.Y. 11042 Prod No. 140.03, 140.04). Beads may be coated (coating methods are well-known to those skilled in the art), or generally by dissolving the coating material in carbonate buffer (pH 9.6, 0.2 M) or other method known in the art. Use of beads conveniently allows the quantity of protein bound to the bead surface to be determined with a good degree of accuracy. Standard Fc-protein quantification methods can be used for coupled protein quantification on beads. Any suitable method can be used, with reference to a relevant standard within the dynamic range of the assay. DELFIA, ELISA or other methods could be used.

Agonism activity of an antibody can also be measured in primary human T-lymphocytes . The ability of an antibody (e.g. multispecific antibody) to indu in such T-cells is indicative of ICOS agonism. Preferably, an antibody will show significant ($p<0.05$) induction of IFNγ at 5 μg/mL compared with control antibody in a T-cell activation assay. An anti-ICOS antibody may stimulate T-cell activation to a greater degree than ICOS-L or C398.4 in such an assay. Thus, the antibody may show significantly ($p<0.05$) grea compared with the control or reference antibody in a T-cell activation assay. -2 induction may be measured as an alternative assay readout.

Agonism of an anti-ICOS antibody may contribute to its ability to change the balance between populations of T_{Reg} and T_{Eff} cells e.g., in a site of pathology such as a tumour microenvironment, in favour of T_{Eff} cells. The ability of an antibody to enhance tumour cell killing by activated ICOS-positive effector T-cells may be determined, as discussed elsewhere herein.

Arrangement 8. A multispecific antibody according to any preceding arrangement, which binds (and optionally has specificity for) mouse ICOS and/or cynomolgus ICOS.

The multispecific antibodies described herein may be cross-reactive, and may for example bind the extracellular domain of mouse ICOS as well as human ICOS. The multispecific antibodies may bind other non-human ICOS, including ICOS of primates, such as cynomolgus monkey. An anti-ICOS multispecific antibody intended for therapeutic use in humans must bind human ICOS, whereas binding to ICOS of other species would not have direct therapeutic relevance in the human clinical context. Regardless of the underlying theory, however, cross-reactive antibodies are of high value and are excellent candidates as therapeutic molecules for pre-clinical and clinical studies. Cross-reactivity may be determined as set out for arrangement 2 hereinabove.

Arrangement 9. A multispecific antibody according to any preceding arrangement which is a bispecific antibody.

A bispecific antibody has any of the meanings set out hereinabove.

Arrangement 10. A bispecifc antibody according to arrangement 9, wherein the bispecific antibody format is selected from DVD-Ig, mAb^2, FIT-Ig, mAb-dAb, dock and lock, SEEDbody, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH3, Diabody-CH3, minibody, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, in particular mAb^2, knob-in-holes, knob-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs and FIT-Ig, e.g. mAb^2 and FIT-Ig.

In one embodiment, the bispecific antibody format is as described in any of concepts 37 to 40 described hereinabove, or as described in the definitions section. In one embodiment, the bispecific antibody format is a mAb^2, wherein the ICOS binding is provided by the Fcab portion of the bispecific antibody. In another embodiment, the the bispecific antibody format is a mAb^2, wherein the ICOS binding is provided by the Fab portion of the bispecific antibody.

In another embodiment, the bispecific antibody is not a mAb^2 bispecific antibody.

Arrangement 11. A multispecific antibody according to any one of arrangements 1 to 8 which is a dual binding antibody.

A dual-binding antibody has any of the meanings set out hereinabove.

Arrangement 12. A multispecific, bispecific or dual binding antibody according to any one of arrangements 1 to 11, wherein the another target antigen is selected from immune checkpoint inhibitors, immune modulators and immune activators.

Arrangement 13. A multispecific, bispecific or dual-binding antibody according to arrangement 12, wherein the another target antigen is selected from PD-1, PD-L1, CTLA-4, TIGIT, TIM-3, LAG-3, VISTA, BTLA, HVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10, CD155, CD137, GITR, OX40, CXCR3, CD27 and CD3.

Arrangement 13a. A multispecific, bispecific or dual-binding antibody according to arrangement 12, wherein the another target antigen is selected from PD-1, PD-L1, CTLA-4, TIGIT, TIM-3, LAG-3, VISTA, BTLA, HVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10, CD155, CD137, GITR, OX40, CXCR3 and CD3.

In one embodiment, the antigen-binding site which binds the another target antigen is provided for by any of the CDRH1, CDRH2, CDR3, CDRL1, CDRL2 and CDRL3, or the V_H, or the V_L or the V_H and V_L regions from any one of the antibodies against the targets listed in arrangement 13 which are described in more detail in aspect 1a hereinabove.

Arrangement 14. A multispecific, bispecific or dual-binding antibody according to arrangement 13, wherein the another target antigen is selected from PD-L1, TIGIT, TIM-3, LAG-
CXCR4, BTLA, HVEM, CSF1R, agonistic anti-CXCR3 antibodies), CD137, GITR and OX40.

Arrangement 15. A multispecific, bispecific or dual-binding antibody according to arrangement 14, wherein the another target antigen is PD-L1 (e.g. human PD-L1).

Arrangement 16. A multispecific, bispecific or dual-binding antibody according to arrangemnet 15, wherein the binding (and optionally specificity for) PD-L1 is provided by any of the antibodies or fragments as defined in concepts 1 to 70.

Arrangement 17. A multispecific, bispecific or dual-binding antibody according to arrangement 15 or arrangement 16, which comprises a V_H domain comprising a CDRH1, a CDRH2 and a CDRH3 which V_H domain has specificity for human PD-L1.

Arrangemnt 18. A multispecific, bispecific or dual-binding antibody according to any one of arrangements 15 to 17, which comprises a V_L domain comprising a CDRL1, a CDRL2 and a CDRL3, which V_L domain as specificity for human PD-L1.

Arrangement 19. A multispecific, bispecific or dual-binding antibody according to arrangement 17 or arrangement 18, wherein the V_H and/or V_L domain is any of V_H and/or V_L domains from atezolizumab (Roche), avelumab (Merck), BMS-936559 (BMS), durvalumab (Medimmune) or from any of the PD-L1 antibodies disclosed in WO2016/061142, WO2016/022630, WO2016/007235, WO2015/173267, WO2015/181342, WO2015/109124, WO2015/112805, WO2015/061668, WO2014/159562, WO2014/165082, WO2014/100079, WO2014/055897, WO2013/181634, WO2013/173223, WO2013/079174, WO2012/145493, WO2011/066389, WO2010/077634, WO2010/036959 or WO2007/005874.

Arrangement 20. A multispecific, bispecific or dual-binding antibody according to arrangement 17 or arrangement 18, wherein the V_H and/or V_L domain is any of V_H and/or V_L domains described in concepts 1 to 70.

Arrangement 21. A multispecific, bispecific or dual-binding antibody according to any one of arrangements 15 to 20, which binds (and optionally has specificity for) mouse PD-L1 and/or cynomolgus PD-L1.

Cross reactivity may be as described hereinabove for arrangement 2 or concept 27.

Arrangement 22. A composition comprising a multispecific, bispecific or dual-binding antibody as defined in any preceding arrangement and a pharmaceutically acceptable excipient, diluent or carrier and optionally further comprising a further therapeutic agent independently selected from the group consisting of:

a) other immune checkpoint inhibitors (such as anti-TIM-3 antibodies, anti-PD-1 antibodies, anti-CTLA-4 antibodies, anti-TIGIT antibodies and anti-LAG-3 antibodies);

b) immune stimulators (such as anti-OX40 antibodies, anti-GITR antibodies, anti-CD137 antibodies, anti-ICOS antibodies and anti-CD40 antibodies);

c) chemokine receptor antagonists (such as CXCR4, CCR4 and CXCR2);

d) targeted kinase inhibitors (such as CSF-1R or VEGFR inhibitors);

e) angiogenesis inhibitors (such as anti-VEGF-A or Delta-like Ligand-4);

f) immune stimulating peptides or chemokines (such as CXCL9 or CXCL10);

g) cytokines (such as IL-15 and IL-21);

h) bispecific T-cell engagers (BiTEs) having at least one specificity against CD3 (e.g. CD3/CD19 BiTE);

i) other bi-specific molecules (for example IL-15-containing molecules targeted towards tumour associated antigens, for example Epidermal growth factor receptors such as EGFR, Her-2, New York Esophageal Cancer-1 (NY-ESO-1), GD2, EpCAM or Melanoma Associated Antigen-3 (MAGE-A3));

j) oncolytic viruses (such as HSV virus (optionally which secretes GMCSF), Newcastle disease virus and Vaccinia virus);

k) vaccination with tumour associated antigens (such as New York Esophageal Cancer-1 [NY-ESO-1], Melanoma Associated Antigen-3 [MAGE-3]);

l) cell-based therapies (such as chimeric Antigen Receptor-T-cells (CAR-T) for example expressing anti-CD19, anti-EpCam or anti-mesothelin);

m) bi-specific NK cell engagers having a specificity against an activating MK receptor such as NKG2D or CD16a; and

n) adoptive transfer of tumour specific T-cells or LAK cells.

The antibodies may be any of the sequences or antibodies described in arrangement 5 or detailed in aspect 1a. Other features of this arrangement may be as described in concept 49.

Arrangement 22a. A pharmaceutical composition according to arrangement 22, or a kit comprising a pharmaceutical composition as defined in arrangement 22, wherein the composition is for treating and/or preventing a condition or disease selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease, diffuse large B-cell lymphoma.

Arrangement 22b. A pharmaceutical composition according to arrangement 22 or arrangement 22a in combination with, or kit according to arrangement 22a comprising, a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the multispecific, bispecific or dual-binding antibody.

Arrangement 23. A multispecific, bispecific or dual-binding antibody as defined in any one of arrangements 1 to 21 for use in treating or preventing a disease or condition, selected from neurological disease, neoplastic or non-neoplastic disease, chronic viral infections, and malignant

tumours; such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

Arrangement 24. Use of a multispecific, bispecific or dual-binding antibody as defined in any one of arrangements 1 to 21 in the manufacture of a medicament for administration to a human for treating or preventing a disease or condition in the human selected from neurological disease, neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

Arrangement 25. A method of treating or preventing a disease or condition selected from neurological disease, neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas) in a human, comprising administering to said human a therapeutically effective amount of a multispecific, bispecific or dual-binding antibody as defined in any one of arrangements 1 to 21, wherein the disease or condition is thereby treated or prevented.

The diseases and conditions which may be treated or prevented by the multispecific, bisecific or dual-binding antibodies provided for in these arrangements may be any of the diseases provided for in, for example concepts 41 to 45, aspects 51 to 55, or in any of the sentences described herein.

Arrangement 26. The multispecific, bispecific or dual-binding antibody according to arrangement 23, the use according to arrangement 24 or the method according to arrangement 25, wherein the neurological disease is a neurodegenerative disease, disorder or condition, optionally wherein the

neurodegenerative disease, disorder or condition is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, corticobasal degeneration, Rett syndrome, a retinal degeneration disorder selected from age-related macular degeneration and retinitis pigmentosa; anterior ischemic optic neuropathy, glaucoma, uveitis, depression, trauma-associated stress or post-traumatic stress disorder, frontotemporal dementia, Lewy body dementias, mild cognitive impairments, posterior cortical atrophy, primary progressive aphasia and progressive supranuclear palsy or aged-related dementia, in particular Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease, and e.g. Alzheimer's disease.

Arrangement 27. The multispecific, bispecific or dual-binding antibody according to arrangement 23, the use according to arrangement 24 or the method according to arrangement 25, wherein the cancer is selected from melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or is selected from virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas.

Arrangement 28. The multispecific, bispecific or dual-binding antibody, the use or the method according to any one of arrangements 23 to 27, further comprising administering to the human a further therapy, for example a further therapeutic agent, optionally wherein the further therapeutic agent is independently selected from the group consisting of:

a. other immune checkpoint inhibitors (such as anti-TIM-3 antibodies, anti-PD-1 antibodies, anti-CTLA-4 antibodies, anti-TIGIT antibodies and anti-LAG-3 antibodies);
b. immune stimulators (such as anti-OX40 antibodies, anti-GITR antibodies, anti-CD137 antibodies and anti-CD40 antibodies);
c. chemokine receptor antagonists (such as CXCR4, CCR4 and CXCR2);
d. targeted kinase inhibitors (such as CSF-1R or VEGFR inhibitors);
e. angiogenesis inhibitors (such as anti-VEGF-A or Delta-like Ligand-4);
f. immune stimulating peptides or chemokines (such as CXCL9 or CXCL10);
g. cytokines (such as IL-15 and IL-21);
h. bispecific T-cell engagers (BiTEs) having at least one specificity against CD3 (e.g. CD3/CD19 BiTE);
i. other bi-specific molecules (for example IL-15-containing molecules targeted towards tumour associated antigens, for example Epidermal growth factor receptors such as EGFR, Her-2, New York Esophageal Cancer-1 (NY-ESO-1), GD2, EpCAM or Melanoma Associated Antigen-3 (MAGE-A3));
j. oncolytic viruses (such as HSV virus (optionally which secretes GMCSF), Newcastle disease virus and Vaccinia virus);

k. vaccination with tumour associated antigens (such as New York Esophageal Cancer-1 [NY-ESO-1], Melanoma Associated Antigen-3 [MAGE-3]);

l. cell-based therapies (such as chimeric Antigen Receptor-T-cells (CAR-T) for example expressing anti-CD19, anti-EpCam or anti-mesothelin);

m. bi-specific NK cell engagers having a specificity against an activating MK receptor such as NKG2D or CD16a; and

n. adoptive transfer of tumour specific T-cells or LAK cells,

or optionally wherein the further therapy is chemotherapy, radiotherapy and surgical removal of tumours.

Radiotherapy may be single dose or in fractionated doses, either delivered to affected tissues directly or to the whole body.

In this arrangement, any of the features and embodiments of concept 46 apply

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In this aspect, the bispecific molecules include "bispecific antibodies" and antibody fusion proteins, including those formats and molecules described in concepts 37 to 40.

Arrangement 29. A nucleic acid that encodes a heavy chain and/or a light chain of a multispecific, bispecific or dual-binding antibody as defined in any one of arrangements 1 to 21.

Arrangement 30. A vector comprising the nucleic acid as defined in arrangement 29; optionally wherein the vector is a CHO or HEK293 vector.

Arrangement 31. A host comprising the nucleic acid as defined in arrangement 29 or the vector as defined in arrangement 30.

6. Uses for antibodies and immunocytokines

Unless otherwise apparent from the context, the uses for antibodies or fragments applies to the immunocytokines and multispecific (e.g. bispecific or dual-binding antibodies) of the invention.

Therapeutic

In one embodiment, the PD-L1 specific antibodies described herein and antigen binding fragments thereof can be used for therapeutic modulation of the PD-1/PD-L1 pathway. In one embodiment, the PD-L1 specific antibody or fragment thereof is as described in any concept, aspect or embodiment herein.

In one embodiment, the antibody or antibody binding fragment specifically binds to PD-L1 and thereby inhibits PD-L1 activity. In another embodiment, the antibody or antibody binding fragment specifically binds to PD-L1 and thereby inhibits binding of PD-L1 to PD-1. In another embodiment, the antibody or antibody binding fragment specifically binds to PD-L1 and thereby inhibits binding of PD-

L1 to B7-1. In yet another embodiment, the antibody or antigen binding fragment thereof blocks PD-L1 induced T-cell suppression and thereby enhance anti-tumour immunity.

In yet another embodiment, the antibody or antigen binding fragment thereof is capable of stimulating one or more of the following activities: T-cell proliferation, IFN- , CD25 and/or IL-2 secretion in mixed lymphocyte reactions.

In one embodiment, the antibody or antigen binding fragment thereof specifically binds PD-L1 and inhibits PD-L1 induced cell proliferation, for example, tumour cell proliferation and/or inhibits tumour cell survival. In another embodiment, the antibody or antigen binding fragment thereof specifically binds PD-L1 and thereby inhibits PD-L1 mediated suppression of T-cells, including, but not limited to, tumour reactive T-cells, thereby enhancing anti-tumour cytolytic T-cell activity. In other embodiments, the antibodies or binding fragments thereof as described herein inhibit tumour cell adhesion, motility, invasion and cellular metastasis, and reduce tumour growth. In other embodiments, the antibodies or binding fragments thereof can bind to cells expressing PD-L1, including tumour and non-tumour cells, and recruit, by means of interaction with the Fc portion of the antibody, cellular effector functions against the target cells by mechanisms including but not limited to antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP).

Still further embodiments include methods of treating a proliferative or invasion-related disease in a mammal by administering to the animal a therapeutically effective dose of an antibody or antigen binding fragment thereof. In another embodiment, the antibodies or antigen binding fragments thereof can be used in a method for treating a mammal suffering from a disease selected from: neoplastic or non-neoplastic disease, chronic viral infection, and a malignant tumour, wherein the method includes administering to the mammal a therapeutically effective dose of an antibody or antigen binding fragment thereof.

Still further embodiments include methods of treating a disease of immunological dysfunction in a mammal by administering to the animal a therapeutically effective dose of an antibody or antigen binding fragment thereof as described herein. Exemplary immunological dysfunction in humans includes diseases of neurological deficit, such as Alzheimer's disease.

It has further been proposed that an immune response, particularly an IFNγ-dependent systemic immune response, could be beneficial for treatment of Alzheimer's disease and other CNS pathologies that share a neuroinflammatory component. WO2015/136541 (incorporated herein by reference) proposes treatment of Alzheimer's disease using an anti-PD-1 antibody (also see Baruch K. ., PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease, Nature Medicine, 2016, 22(2):137-137).

Thus, in one embodiment, the antibody or antigen binding fragment thereof specifically binds PD-L1 and reduces the level of systemic immunosuppression in an individual by release of a restraint imposed on the immune system by PD-1/PD-L1 immune checkpoint pathway. In an aspect, PD-1/PD-

L1 inhibitory immune checkpoint pathway blockade results in transient relief the systemic adaptive immune activity from suppression, which results in a transiently augmented immune response in the periphery, mainly manifested by elevation of IFN- - -producing cells. Increased IFN- may enable the brain's choroid plexus to allow selective leukocyte trafficking and infiltration of T-cells and monocytes into the damaged CNS, homing of these immune cells to sites of neurodegenerative pathology and neuroinflammation, and may modulate the environment to become less toxic and more permissive for clearance of toxic agents, rescue of neurons, regeneration and repair.

Thus, the PD-L1 mediated disease or condition is a neurodegenerative disease, disorder or condition. In one embodiment, the neurodegenerative disease, disorder or condition is Alzheimer's disease. In another embodiment, the neurodegenerative disease, disorder or condition is selected from amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, corticobasal degeneration, Rett syndrome, a retinal degeneration disorder selected from age-related macular degeneration and retinitis pigmentosa; anterior ischemic optic neuropathy, glaucoma, uveitis, depression, trauma-associated stress or post-traumatic stress disorder, frontotemporal dementia, Lewy body dementias, mild cognitive impairments, posterior cortical atrophy, primary progressive aphasia and progressive supranuclear palsy or aged-related dementia. In another embodiment, the neurodegenerative disease, disorder or condition is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease.

Anti-PD-L1 antibodies as described herein may be used in the treatment of Alzheimer's disease or other neurodegenerative diseases, optionally in combination with one or more other immune checkpoint inhibitors (such as anti-TIM-3 antibodies, anti-CTLA-4 antibodies, anti-TIGIT antibodies and anti-LAG-3 antibodies) or one or more other immune stimulators (such as anti-OX40 antibodies, anti-GITR antibodies, anti-CD137 antibodies, anti-ICOS antibodies and anti-CD40 antibodies, including those which are specifically described in Aspect 1a herein). Other combination partners include any of the the active agents as listed in claim 10 of WO2015/136541, which is incorporated herein by reference.

Any of the PD-L1 antibodies described herein (including at least the antibodies described in any of concepts 1 to 40, and the PD-L1 antibodies described in aspect 1a) may be used for the treatment of the neurodegenerative diseases, disorders or conditions described above.

Exemplary cancers in humans include a Merkel cell carcinoma, breast cancer, prostate cancer, basal cell carcinoma, biliary tract cancer, bladder cancer, bone cancer, brain and CNS cancer (e.g. gliomblastoma), cervical cancer, choriocarcinoma, colon and rectum cancer, connective tissue cancer, cancer of the digestive system; endometrial cancer, esophageal cancer; eye cancer; cancer of the head and neck; nasopharyngeal cancer; gastric cancer; intra-epithelial neoplasm; kidney cancer; larynx cancer; leukemia; liver cancer; lung cancer (e.g. small cell and non-small cell); lymphoma

including Hodgkin's and Non-Hodgkin's lymphoma including but not limited to DLBCL; Chronic lymphocytic leukaemia, melanoma; uveal melanoma, myeloma, neuroblastoma, oral cavity cancer (e.g., lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer, retinoblastoma; rhabdomyosarcoma; rectal cancer, renal cancer (renal cell carcinoma (RCC)), cancer of the respiratory system; sarcoma, skin cancer; stomach cancer, testicular cancer, thyroid cancer; uterine cancer, cancer of the urinary system, as well as other carcinomas and sarcomas. Further examples of virally induced cancers including; Nasopharyngeal carcinoma, certain Types of NHL (for example but not limited to EBV+ CNS lymphomas, DLBCL and BL, Hodgkins lymphoma (thought to be EBV driven) HPV-related cervical and head and neck squamous cell carcinomas); HBV hepatocellular carcinoma.

Exemplary chronic infections in humans include HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV).

Proliferative or invasion-related diseases that can be treated with the antibodies or antigen binding fragments described herein include neoplastic diseases, and the metastasis associated with such neoplastic disease, such as, melanoma, uveal melanoma, skin cancer, small cell lung cancer, non-small cell lung cancer, salivary gland, glioma, hepatocellular (liver) carcinoma, gallbladder cancer, thyroid tumour, bone cancer, gastric (stomach) cancer, prostate cancer, breast cancer (including triple negative breast cancer), ovarian cancer, cervical cancer, uterine cancer, vulval cancer, endometrial cancer, testicular cancer, bladder cancer, lung cancer, glioblastoma, thyroid cancer, endometrial cancer, kidney cancer, colon cancer, colorectal cancer, pancreatic cancer, esophageal carcinoma, brain/CNS cancers, neuronal cancers, head and neck cancers (including but not limited to squamous cell carcinoma of the head and neck (SCCHN)), mesothelioma, sarcomas, biliary (cholangiocarcinoma), small bowel adenocarcinoma, pediatric malignancies, epidermoid carcinoma, sarcomas, cancer of the pleural/peritoneal membranes and leukaemia, including acute myeloid leukaemia, acute lymphoblastic leukaemia, and multiple myeloma. Treatable chronic viral infections include HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) in humans, simian immunodeficiency virus (SIV) in monkeys, and lymphocytic choriomeningitis virus (LCMV) in mice.

The antibody or antigen binding fragment thereof can be administered alone, or in combination with other antibodies or chemo therapeutic drugs, radiation therapy or therapeutic vaccines. In one embodiment, the antibody or antigen binding fragment thereof is administered as an antibody-drug conjugate in which the antibody or antigen binding fragment thereof is linked to a drug moiety such as a cytotoxic or cytostatic agent. The use of antibody-drug conjugates for the local delivery of cytotoxic or cytostatic agents in the treatment of cancer allows targeted delivery of the drug moiety to tumours, and intracellular accumulation therein, where systemic administration of unconjugated drug may result in unacceptable levels of toxicity. Drugs in antibody drug conjugates can include, but are not limited to, daunomycin, doxorubicin, methotrexate, and vindesine. Toxins can also be used in antibody-toxin conjugates, including, for example, bacterial toxins such as diphtheria toxin, plant toxins such as ricin, small molecule toxins such as geldanamycin. The toxins may effect

their cytotoxic and cytostatic effects by mechanisms including tubulin binding, DNA binding, or topoisomerase.

Detection

In another embodiment, the antibodies or antigen binding fragments can be used to detect the presence, absence and/or level of surface expressed PD-L1 expression in a sample. PD-L1 surface expression can be detected in vivo and/or in vitro and is useful in helping diagnose diseases or conditions that involve expression and/or overexpression of PD-L1.

In another embodiment, the PD-L1 specific antibodies or antigen binding fragments thereof can be used for the assessment of expression and localization of PD-L1 in a biological sample from a patient. In one embodiment, the biological sample is a tissue sample and PD-L1 expression is detected using known methods such as FLOW cytometry, IHC in fresh tissue, IHC in FFPE tissue and/or IHC in frozen tissue. In other embodiments, the biological sample is blood, plasma or serum.

In one embodiment, the antibody or antibody fragment described herein is labeled with a detectable moiety, for example, a radiolabel, fluorescent label, enzymatic label chemiluminescent labeled or a biotinyl group. Radioisotopes or radionuclides may include ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{115}In, ^{125}I, ^{131}I, fluorescent labels may include rhodamine, lanthanide phosphors or FITC and enzymatic labels may include horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase. Additional labels include, by way of illustration and not limitation: enzymes, such as glucose-6-phosphate dehydrogenase ("G6PDH"), alpha-D- galactosidase, glucose oxydase, glucose amylase, carbonic anhydrase, acetylcholinesterase, lysozyme, malate dehydrogenase and peroxidase; dyes; additional fluorescent labels or fluorescers include, such as fluorescein and its derivatives, fluorochrome, GFP (GFP for "Green Fluorescent Protein"), dansyl, umbelliferone, phycoerythrin, phycocyanin, allophycocyanin, o- phthaldehyde, and fiuorescamine; fluorophores such as lanthanide cryptates and chelates e.g. Europium etc (Perkin Elmer and Cisbio Assays); chemoluminescent labels or chemiluminescers, such as isoluminol, luminol and the dioxetanes; sensitisers; coenzymes; enzyme substrates; particles, such as latex or carbon particles; metal sol; crystallite; liposomes; cells, etc., which may be further labelled with a dye, catalyst or other detectable group; molecules such as biotin, digoxygenin or 5-bromodeoxyuridine; toxin moieties, such as for example a toxin moiety selected from a group of Pseudomonas exotoxin (PE or a cytotoxic fragment or mutant thereof), Diptheria toxin or a cytotoxic fragment or mutant thereof, a botulinum toxin A, B, C, D, E or F, ricin or a cytotoxic fragment thereof e.g. ricin A, abrin or a cytotoxic fragment thereof, saporin or a cytotoxic fragment thereof, pokeweed antiviral toxin or a cytotoxic fragment thereof and bryodin 1 or a cytotoxic fragment thereof.

In one embodiment, the antibody or antigen binding fragment thereof can be administered to a patient, wherein the antibody or antigen binding fragment is conjugated to a label. The presence of

the label in the patient can be measured or observed, wherein a relatively high amount of the label may indicate a high risk of disease and a relatively low amount of the label may indicate a relatively low risk of the disease. In one embodiment, the label is a contrast agent, isotopic tag, or fluorescent marker, such as green fluorescent protein.

In one embodiment, the antibody or antigen binding fragment is used to monitor therapy that involves the use of other therapeutic agents, including, for example, chemotherapeutic agents or other antibodies that specifically bind PD-L1. In one embodiment, the antibody does not compete with the therapeutic PD-L1 antibodies.

Guide patient selection

In one embodiment, detection of PD-L1 expression can be used to guide patient selection. In one embodiment, the antibodies or antigen binding fragments thereof can be used to assist in patient selection for therapeutic antibody treatment with an anti-PD-L1 antibody, including, but not limited to anti-PD-L1 antibodies disclosed in WO2011/066389, entitled "Targeted Binding Agents Against B7-H1", which antibodies and sequences are incorporated herein by reference. In another embodiment, the antibodies or antigen binding fragments thereof can be used to assist in patient selection for treatment with immunotherapies such as anti-PD-L1, anti-CTLA4, anti-OX40, anti-PD-1, vaccines etc. In some cases, higher levels of PD-L1 may be indicative of successful therapy, whereas lower levels may indicate a reduced likelihood of success. Preferential expression of splice variants and/or protein processing may produce unique protein mixture profiles which may impact a patient's response to treatment or may change following treatment. These profiles may help to identify patients and define patient subsets who should receive treatment, continue to receive treatment or who should receive an alternative treatment. In another embodiment, the antibodies or antigen binding fragments thereof can be used for detection of PD-L1 isoforms. Patient samples can include, for example, blood, plasma, serum, sputum, saliva, urine, CSF, tears, exhaled exogenous particle samples, cell supernatant, cell or tissue lysate or tissue samples.

In one embodiment, the antibodies or antigen binding fragments thereof can be used to identify the presence, absence and/or level of PD-L1 expression at baseline, i.e., before treatment.

In another embodiment, the PD-L1 specific antibodies or antigen binding fragments thereof can be used as an exclusion marker to suggest treatment with therapies that do not target PD-L1. In another embodiment, the PD-L1 specific antibodies or antigen binding fragments thereof can be used as a prognostic marker for life expectancy. In particular, PD-L1 expression on tumours is linked to poor prognosis and life expectancy can be estimated based on historical data within tumour types.

Methods for detection of proteins are known, and include, for example, IHC, FLOW cytometery, Western blotting and Mass Spectroscopy, Immunoprecipitation, aptamers, immuno- PCR, and protein array.

Guide therapy

The antibodies can be used to guide therapy. For example, the antibodies or antigen binding fragments thereof can be used to identify the presence, absence and/or level of PD-L1 expression during or after treatment. In one embodiment, the antibodies or antigen binding fragments thereof can be used as early response biomarkers to assist in patient management, drug approval and reimbursement. In another embodiment, the antibodies or antigen binding fragments thereof can be used to identify the presence, absence and/or level of PD-L1 expression to help guide therapy. For example, PD-L1 expression can help determine whether the treatment is effective, and hence, whether or not treatment should be continued, or whether the dose should be adjusted (increased or decreased) and whether a combination regimen should be changed. For example, in one embodiment, the PD-L1 specific antibodies or antigen binding fragments thereof can be used for determining receptor occupancy of PD-L1 on cells in a patient treated with anti- PD-L1 therapy for dose setting (PK/PD). In particular, receptor occupancy can be used as a measure of target engagement or target coverage. Estimates of the amount or duration of target engagement needed to elicit a biological or clinical response could be used to determine if a patient has been dosed sufficiently or not. In particular, the antibodies can be used to assist in evaluating the relationship between, dose, exposure, receptor occupancy, pharmacodynamic response and clinical benefit.

Monitor efficacy of therapy

In another embodiment, the PD-L1 specific antibodies or antigen binding fragments thereof can be used for patient monitoring, to help evaluate whether a course of treatment is effective and whether or not treatment should be continued. For example, in one embodiment, the antibodies or antigen binding fragments thereof can be used detect expression before a patient receives therapeutic treatment that targets PD-L1. In another embodiment, the antibodies or antigen binding fragments thereof can be used to detect expression during therapy or after a patient has received therapeutic anti-PD-L1 treatment. In another embodiment, the antibodies or antigen binding fragments thereof can be used as an early response marker to assist in the determination as to whether or not a course of therapy is effective and should be continued or discontinued. In one embodiment, the expression of PD-L1 is detected after washout, wherein the term "washout" refers to a period of time after which the administered drug has been eliminated from the body. In particular, expression of PD-L1 may be detected after washout if the patient is treated with anti-PD-L1 therapy that competes with the detection antibody. However, if the patient is treated with an antibody that does not compete with an anti-PD-L1 antibody, such as anti-CTLA-4 or anti-PD-1, detection can be performed without waiting for washout. In another embodiment, the detection antibody can bind to PD-L1 but not compete with a therapeutic antibody that binds to PD-L1. In this situation, washout may not be necessary. The washout period can vary depending upon many factors, but is generally a period of at least about 1, 2, 3, 4, 5, or 6 weeks and up to about 1, 2, 3, 4, 5 or 6 months from the most recent chemotherapy or immunotherapy treatment. The antibodies or antigen binding fragments thereof can be used to determine expression of PD-L1 on biopsy samples or on circulating tumour cells (CTC).

In one embodiment, labelled antibodies or antigen binding fragments thereof can be used to identify a peripheral correlate to enable non-invasive assessment of tumour status pre, during and post treatment.

Methods for detection of proteins are known, and include, for example, IHC, flow cytometery, Western blotting and Mass Spectroscopy, immunoprecipitation, aptamers, immuno- PCR., and protein array.

Identify protein binding partners for PD-L1

In another embodiment, antibodies or antigen binding fragments thereof can be used as a capture reagent or detection reagent for examination of the protein binding partners of PD-L1 protein species in the context of a protein "pull-down." A protein "pull down" refers to immunoprecipitation of intact protein complexes, such as antigen along with any proteins or ligands that are bound to it - also known as co-immunoprecipitation (Co-IP). Co-IP works by selecting an antibody that targets a known protein that is believed to be a member of a larger complex of proteins. By targeting the known member with an antibody it may become possible to pull the entire protein complex out of solution and thereby identify unknown members of the complex. Complete understanding of the regulation of immune recognition through and PD-1 axis vs. CTLA-4 etc. is not fully understood. As such, antibodies and antigen binding fragments could improve knowledge of the interplay among accessory proteins and factors, which may determine a patient's propensity to respond to specific therapies or immunotherapy in general.

7. Pharmaceutical compositions

Unless otherwise apparent from the context, the compositions for antibodies or fragments applies to the immunocytokines and multispecific (e.g. bispecific or dual-binding antibodies) of the invention.

In one embodiment, there is provided a pharmaceutical composition comprising an effective amount of an antibody or antigen binding fragment and a pharmaceutically acceptable carrier. An effective amount of antibody to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. In one embodiment, the composition includes other excipients or stabilizers.

Pharmaceutically acceptable carriers are known and include carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as Ethylenediaminetetraacetic acid (EDTA); sugar alcohols such as mannitol or

sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

The antibodies or antigen binding fragments can be administered intravenously or through the nose, lung, for example, as a liquid or powder aerosol (lyophilized). The composition can also be administered parenterally or subcutaneously. When administered systemically, the composition should be sterile, pyrogen-free and in a physiologically acceptable solution having due regard for pH, isotonicity and stability. These conditions are known to those skilled in the art.

Methods of administering a prophylactic or therapeutic agent (e.g., an antibody as disclosed herein), or pharmaceutical composition include, but are not limited to, parenteral administration (e.g., intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (e.g., intranasal and oral routes). In a specific embodiment, a prophylactic or therapeutic agent (e.g., an antibody as disclosed herein), or a pharmaceutical composition is administered intranasally, intramuscularly, intravenously, or subcutaneously. The prophylactic or therapeutic agents, or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, intranasal mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. Each dose may or may not be administered by an identical route of administration. In one embodiment, an anti-PD-L1 antibody or fragment as disclosed herein may be administered multiple routes of administration simultaneously or subsequently to other doses of the same or a different anti-PD-L1 antibody or fragment as disclosed herein.

Various delivery systems are known and can be used to administer a prophylactic or therapeutic agent (e.g., an antibody or fragment as disclosed herein), including, but not limited to, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. In addition, pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, e.g., U.S. Pat. Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO92/19244, WO97/32572, WO97/44013, WO98/31346, and WO99/66903, each of which is incorporated herein by reference their entirety.

In a specific embodiment, it may be desirable to administer a prophylactic or therapeutic agent, or a pharmaceutical composition as described herein locally to the area in need of treatment. This may be achieved by, for example, local infusion, by topical administration (e.g., by intranasal spray), by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibres. When administering an anti-PD-L1 antibody or fragment, care must be taken to use materials to which the antibody does not absorb.

8. Kits and articles of manufacture

Unless otherwise apparent from the context, the kits and articles of manufacture for antibodies or fragments applies to the immunocytokines and multispecific (e.g. bispecific or dual-binding antibodies) of the invention.

In one embodiment, the invention provides a kit for detecting PD-L1 in a biological sample. The kit can be used to screen for PD-L1 related diseases. In one embodiment, the kit includes an antibody or antigen binding fragment and a means for determining whether the antibody or antigen binding fragment is bound to PD-L1 in a sample. In one embodiment, the antibody or antigen binding fragment is labelled. In another embodiment, the antibody or antigen binding fragment is an unlabelled primary antibody and the kit includes means for detecting the primary antibody. In one embodiment, the means for detecting includes a labelled secondary antibody that is an anti-immmunoglobulin antibody. The antibody may be labelled with any suitable marker, including, for example, a fluorochrome, an enzyme, a radionuclide and a radiopaque material. Suitable antibodies and antigen binding fragments are described in detail above.

In one embodiment, a kit for detecting PD-L1 is provided, wherein the kit includes an antibody or antigen binding fragment described herein. In one embodiment, the kit may also include instructions and one or more reagents for detecting PD-L1. In one embodiment, the kit includes an antigen or antigen binding fragment described herein, along with instructions for preparing a formalin-fixed paraffin-embedded (FFPE) tissue sample for IHC and/or one or more reagents for IHC. In one embodiment, the kit includes an antigen or antigen binding fragment described herein as a primary antibody and a secondary antibody that specifically binds thereto. In one embodiment, the kit includes a labeled antigen or antigen binding fragment described herein, wherein the label includes a fluorescent label such as fluoroscein or rhodamine or an enzymatic reporter such as horseradish peroxidase (HRP) or alkaline phosphatase (AP). In one embodiment, the kit includes a blocking reagent that includes at least about 1% and up to about 5%, or between about 2% and 3%, or about 2% cold water fish skin gelatin protein (CWF) in a buffer, such as phosphate buffered saline (PBS). In one embodiment, the kit includes buffer for antigen retrieval, such as a citrate buffer, for example sodium citrate, at a concentration of at least about 1, 2, 5, or 10 mM and up to about 10, 15 or 20 mM and at a pH between about 5.5 and 9, or a pH of about 6.

In another embodiment, a kit for treating diseases involving the expression of PD-L1 is provided, wherein the kit includes an antibody or antigen binding fragment described herein and instructions to administer the antibody or antigen binding fragment to a subject in need of treatment. There is also provided a pharmaceutical or diagnostic pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions as disclosed herein, such as one or more anti-PD-L1 antibodies or fragments provided herein. Optionally associated with such container(s) can 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, e.g., an authorisation number.

In another embodiment, an article of manufacture that includes a container in which a composition containing an antibody or antigen binding fragment described herein and a package insert or label indicating that the composition can be used to treat diseases characterized by the expression or overexpression of PD-L1 is provided. In one embodiment, there is provided a kit for treating and/or preventing a PD-L1-mediated condition or disease, the kit comprising an antibody or fragment as disclosed herein in any embodiment or combination of embodiments (and optionally a further therapeutic agent as described elsewhere herein) optionally in combination with a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the antibody or fragment. In another embodiment, the kit comprises an antibody or antigen binding fragment thereof contained within a container or an IV bag. In another embodiment, the container or IV bag is a sterile container or a sterile IV bag. In another embodiment, the antibody or antigen binding fragment therefore is formulated into a pharmaceutical composition contained within a (sterile) container or contained within a (sterile) IV bag. In a further embodiment, the kit further comprises instructions for use.

9. Examples

Example 1 - Antigen Preparation, Immunization Procedures, and Hybridoma Generation

The following example provides a detailed description of the generation and identification of a panel of anti-human PD-L1 monoclonal antibodies using the KyMouse™ system (see, e.g., WO2011/004192, WO2011/158009 and WO2013/061098). To this end, genetically engineered mice containing a large number of human immunoglobulin genes were immunized with soluble recombinant human PD-L1 or surface expressed human PD-L1 displayed on mouse embryonic fibroblast (MEF) cells. Various immunization regimens, including conventional intraperitoneal injections as well as a rapid immunisation at multiple sites (RIMMS) regimen were set up, boosting animals over several weeks (see detailed methods below). At the end of each regimen, secondary lymphoid tissue such as the spleen, and in some cases, the lymph nodes were removed. Tissues were prepared into a single cell suspension and fused with SP2/0 cells to generate a stable hybridoma cell line.

Materials and Methods

a) Generation of stably transfected MEF and CHO-S cells expressing human PD-L1:

Full length human PD-L1 sequence (SEQ ID No:1 also known as B7-H1) was codon optimized for mammalian expression and cloned into an expression vector under the CMV promoter flanked by 3′ and 5′ specific terminal repeat sequences, facilitating stable integration into the cell genome (see: "A hyperactive transposase for mammalian applications"; Yusa K., , Proc. Natl. Acad. Sci. U S A., 108(4): 1531-6, 2011 Jan 25). Furthermore, the expression vector contained

a puromycin selection cassette to facilitate stable cell line generation. The human PD-L1 expression plasmid was co-transfected with a plasmid encoding transposase into an in-house derived mouse embryonic fibroblast (MEF) cell line (embryos used to generate this line were obtained from a 129S5 crossed to C57/BL6 female mouse) and CHO-S cells using the FreeStyle Max transfection reagent (Invitrogen) according to manufacturer instructions. 24 hours after transfection, the media was supplemented with puromycin and grown for at least two weeks to select a stable cell line with complete medium being exchanged every 3 to 4 days. The expression of hPD-L1 was assessed by flow cytometry using an anti-human PD-L1–PE conjugated antibody (eBioscience). Complete MEF media was made up of Dulbecco's Modified Eagle's Medium (Gibco) supplemented with 10% v/v fetal bovine serum (Gibco). Complete CHO-S media was made up of CD-CHO media (Gibco) supplemented with 8 mM Glutamax (Gibco). Transfected CHO cells were used for screening purposes (see Example 2).

b) Preparation of MEF cells for mouse immunizations:

Cell culture medium was removed and cells washed once with 1× PBS. Cells were treated for 5 minutes with trypsin to loosen cells from tissue culture surface. Cells were collected and trypsin neutralized by the addition of complete MEF media. Cells were then centrifuged at 300 for 10 minutes and washed with 25 mL of 1× PBS. Cells were counted and resuspended at the appropriate concentration in 1× PBS.

c) Immunisations with PD-L1

Genetically engineered Kymouse™ HK strain, containing human immunoglobulin genes producing human kappa (HK) light chain antibodies (Lee , Nature Biotechnology, 32, 6-363, 2014) were immunized by various immunisation regimens for the generation of human anti-PD-L1 antibodies.

Mice were immunised either with soluble recombinant hPD-L1 (R&D Systems, 156-B7, Fc chimera) using a modified sub-cutaneous immunisation procedure (RIMMS; modified after Kilpatrick , "Rapid development of affinity matured monoclonal antibodies using RIMMS"; Hybridoma. 1997 Aug;16(4):381-9, hereafter referred to as KM031), or by using soluble recombinant hPD-L1 in a prime-rest-boost regime by sub-cutaneous administration (hereafter referred to as KM032) or by combination of soluble recombinant hPD-L1 and stably transfected MEF cells expressing hPD-L1 administered intra-peritoneally (hereafter referred to as KM033). Sigma Adjuvant System was used for all immunisations and rest intervals were usually between 2 and 3 weeks. Where protein was used as the immunogen, CpG (Hokkaido System Science) was also administered. Serum from serial or terminal blood samples were analysed for the presence of specific antibodies by ELISA and flow cytometry and the titre data was used (where possible) to select mice to be used for hybridoma fusions. A further regimen, KM042 immunising with MEF-PD-L1 cells alone, or protein alone in a prime-rest-boost setting, was also performed, but out of six antibodies confirmed to bind to hPD-L1, no neutralising antibodies were identified.

d) Cloning and expression of recombinant proteins

DNA sequences encoding PD-L1 were purchased as synthetic DNA strings and cloned into appropriate mammalian expression vectors for transient expression in Expi293 and CHO cells. The sequence listing shows the sequences of the antigens, where available, and affinity tags for purification/labelling (shown in bold and underlined), see Seq ID Nos:3 to 6.

e) Determining serum titre by reverse PD-L1 ELISA Protocol

Titres in mouse serum samples were determined using a reverse PD-L1 ELISA protocol. Anti-mouse IgG capture ant diluted in PBS, 50 /well) was adsorbed to 96 well low auto-fluorescent, high protein binding plates (Costar) overnight at 4 °C. Excess IgG was removed by washing three times with PBS-Tween (0.1% v/v) and the wells were blocked with 1% w/v bovine serum albumin (BSA, Sigma) in PBS for 1 hour at room temperature, after which plates were washed three times with PBS-Tween (0.1% v/v). Serial ten-fold dilutions of mouse serum were prepared, diluting samples in reagent diluent (0.1% w/v BSA/PBS). /well of this titration was then added to ELISA plates. To determine the change in activity level due to immunization, serum from each animal prior to immunization was diluted to 1/100 in reagent diluent and 50 µL/well added to the ELISA plate. Following incubation, plates were washed as before to remove unbound proteins. Biotinylated hPD-L1-his (in-house generated protein, Seq ID No: 3, labelled in-house using Sulfo-NHS-LC-Biotin (Thermo)), used at 100 ng/m /well) was then added to the plates and incubated at room temperature for 1 hour. Unbound biotinylated hPD-L1 was removed by washing with PBS-Tween (0.1% v/v), while the remaining biotinylated hPD-L1 was detected by addition of streptavidin-HRP (Sigma) diluted 1/10,000 in reagent diluent. Following incubation for 1 hour at room temperature, plates were washed as described before and 50 TMB (Sigma) was added to the plate. The reaction was stopped by adding 50 1M sulphuric acid (Fluka Analytical). The OD at 450 nm was measured on an Envision plate reader (PerkinElmer). Titres were not performed for KM032 as only one mouse was immunised. For KM031, titres were performed on terminal bleeds only.

f) Determination of serum titres by flow cytometry using CHO-S expressed hPD-L1

CHO-S cells expressing hPD-L1, suspended in FACS buffer (PBS + 1% w/v BSA + 0.1% w/v sodium azide) were distributed to a 96-well, V-bottom plate (Greiner) at a density of 10^5 cells per well. A titration of mouse serum was prepared, diluting samples in FACS buffer. 25 /well of this titration was then added to the cell plate. To determine the change in activity level due to immunization, serum from each animal prior to immunization was diluted to 1/100 in FACS buffer and 25 µL/well added to the cells. Cells were incubated at 4 °C for 1 hour. Cells were washed twice with 150 µL PBS, centrifuging after each wash step and aspirating supernatant (centrifuged at 300 × for 3 minutes). To detect antibody binding, PE goat-anti-mouse IgG (Jackson ImmunoResearch) was diluted 1/500 in FACS buffer and 50 µL was added to the cells. Cells were incubated 1 hour at 4 °C in the dark, then washed twice with 150 µL PBS as above. To fix cells, 100 µL 2% v/v paraformaldehyde was added and cells incubated for 30 minutes at 4 °C. Cells were then pelleted by centrifugation at 300 × and

the plates resuspended in 100 µL of FACS buffer. PE signal intensity (geometric mean) was measured by flow cytometry using a BD FACS Array instrument. Titres were performed by this method for KM033 only.

g) Murine tissue isolation and preparation

Following final boost, mice were culled and spleens were excised from immunized mice, washed in 1× PBS and kept on ice until further processing. Tissues were prepared in buffer containing 1× PBS (Invitrogen) and 3% heat-inactivated FBS (Invitrogen). Splenocytes were dispersed by mashing the tissue through a 45 µm strainer (BD Falcon) and rinsing with 30 mL 3% FBS/PBS buffer before centrifugation at 700 g for 10 minutes at 4 °C. To remove red blood cells, the pelleted splenocytes were resuspended in 4 mL Red Blood Cell Lysis Buffer (Sigma). After 4 minutes of incubation, the lysis reaction was stopped by addition of 3% FBS/1× PBS buffer. Cell clumps were filtered out with a 45 µm strainer. The remaining splenocytes were pelleted for further procedures. For KM031 and KM032, axillary, inguinal and mesenteric lymph nodes were also removed and placed in sterile 1× PBS on ice until further processing. The lymph nodes were processed separately from splenocytes. Lymph node cells were prepared as above, but did not undergo red blood cell lysis. The remaining lymph node cells were pelleted for further procedures.

h) Hybridoma Fusion

Spleen and lymph node cells were pooled from KM031 and also from KM032 and subjected to a negative selection method using the MACS® Separation system. Briefly, where lymph nodes were used those cells were pooled with the splenocytes from the corresponding mice after red blood cell lysis and total cell number determined. Cells were resuspended in 100 µL 3% FBS/PBS buffer per 10^7 cells, before adding 10 -Antibody Cocktail (Cat# 130-095-813) per 10^7 total cells and 10 µL of anti-IgD-Biotin antibody (Cat# 130-096-979) and incubated for 10 minutes at 4 °C. 2 mL FBS/PBS buffer was added and the cells were spun down at 700 g for 10 minutes. The supernatant was aspirated completely and 100 uL fresh buffer was added, then 30 uL Anti-Biotin MicroBeads (Cat# 130-047-302) was added per 10^7 cells along with 7 µL Anti-Mouse IgM MicroBeads (Miltenyi Biotec). The cells were incubated for 15 minutes in the refrigerator. The cells/MicroBeads mixture was then applied to a pre-wetted LD column (Miltenyi Biotec) placed in a magnetic MACS Separator and washed with 3% FBS/PBS buffer. The unlabelled cells that flowed through the column were collected in 3% FBS/PBS buffer.

KM033 cells were subjected to a positive selection method using the MACS® Separation system. After red blood cell lysis, splenocytes were resuspended in 80 µL 3% FBS/PBS buffer per 10^7 cells, before adding anti-mouse IgG1 (Cat# 130-047-101) plus anti-mouse IgG2a+b MicroBeads (Cat# 130-047-201) and incubated for 15 minutes at 4 °C. The cell/MicroBead mixture was then applied to a pre-wetted LS column (Miltenyi Biotec) placed in a magnetic MACS Separator and washed with 3% FBS/PBS buffer. IgG positive cells were collected in the labelled, column-bound fraction in 3% FBS/PBS buffer.

Enriched B-cells were treated with CpG (Hokkaido System Science) overnight (final concentration 25 µM) and the following day washed once in BSA fusion buffer (0.3 M D-Sorbitol, 0.11 mM calcium acetate hydrate, 0.5 mM magnesium acetate tetrahydrate and 0.1% BSA (v/w), adjusted to pH 7.2). Washed cells were resuspended in 200 µL BSA fusion buffer and cell count determined. SP2/0 cells were treated in the same way, but washed twice instead of once with BSA fusion buffer. B-cells fused at a ratio of 3:1 with SP2/0 myeloma cells by electrofusion using a BTX ECM 2001 Electro Cell Manipulator (Harvard Apparatus). Each fusion was left overnight in recovery medium (Dulbecco's Modified Eagle's Medium (high glucose, no phenol red) supplemented with OPI (Sigma), 1× L-Glutamax (Gibco), 20% FBS (Gibco, batch-tested for hybridoma) and 0.05 mM 2-mercaptoethanol), then resuspended in 1 part recovery medium and 9 parts semi-solid medium (ClonaCell-HY Hybridoma Selection Medium D, Stemcell Technologies) and seeded onto 10 cm petri dishes. Visible colonies were picked 12 days later into 96-well plates and cultured for another 2 to 3 days prior to screening.

Example 2 - Hybridoma supernatant screening

After generation of hybridoma clones, the hybridoma supernatant was assessed in a sequential primary and secondary screen and appropriate hybridoma clones selected based on criteria of antibody binding to human PD-L1 and receptor neutralization activity. In the screening cascades described,

9317 hybridoma clones were tested and 120 identified as primary hits. Thereafter, 36 hybridoma clones were confirmed by using secondary screening criteria (see details in Materials and Methods and Table 1). Among the clones identified by secondary screen, four clones were selected by the inventors to be part of the antibody shortlist, dependent upon desired selection criteria (see details in Example 3).

Materials and Methods

a) Primary screen - Binding to cell-expressed human PD-L1

Supernatants collected from hybridoma cells were screened for the ability of secreted antibodies to bind to hPD-L1 expressed on the surface of CHO-S cells. To determine CHO-S hPD-L1 binding, cells were plated in black-walled, clear-bottom tissue culture treated 384-well plates (Costar) at 1×10^4/well in 80 µL F12 media (Gibco) supplemented with 10% FBS (Gibco) and cultured overnight at 37 °C, 5 % CO_2. Culture media was removed from 384-well assay plates. At least 5 µL of hybridoma supernatant or 5 L MIH1 at 2 µg/mL in hybridoma maintaining media (HMM) or isotype IgG1 control antibody (referred to in some instances as Cm7, Sigma M9269, at a final concentration of 1 µg/mL) diluted in HMM were added to each well. HMM was made up of Advanced DMEM (Gibco) supplemented with 1× Glutamax (Gibco), 20% v/v FBS (Gibco), 0.05 mM β-Mercaptoethanol, 1× HT supplement (Gibco), and 1× penicillin/streptomycin (Gibco). 45 µL FACS buffer containing 500 ng/mL IRDye 800CW anti-Mouse Ab (LICOR) and 0.2 µM DRAQ5 (Biostatus) was added to each well. DRAQ5 was not added to background wells. Plates were incubated for 1 hour at 4 °C. Supernatant was aspirated and 25 µL 4% v/v paraformaldehyde added and plates were incubated for 15 minutes at room temperature. Plates were washed twice with 100 µL PBS and then the wash buffer was completely removed. Fluorescence intensity was read by scanning plates using an Odyssey Infrared Imaging System (LI-COR®). Anti-mouse binding (800 nm channel) was normalised to cell number (700 nm channel) according to the LI-COR® recommended algorithm. Percent effect was calculated as detailed below (Equation 1). Total binding was defined using reference antibody at a final assay concentration of 0.2 µg/mL. Non-specific binding was defined using mouse IgG1 isotype control (Sigma) at a final assay concentration of 0.2 µg/mL. Criteria for hit selection were based on assay signal and visual inspection of scanned plates.

Equation 1: Calculation of Percentage Effect from Primary Screen (LI-COR) and HTRF

Using 800% Resp values (LI-COR) or 665/620 nm ratio (see Equation 2) (HTRF)

$$\text{Percent effect} = \frac{(\text{sample well} - \text{non-specific binding})}{(\text{total binding} - \text{non-specific binding})} \times 100$$

Non-specific binding = values from wells containing isotype control mouse IgG1

Total Binding = values from wells containing reference antibody

b) Primary screen: Binding to recombinant human PD-L1

In parallel to screening for binding to CHO-S expressed PD-L1, supernatants collected from hybridoma wells were screened for the ability of secreted antibodies to bind to hPD-L1 expressed as a recombinant protein (produced in-house). Binding of secreted antibodies to recombinant PD-L1 were identified by HTRF® (Homogeneous Time-Resolved Fluorescence, Cisbio) assay format using biotinylated hPD-L1. 10 µL hybridoma supernatant was transferred to a white 384 well, low-volume, non-binding surface polystyrene plate (Greiner). 5 µL 230 nM biotinylated hPD-L1 his diluted in HTRF assay buffer (PBS (Sigma) + 0.53 M KF (Sigma) + 0.1% w/v BSA (Sigma)) was pre-incubated with 10 µL hybridoma supernatant or 10 µL reference antibody diluted to 3.3 nM working concentration for 1 hour at room temperature. For negative control wells, 10 µL HMM was added. Streptavidin D2 (Cisbio), and goat anti-mouse IgG (Southern Biotech) labelled with Europium cryptate (Cisbio) were both diluted 1/100 in HTRF assay buffer, and 5 L of this mixture added to all wells. The plate was left to incubate in the dark for 2 hours prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer). More details of the HTRF® assay technology can be found in Mathis (1995) Clinical Chemistry 41(9), 1391-1397.

Data were analysed by calculating 665/620 ratio and percent effect for each sample according to Equation 2 and Equation 1 respectively.

Equation 2: Calculation of 665/620 ratio

$$665/620 \text{ ratio} = (\text{sample } 665/620 \text{ nm value}) \times 10000$$

In general, criteria for hit selection were based on greater than or equal to 10 percent effect. In some instances, hit selection was based on greater than or equal to 20 percent effect.

Progression to secondary screen was based on a combination of data from recombinant PD-L1 binding hits and binding to human PD-L1 expressed on CHO cells.

c) Secondary screen: Binding to cell expressed recombinant human PD-L1 or natively expressed hPD-L1 and binding affinity

To determine whether wells selected using the primary screen selection criteria had the required characteristics set by the inventors, a number of assays were performed. Hybridoma clones selected as hits from primary screening were cultured for 3 days and the supernatants collected from hybridoma cells were tested to assess whether the secreted antibodies that bind to in some cases CHO-S expressed hPD-L1, or in some cases ES2 cells. In addition, the ability to neutralise recombinant hPD-1 Fc, binding to CHO-S hPD-L1 or ES2 cells was also assessed. Binding of antibodies to human PD-L1 by SPR was also tested.

d) Binding to cell expressed hPD-L1 and neutralisation and hPD-L1 binding to PD-1

Binding of hybridoma supernatants was tested for ability to bind to either CHO-S cells expressing hPD-L1 or ES2 cells. CHO-S cells expressing hPD-L1 (generated in-house), or ES2 cells (ATCC CRL-1978) natively expressing hPD-L1 were diluted in FACS buffer and were distributed to a

96-well, V-bottom plate (Greiner) at a density of 0.5 to 1×10^5 cells per well. Cells were washed with 150 µL PBS and centrifuged at 300 g for 3 minutes. Supernatant was aspirated and 150 µL PBS added. This wash step was repeated.

50 µL hybridoma supernatant or purified hybridoma material was added to the washed cells, to which 500 ng/mL human PD-1 Fc (in-house, Seq ID No:6) was added. Reference antibody was added to medium at 2 µg/mL. Where purified material was used, titrations were prepared from a top concentration of 600 nM before addition to cells. When supernatants were used, neat supernatant, and three serial two-fold dilutions were added to cells. Cells were incubated at 4 °C for 30 minutes. Cells were washed twice with 150 µL FACS buffer, centrifuging at 300 g for 3 minutes after each wash step and aspirating supernatant.

To detect antibody and receptor binding, 50 µL goat anti-human IgG-PE (Jackson ImmunoResearch) and APC anti-mouse IgG (Jackson ImmunoResearch) diluted 1/500 in FACS buffer was added to the cells. Cells were incubated for 30 minutes at 4 °C in the dark. Cells were washed twice as above and resuspended in FACS buffer for analysis. PE and APC signal intensity (geometric mean) was measured by flow cytometry using a BD FACS Array instrument. Data was plotted as geometric mean values without further calculation.

e) Determination of affinity by surface plasmon resonance

Label-free surface plasmon resonance (SPR) analysis was carried out on the ProteOn XPR36 (BioRad) array SPR machine. An anti-mouse IgG capture surface was created on a GLC biosensor chip using amine coupling of an anti-mouse IgG from GE Healthcare. Test antibodies were captured on this surface and human PD-L1 (in-house) was used as the analyte at 256 nM, 64 nM, 16 nM, 4 nM and 1 nM. The assay was carried out at 25 °C using HBS-EP (Teknova H8022). Buffer alone was used to reference the binding sensorgrams. The data was analysed using the 1:1 model inherent to the ProteOn XPR36 analysis software. In some instances, hybridoma supernatants were used as the source of antibody; in other instances, antibody was purified from hybridoma supernatant prior to analysis (see below). In some instances, a Protein A/G capture surface was used. This was created on a GLM biosensor chip using amine coupling of Protein A/G from Biorbyt.

f) Purification of antibodies from hybridoma supernatant

Protein G resin in a gravity-flow column was first washed with water, then 50 mM sodium hydroxide or IgG Elute (Pierce) and was then equilibrated with tissue culture grade PBS. Clarified hybridoma supernatant containing 10% v/v 10× tissue culture grade PBS was applied several times to the equilibrated protein G column. Resin was washed with tissue culture grade PBS to remove unbound material. Antibody was then eluted with IgG Elute (Pierce) and the eluted fraction was then neutralized with 100 mM final TRIS, at pH 8.0. The eluted fraction was then concentrated down to <1.5 mL by centrifugation in a 10 kDa cut-off centrifugal filter unit. Tissue culture grade PBS was then added and the sample was concentrated down again to <1.5 mL. Protein concentration was quantified

at OD_{280} using the molar extinction coefficient inherent to the Nanodrop for IgG. Finally, sample was analysed on a SDS-PAGE to assess purity.

Table 1 - Summary of hybridoma clone screening

Experiment ID	Number of hybridoma screened	Number of Primary hits cherry picked	Number of secondary hits confirmed	Number of Lead Candidate mAbs
KM031	1872	41	4	0
KM032	115	14	6	1
KM033	7330	66	26	1

Example 3 - Antibody shortlist selection criteria

Binding to hPD-L1 natively expressed on ES2 cells, and neutralisation of recombinant human PD-1 binding to ES2 cells were used as criteria for secondary screen hit selection. Hits to progress to purification and further characterisation were determined by a combination of high affinity for human PD-L1 and neutralisation capacity.

After the selection and characterization of shortlisted antibodies, their fully-human variable domains were recovered using RT-PCR using a mixture of forward and reverse primers. Antibodies were reformatted into a human IgG1 backbone and expressed using a transient expression system in CHO-S cells.

Materials and Methods

a) RNA isolation from hybridoma cells

Total RNA was extracted from hybridoma cells using TRIzol™ Reagent (Invitrogen). The quantity and quality of the isolated RNA was analysed spectrophotometrically.

b) Antibody variable domain recovery by RT-PCR

Selected clones were used to prepare total RNA, which was used in an RT-PCR reaction to recover the heavy and light chain V-regions. Murine IgG-specific reverse primers and human Ig-leader sequence-specific forward primer sets were used for the heavy chains. Murine kappa constant region specific reverse primers and human kappa-leader sequence specific forward primer sets were used for the kappa light chains. The RT-PCR products were separated by agarose gel electrophoresis with the DNA of the predicted size being gel purified and sequenced in the forward and reverse directions. Alternatively, the RT-PCR products were subcloned into a cloning vector and DNA of individual colonies submitted for sequencing.

Example 4 - Selection of final lead panel

Recombinantly expressed antibodies were analysed by SPR to confirm binding to cynomolgus monkey PD-L1, as well as human PD-L1. Antibodies were also tested in a dendritic cell-T-cell mixed lymphocyte reaction (MLR) for ability to enhance IFN production (Figure 1). Antibodies with

consistent immune-stimulatory effects in the MLR, and binding to both human and cynomolgus PD-L1 were selected as the final lead panel – these were designated as clone 84G09 and clone 1D05. Data in Figure 1 is from a single experiment. A further five experiments were conducted and showed similar results (84G09 showed activity in 3 out of 5 experiments, 1D05 showed activity in 3 out of 4 experiments, 1A01 showed activity is 1 out of 3 experiments and 8B09 showed activity in 0 out of 3 experiments). One further experiment failed (including positive control).

Materials and Methods

a) Surface plasmon resonance for analysis of antibodies with human constant region

Label-free surface plasmon resonance (SPR) analysis was carried out on the ProteOn XPR36 (BioRad) array SPR machine. An anti-human IgG capture surface was created on a GLC biosensor chip using a combination of anti-human Fc antibodies (Jackson Labs 09-005-008,109-006-008 and 309-006-008) by amine coupling. Test antibodies were captured on this surface and human PD-L1-his and cynomolgus monkey PD-L1-FLAG (in-house, Seq ID No: 5) was used as the analyte at 128 nM, 32 nM, 8 nM, 2 nM, 0.5 nM and 0 nM. The data was analysed using the 1:1 model inherent to the ProteOn XPR36 analysis software.

b) Dendritic cell – T-cell MLR (Mixed Lymphocyte Reaction)

Dendritic cells were generated from monocytic precursors. Monocytic precursors were isolated from peripheral blood mononuclear cells (PBMCs) isolated using Ficoll-Paque plus (GE Healthcare) density gradient centrifugation from leukoreduction system chambers (NHSBT). Monocytes were isolated from PBMCs using negative selection magnetic separation beads (Miltenyi Biotec). Monocytes were plated in 96-well, flat-bottom TC plates at 5×10^4/well and 1×10^4/well and cultured with cytokines GM-CSF and IL-4 (both Peprotech) at 100 ng/mL for 7 days in culture media (Advanced RPMI (Gibco) supplemented with 10% v/v FBS and 2 nM glutamine (culture medium).

After 7 days, T-cells were purified from allogeneic PBMC using negative selection magnetic separation beads (Miltenyi). After purification, the isolation buffer was removed by centrifugation and aspiration. The cells were resuspended at 1×10^6 cells/mL -cells were added to all wells with the exception of the DC-only wells. An additional 100 µL of culture medium was added to the DC-only and T-cell-only wells. Serial three-fold dilutions of antibodies were prepared in culture medium (top concentration 60 nM final). 10 µL of each dilution was added to cells.

The cells were incubated for five days at 37 °C. After this period IFN- was measured by Duoset ELISA (R&D Systems) according to manufacturer's instructions.

Example 5 - In depth characterisation of lead antibodies

Lead antibodies 84G09 and 1D05 were subjected to in-depth characterisation, including SPR at 37 °C, full titrations of antibodies in neutralisation assays, and confirmation of binding to PD-L1 but not PD-L2. Antibodies were also expressed with a human IgG4(PE) constant region (Seq ID No:199) for analysis by mixed lymphocyte reaction. Lead antibodies retain sub-nanomolar affinity at 37 °C, and

show potent neutralisation of PD-L1 binding to both PD-1 and CD80. Antibodies do not cross-react with PD-L2, bind natively expressed PD-L1 on dendritic cells, and are potent stimulators of IFN production in an MLR.

a) Human PD-L1/PD-1 neutralisation assay (ELISA)

PD-1 Fc (in house, Seq ID No:6) diluted to 1 µg/mL was adsorbed to 96-well, low auto-fluorescent, high protein binding plates (Costar) overnight at 4 °C. Excess protein was removed by washing with PBS-Tween (0.1% v/v) and the wells were blocked with 1% w/v bovine serum albumin (BSA, Sigma) in PBS for 1 hour at room temperature, after which plates were washed as described previously. 30 µL titration (1/3 dilution) of antibody was added to a 96-well non-binding plate diluted in ELISA assay buffer (PBS + 0.1% BSA). 30 µL biotinylated PD-L1 his (in-house, Seq ID No:3) at 50 nM working concentration (25 nM final assay concentration [FAC]) was added to the plate excluding control wells where 30 µL ELISA assay buffer was added. The plate was incubated for 30 minutes before transferring 50 µL to the coated plates. The coated plates were incubated for 1 hour at room temperature. Excess protein was removed by washing with PBS-Tween (0.1% v/v). PD-L1 binding was detected using streptavidin labelled Europium (Perkin Elmer) diluted 1/1000 in DELFIA assay buffer (Perkin Elmer). Plates were washed with TBS (Tris buffered saline)-Tween (0.1% v/v) and 50 µL/well of DELFIA Enhancement solution (Perkin Elmer) was added to the plate. Time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Percentage of specific binding was calculated using Equation 3. IC_{50} values were determined using GraphPad Prism software by curve fitting using a four-parameter logistic equation (Equation 4). Results are shown in Figure 2 and summarised in Table 2.

Equation 3: Percentage of receptor binding (ELISA)

Based on fluorescence at 615 nm

$$\% \text{ of specific binding} = \frac{\text{sample value - non-specific binding}}{\text{total binding - non-specific binding}} \times 100$$

Total binding = biotinylated PD-L1 (no antibody)

Non-specific binding = no biotinylated PD-L1

Equation 4: Four Parameter logistic calculation

$$Y=\text{Bottom} + (\text{Top-Bottom})/(1+10^{((\text{LogIC50-X})*\text{HillSlope})})$$

X = logarithm of concentration.

Y = specific binding (Equation 3)

Top and Bottom = Plateaus in same units as Y (specific binding)

Log IC_{50} in same units as X. Y starts at Bottom and goes to Top with a sigmoid shape. Specific binding decreases as X increases.

c) CHO human PD-L1/PD-1 or CD80 neutralisation assay (flow cytometry)

CHO-S cells untransfected (referred to as WT) or transfected with hPD-L1 were diluted in FACS buffer and were distributed to a 96-well V-bottom plate (Greiner) at a density of 1×10^5 cells per well in 50 µL. Biotinylated human PD-1-Fc (in-house expressed, Seq ID No:6) or CD80-Fc (R&D Systems) were prepared as a titration from 1 µM final assay concentration (FAC), 1/2 dilution series in FACS buffer. Antibody titrations were prepared from 300 nM working concentration, 150 nM FAC, as a 1/3 dilution series in FACS buffer. Biotinylated PD-1 or CD80 were diluted in FACS buffer to 60 nM working concentration, 30 nM FAC. Plates were centrifuged at 300 x for 3 minutes to supernatant aspirated. 25 µL ligand and 25 µL antibody solution (or 50 µL of ligand titration) were added to cells and incubated at 4 °C for 1 hour. Cells were washed with 150 µL of PBS and centrifuged at 300 g for 3 minutes. Supernatant was aspirated and 150 µL PBS added. This wash step was repeated. Presence of bound CD80 or PD-1 was detected by addition of 50 µL of streptavidin-AlexaFluor 647 (Jackson ImmunoResearch) diluted 1/500 in FACS buffer. Cells were incubated 30 minutes at 4 °C in the dark. Cells were washed as described above. To fix cells, 100 µL 2% v/v paraformaldehyde was added and cells incubated for 30 minutes at 4 °C, cells were pelleted by centrifugation at 300 x and the plates resuspended in 100 µL FACS buffer. AlexaFluor 647 signal intensity (geometric mean) was measured by flow cytometry using a BD FACS Array instrument. Results are shown in Figures 3 and 4 and summarised in Table 2.

Equation 5: Percentage of receptor binding (flow cytometry)

Based on geometric mean fluorescence

$$\% \text{ of specific binding} = \frac{\text{sample value - non-specific binding}}{\text{total binding - non-specific binding}} \times 100$$

Total binding = biotinylated PD-1 or CD80 only (no antibody)

Non-specific binding = no ligand streptavidin AlexaFluor 647 only

Table 2: Summary of lead antibody binding and neutralisation of PD-L1 binding to PD-1 or CD80

			Receptor Neutralisation (mean of n=3)		
Clone ID	**Human PD-L1 (nM at 37 °C)**	**Cyno PD-L1 (nM at 37 °C)**	**PD-L1/PD-1 neutralisation (FACS) IC_{50} (nM)**	**PD-L1/CD80 neutralisation (FACS) IC_{50} (nM)**	**PD-L1/PD-1 neutralisation (ELISA) IC_{50} (nM)**
1D05	0.42 K_{on} =1.85 µM K_{off} =0.779 mM	0.43 K_{on} = 1.89 µM K_{off} = 0.813 mM	2.21	1.18	5.21
84G09	0.43 K_{on} = 2.43 µM K_{off} = 1.05 mM	0.52 K_{on} =2.61 µM K_{off} = 1.35 mM	1.82	1.60	7.90
Benchmark	0.25	4.79	1.85	1.42	14.1

d) PD-L1/PD-L2 binding

PD-L1-Fc (R&D Systems) and PD-L2-Fc (R&D Systems) were diluted to 2 µg/mL and separately adsorbed to 96-well, high protein binding plates (Greiner) overnight at 4 °C, 50 µL/well. Excess protein was removed by washing with PBS-Tween (0.1% v/v) and the wells were blocked with 250 µL/well Pierce Protein Free Blocking Buffer (Thermo, 37572) for 1 hour, after which plates were washed as described previously. Biotinylated anti-PD-L1 antibodies (in-house) or anti-PD-L2 control antibody (R&D Systems) were diluted in blocking buffer and three-fold serial dilutions performed from 10 µg/mL. 100 µL each antibody dilution was added to the plates in duplicate and incubated for 1 hour at room temperature, before washing as stated above. Antibody binding was detected using streptavidin labelled Europium (Perkin Elmer) diluted 1/1000 in DELFIA Assay buffer (Perkin Elmer). Plates were washed with TBS (Tris buffered saline)-Tween (0.1% v/v) and 50 µL/well of DELFIA Enhancement solution (Perkin Elmer) was added to the plate. Time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Results are shown in Figure 5.

e) SPR Analysis

Label-free surface plasmon resonance (SPR) analysis was performed as per Example 4, except the assay was performed at 37 °C. Additionally, due to artefacts of running the assay at 37 °C, the best referencing of the binding sensorgrams was found to be using a sensorgrams from a negative control antibody using the same concentrations of human PD-L1. Results are shown in Table 2.

f) Mixed lymphocyte reaction

Expanded $CD4^+$ T-cells were thawed and rested in AIM V© medium (Gibco) at 37 °C, 5% CO_2 overnight prior to the assay day. Serial dilutions of anti-human PD-L1 mAbs were prepared in the AIM medium at 4× final concentration. 50 µL of diluted mAbs was added to 96-well, U-bottom plates. 1×10^4 immature dendritic cells (iDC) in 50 µL AIM medium and 1×10^5 expanded $CD4^+$ T-cells (expanded using Dynabeads Human T-Activator CD3/CD28 by Life Technologies (Invitrogen/Applied Biosystems; Cat No: 11131D), according to manufacturer's instructions) in 100 µL AIM medium were added to the antibody dilutions in each well. Control wells include: $CD4^+$ T-cells alone, iDC alone, $CD4^+$ T-cell and iDC with or without IgG isotype control antibodies in 200 µL AIM medium. Reaction plates were incubated for 5 days in a humidified incubator (37 °C in 5% CO_2). At the end of the assay, the plate was spun down (528 x for 3 minutes) and 100 µL of supernatant was collected from the wells by gentle pipetting. Supernatants were analysed using human IFN Quantikine ELISA kit (R&D Systems) according to manufacturer's instructions. Results are shown in Figure 6.

g) Sequencing and characterisation of gene segment usage of 1D05 and 84G09

Antibodies were sequenced by Source Bioscience, and V-genes were compared to germline sequences.

Table 3 – V region usage of lead antibodies

Antibody clone ID	V gene	D gene	J gene	CDRH3 length (aa)	non-germline CDRH3 (aa)	V gene	J gene	CDRL3 length (aa)	Non-germline CDRL3 (aa)
1D05	IGHV3-9*01	IGHD3-10*01	IGHJ5*02	16	6	IGKV1D-39*01	IGKJ5*1	9	0
84G09	IGHV3-9*01	IGHD3-10*01	IGHJ5*02	15	4	IGKV1D-39*01	IGKJ5*1	9	1

h) Binding of lead antibodies to natively expressed PD-L1

84G09 and 1D05 were labelled with AlexaFluor647 and used to stain dendritic cells derived from monocytic precursors. This shows that lead antibodies bind PD-L1 that is natively expressed on human dendritic cells. Data is shown in Figure 7.

Materials and Methods

PBMC were suspended in RPMI 1640 medium without additives and allowed to adhere to a tissue culture flask for two hours at 37 °C. Non-adherent cells were removed and the flask washed three times with PBS. PBS was removed and replaced with RPMI 10% hiFBS (Gibco) containing 100 ng/mL GM-CSF and IL-4 (both Peprotech). Cells were cultured at 37 °C for 7 days, and then removed from flask using a cell scraper.

Cells were resuspended in FACS buffer (PBS 1% w/v BSA 0.1% w/v sodium azide) and plated at 10^5 cells/well, and incubated with Trustain FcX (Biolegend) for 10 min to prevent antibody binding to FcγR. AlexaFluor647 labelled antibodies were added at a final concentration of 5 µg/mL and incubated at 4 °C for 1 hour. Cells were then washed three times in FACS buffer and fixed for 20 min in 4% paraformaldehyde (Affymetrix). After fixation, cells were washed three times as before and resuspended in FACS buffer for analysis by flow cytometry. Data was acquired using the MACSQuant flow cytometer (Miltenyi Biotec) and analysed in FlowJo v10.

Example 6 - Antigen Preparation, Immunization Procedures, and antigen-specific B cell sorting and V-region recovery

Additional anti-human PD-L1 monoclonal antibodies were generated using the KyMouse™ system previously described. Genetically engineered HK mice were immunized with soluble recombinant human and mouse PD-L1 or surface expressed human and mouse PD-L1 displayed on mouse embryonic fibroblast (MEF) cells. Serum titres were performed by reverse ELISA and mice with the highest titres were selected for processing. At the end of each regime, spleen and lymph nodes were removed. Tissues were prepared into a single cell suspension and stained for sorting antigen-specific B-cells by FACS.

Materials and Methods

a) Immunisation of mice

Mice were immunised with soluble recombinant human PD-L1 or a combination of human and mouse PD-L1 protein (in-house) as per the schedule described in Example 1 for KM032 (hereafter described as KM121). Mice were also immunised with human PD-L1 protein, and MEF cells expressing human or mouse PD-L1, as per the schedule described in Example 1 for KM033 (hereafter described as KM122). MEF cells expressing mouse PD-L1 were generated as per Example 1, but substituting mouse PD-L1 sequences for the human PD-L1 sequences, and substituting anti-mouse PD-L1 detection antibody (eBioscience) for the anti-human PD-L1 detection antibody.

b) Determining serum titre by reverse PD-L1 ELISA Protocol

Titres in mouse serum samples were determined using a reverse PD-L1 ELISA protocol as per Example 1, with the following changes. In-house generated hPD-L1-his was labelled in-house using Lightning Link kit (Innova Biosciences), and used at 1 µg/mL in reagent diluent; 50 µL/well). Bound hPD-L1 was detected by addition of streptavidin-Europium (Perkin Elmer) diluted 1/1000 in DELFIA assay buffer (Perkin Elmer). Following incubation for 1 hour at room temperature in the dark, plates were washed using TBS (Tris buffered saline)-Tween (0.1% v/v) and 50 µL/well of DELFIA Enhancement solution (Perkin Elmer) was added to the plate. Time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Fluorescence data was plotted as Europium counts.

c) Sorting of antigen-specific B cells and retrieval of V-regions

The methods used were substantially as described in Example 1 of PCT application WO2015/040401, which is incorporated herein by reference. In brief, splenocytes and lymph node cells isolated from KM121 and KM122 immunisation regimes were stained with an antibody cocktail containing markers for the selection of cells of interest (CD19), whereas unwanted cells were excluded from the final sorted population (IgM, IgD, 7AAD). $CD19^+$ B-cells were further labelled with human PD-L1 (Seq ID No:1) and mouse PD-L1 (Seq ID No:325, labelled with AlexaFluor647 and AlexaFluor488, respectively, in-house using Lightning Link kits) to detect B-cells producing specific antibodies – cells binding human PD-L1, or both human and mouse PD-L1 were selected. These cells were single cell sorted by FACS into lysis buffer. V-region sequences were recovered using RT-PCR and two further rounds of PCR, then bridged to mouse IgG1 constant region and expressed in HEK293 cells. Supernatants from HEK293 cells were screened for the presence of PD-L1 binding antibodies. This method is hereafter referred to as BCT.

Example 7 – Supernatant screening

BCT supernatants were screened by HTRF, and selected primary hits further screened for binding to cell-expressed recombinant hPD-L1 and neutralisation of PD-1 binding, and for affinity of binding to human, cynomolgus and mouse PD-L1 recombinant protein by SPR, as described in this Example. KM121 antibodies with an affinity of 1nM or better for human and in some cases also cynomolgus PD-L1 were taken forward for further characterisation. For KM122, antibodies with the capacity to neutralise PD-1 binding to cell-expressed PD-L1 were taken forward, along with high

affinity (<1 nM) binding to both human and cynomolgus PD-L1. Antibodies did not bind to mouse PD-L1.

a) Primary screen - Binding to recombinant human PD-L1 (BCT Supernatants)

Supernatants collected from BCT expression were screened for the ability of secreted antibodies to bind to hPD-L1 expressed as a recombinant protein (produced in-house). Binding of secreted antibodies to recombinant human and mouse PD-L1 were identified by HTRF® (Homogeneous Time-Resolved Fluorescence, Cisbio) assay format using FluoProbes®647H (Innova Biosciences) labelled PD-L1 (referred to herein as 647 hPD-L1 or 647 mPD-L1 for human PD-L1 and mouse PD-L1 labelled with FluoProbes®647H respectively). 5 µL BCT supernatant was transferred to a white 384-well, low-volume, non-binding surface polystyrene plate (Greiner). 5 µL of 25 nM 647 hPD-L1 or 647 mPD-L1 diluted in HTRF assay buffer was added to all wells. Reference antibody was diluted in BCT media (Gibco #A14351-01) to 40 nM and 5 µL added to plate. For negative control wells, 5 µL of mouse IgG1 (Sigma M9269 in some instances referred to as CM7) diluted to 40 nM in BCT media was added. Binding of secreted antibodies to PD-L1 was detected by addition of 10 µL of goat anti-mouse IgG (Southern Biotech) directly labelled with Europium cryptate (Cisbio) diluted 1/2000 in HTRF assay buffer. The plate was left to incubate in the dark for 2 hours prior to reading time resolved fluorescence at 620 nm and 665 nm emission wavelengths using an EnVision plate reader (Perkin Elmer).

Data were analysed by calculating 665/620 ratio and percent effect for each sample according to Equation 2 and Equation 1 respectively.

For KM121, primary hits were selected based on greater than or equal to 30 percent effect whereas for KM122 primary hits were selected based on greater than or equal to 40 percent effect.

Progression to secondary screen was based on data from recombinant PD-L1 binding.

b) Secondary screen - binding to cell expressed hPD-L1 and neutralisation of hPD-L1 binding to PD-1 (BCT Supernatants)

Binding of BCT supernatants were tested for ability to bind to CHO-S cells expressing hPD-L1. CHO-S cells expressing hPD-L1 (generated in-house), were diluted in FACS buffer (PBS 1% BSA 0.1% sodium azide) and were distributed to a 96-well, V-bottom plate (Greiner) at a density of $0.5\text{-}1\times10^5$ cells per well. Cells were washed with 150 µL PBS and centrifuged at 300 g for 3 minutes. Supernatant was aspirated and 150 µL PBS added. This wash step was repeated.

25 µL BCT neat supernatant, reference antibody or control antibody diluted to 300 nM in BCT media was added to the washed cells. 25 µL of 30 nM biotinylated human PD-1 (in-house) was added and cells were incubated at 4 °C for 60 minutes. 150 µL FACS buffer was added and cells washed as described above. To detect biotinylated PD-1 and anti-PD-L1 antibody binding, Streptavidin-647 (Jackson ImmunoResearch) and anti-Mouse PE (Jackson ImmunoResearch) were each diluted 1/500 in FACS buffer and 50 µL of this mixture added to cells. Cells were incubated 4 °C for 60 minutes. Cells were washed twice with 150 µL FACS buffer, centrifuging at 300 g for 3 minutes after each wash

step and aspirating supernatant. Cells were fixed by addition of 50 µL 4% paraformaldehyde overnight. Cells were washed once as above and resuspended in FACS buffer for analysis. PE and APC signal intensity (geometric mean) was measured by flow cytometry using a BD FACS Array instrument. Data was plotted as geometric mean values without further calculation.

For KM121, secondary hits were selected based on high affinity (< 1nM) binding to human PD-L1. For KM122, secondary hits were selected based on comparable high affinity (< 1nM) binding human and cynomolgus PD-L1 and ability to neutralise PD-1 binding to cell-expressed PD-L1. Results are summarised in Table 4.

Table 4 – Summary of BCT clone screening

Experiment ID	Number of BCT supernatants screened	Number of Primary hits cherry picked	Number of secondary hits confirmed
KM121	984	162	7*
KM122	1312	263	45**

* three of these secondary hits were not included in the primary screen and were screened by SPR and neutralisation only

** one hit was identified by primary screen but insufficient material was available for secondary screen. After re-expression, clone was shown to bind human and cynomolgus PD-L1 with affinity of < 1nM and carried forward

c) Analysis of binding by surface plasmon resonance

SPR analysis was carried out on the ProteOn XPR36 Array system. Anti-mouse IgG (GE Healthcare BR-1008-38) was immobilised on a GLM chip by primary amine coupling. Antibodies were directly captured from BCT supernatants. Human, mouse and cynomolgus PD-L1 were used as analytes and passed over the captured antibodies at a single concentration. The binding sensorgrams are double referenced with a 0 nM (ie buffer alone) injection, and the data is analysed using the 1:1 model inherent to the ProteOn analysis software. The assay is carried out at 25 °C and used HBS-EP as running buffer.

Example 8 – Characterisation of selected antibodies

Selected hits were re-expressed with a human IgG1 constant region and sent for sequencing at Source Bioscience. V region usage is listed in Table 5. Hits were then analysed in an ELISA to determine their ability to neutralise PD-L1/PD-1 interactions, and PD-L1/CD80 interactions. All seven KM121 hits neutralised PD-L1/CD80 interactions; however, four antibodies did not neutralise PD-L1/PD-1. Four out of five KM122 hits neutralised both PD-L1/PD-1 and PD-L1/CD80 internations. Results are shown in Figures 8 and 9. Antibodies shown to neutralise both PD-1 and CD80 interactions

with PD-L1 were further screened for their ability to increase IFN in an autologous monocyte-T-cell co-culture assay.

Materials and Methods

a) PD-L1/PD-1 and PD-L1/CD80 neutralisation ELISA

CD80 (R&D Systems) or PD-1 (in-house) diluted to 2.5 µg/mL were adsorbed to 96-well, low auto-fluorescent, high protein binding plates (Costar) overnight at 4° C. Excess protein was removed by washing with PBS-Tween (0.1% v/v) and the wells were blocked with 1% w/v bovine serum albumin (BSA, Sigma) in PBS for 1 hour at room temperature, after which plates were washed with PBS-Tween as above. 60 µL of a titration (three-fold serial dilution) of antibody was added to a 96-well, non-binding plate diluted in ELISA assay buffer (PBS + 0.1% BSA). 60 µL of biotin labelled PD-L1 at 16 nM working concentration (8 nM FAC) was added to the plate excluding control wells where 60 µL ELISA assay buffer was added. The plate was incubated for 30 minutes before transferring 50 µL to the coated plates. The coated plates were incubated for 1 hour at room temperature. Excess protein was removed by washing with PBS-Tween (0.1% v/v). PD-L1 binding was detected using streptavidin labelled europium (Perkin Elmer) diluted 1/1000 in DELFIA assay buffer (Perkin Elmer). The plates were washed with TBS (Tris buffered saline)-Tween (0.1% v/v) and 50 µL/well of DELFIA Enhancement solution (Perkin Elmer) was added to the plate. Time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Percentage specific binding was calculated as defined in Equation 3. IC_{50} values were determined using GraphPad Prism software by curve fitting using a four-parameter logistic equation (Equation 4). Results are shown in Table 4a below. Values for KM121 antibodies are a mean of three independent experiments. Values for KM122 are from a single experiment. ND indicates IC_{50} value not determined, as a complete curve could not be generated.

Table 4a: IC_{50} values for neutralisation of PD-L1 interactions with PD-1 and CD80

Regime	Antibody clone ID	PD-1/PD-L1 IC_{50} (nM)	CD80/PD-L1 IC_{50} (nM)
KM121	411B08	2.22	1.60
KM121	411C04	2.45	1.93
KM121	411D07	ND	9.06
KM121	385F01	2.25	1.76
KM121	386H03	ND	0.74
KM121	389A03	ND	13.18
KM122	416E01	1.72	0.98
KM122	413G05	2.02	1.10
KM122	414B06	1.84	1.00
KM122	413F09	ND	ND
KM122	413D08	1.20	0.67

Selected lead antibodies active in the monocyte-T-cell co-culture assay (see Example 9) were analysed by SPR at 25 and 37 °C. Lead antibodies retained sub-nanomolar affinity binding to PD-L1 even at 37 °C. Antibodies did not bind mouse PD-L1. Results are shown in Table 4b.

Materials and Methods

SPR analysis was performed as per Example 4 with the following amendments: analysis was performed at 37 °C as well as 25 °C to increase the stringency of the assay. Human, cynomolgus and mouse PD-L1 (his-tagged) were generated in house (Seq ID Nos 3, 5 and 326, respectively).

Table 4b - Binding affinities of selected lead antibodies

Clone ID	Temperature	Antigen	KD (nM)
413G05	25 °C	Human	0.024 Kon = 2.57 µM Koff = 62.3 µM
414B06	25 °C	Human	0.172 Kon = 4.09 µM Koff = 0.702 mM
416E01	25 °C	Human	0.193 Kon = 2.34 µM Koff = 45.1 mM
413G05	25 °C	Cyno	0.015 Kon = 2.66 µM Koff = 38.9 mM
414B06	25 °C	Cyno	0.192 Kon = 3.78 µM Koff = 0.726 mM
416E01	25 °C	Cyno	0.411 Kon = 2.44 µM Koff = 1.0 mM
413G05	37 °C	Human	0.050 Kon = 4.67 µM Koff = 0.235 mM
414B06	37 °C	Human	0.778 Kon = 5.88 µM Koff = 4.57 mM
416E01	37 °C	Human	0.511 Kon = 4.34 µM Koff = 2.22 mM
413G05	37 °C	Cyno	0.046 Kon = 4.31 µM Koff = 0.197 mM
414B06	37 °C	Cyno	0.794 Kon = 5.02 µM Koff = 3.98 mM
416E01	37 °C	Cyno	0.998 Kon = 4.03 µM Koff = 4.02 mM

Example 9 – Testing of lead anti-PD-L1 antibodies in an autologous co-culture assay

The effects of anti-PD-L1 antibodies on IFN production are analysed in a co-culture of purified peripheral blood monocytes and $CD45RO^+$ memory T-cells from the same donor. In brief, monocytes

are isolated by negative selection using magnetic separation beads (Miltenyi Biotec). $CD45RO^+$ T-cells are isolated by a first round of negative selection for $CD3^+$ T-cells, and one round of positive selection for $CD45RO^+$ cells (Miltenyi Biotec). Cell subsets are co-cultured at a 1:1 ratio in RPMI 10% hiFBS in the presence of anti-CD3 (UCHT1, eBioscience) to provide TCR stimulation, and antibodies under investigation. Supernatants are taken after 4 days for analysis of IFN by MSD (Meso Scale Discovery).

The experiments were performed as described, except IFNγ production was measured with the R&D systems™ Human IFNγ Duoset® ELISA, using DELFIA® Eu-N1 Streptavidin detection.

Response for IFNγ standard (pg/mL) was plotted versus relative fluorescence response at interpolated from standard curve in pg/mL using a 4-parameter logistic fit as defined by Equation 4. Antibody-induced IFNγ is represented as fold induction compared to assay signal of wells showing background levels of response as defined in Equation 6. Each plot represents mean fold induction for individual donors with at least 2 different donors represented versus antibody concentration Log (M). Results are shown in Figures 22 and 37.

Equation 6

Fold induction = assay response (pg/mL)/ background response (pg/mL)

Background IFN response = IFN concentration (pg/mL) from wells containing monocyte – T-cell co-culture with anti-CD3 stimulation, without antibody.

All five antibodies, in human IgG1 format, induced a specific, dose-dependent increase production by T-cells after 4 days of co-culture with autologous monocytes and anti-CD3 (see Figures 22a and 22b). The two antibodies that induced the highest increase in cytokine production, 413G05 and 414B06, were selected for repeat characterisation by SPR (see Example 8). Antibody 416E01, in human IgG4(PE) format (Seq ID No:199), also induced specific dose-dependent increase in IFN production in the co-culture assay. This antibody was also selected for repeat SPR analysis.

The three selected antibodies were also analysed alongside the two lead antibodies selected in Example 4 (1D05 and 84G09), and a commercial effector enabled benchmark antibody. Antibodies were formatted as human IgG1. All antibodies induced dose-dependent IFN production in this assay (Figure 37 and Table 22).

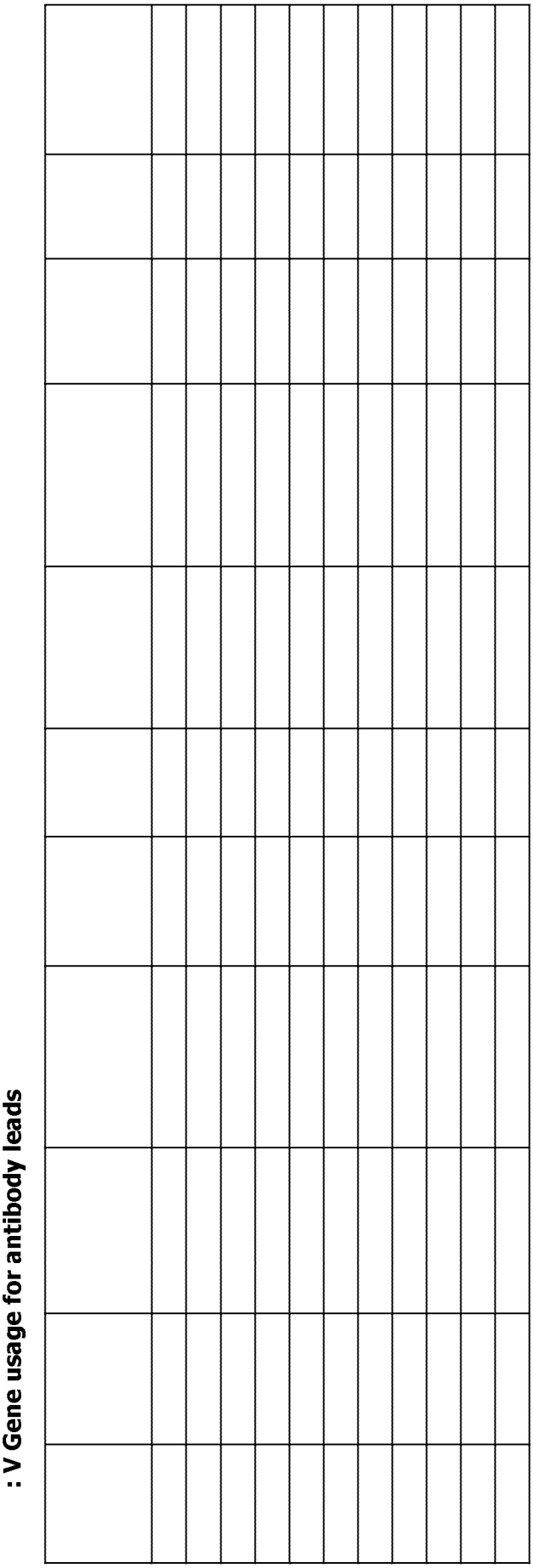

: V Gene usage for antibody leads

Table 22 – Summary of data from monocyte-T cell co-culture experiments.

Antibody name	mean EC50 (nM)	mean fold increase IFNγ
1D05	0.21	3.04
84G09	0.081	3.60
413G05	0.082	2.85
414B06	0.012	3.33
416E01	0.064	2.23
benchmark 2	0.057	2.30

Example 10 – Bispecific FIT-Ig Molecules targeting PD-L1 and TIGIT

Bispecific FIT-Ig constructs were constructed substantially as described in Example 1 of International Application WO2015/103072 (in the name of EpiMab Biotherapeutics, and is incorporated herein by reference).

The bispecific constructs, having a FIT-Ig structure, as described in Figure 1 of WO2015/103072 were expressed in CHO cells with a vector ratio of: Construct 1 DNA: 50%, Construct 2: DNA 25%: Construct 3 DNA 25% of total DNA in the transient transfection. The bispecific molecules were purified by standard Protein A and size exclusion chromatography. In this regard, Construct 1 is the polypeptide chain made up of VL_A-CL-VH_B-CH1-CH2-CH3 in Figure 1 of WO2015/103072. Construct 2 is the polypeptide chain made up of VH_A-CH1 in Figure 1 of WO2015/103072, and Construct 3 is the polypeptide chain made up of VL_B-CL in Figure 1 of WO2015/103072.

SPR analysis was used to determine affinities of the various arms of the bispecific and the parental monospecific antibodies were used to determine if the affinities had been altered in the bispecific molecule. Sequential binding of antigens were used to test whether the bispecific constructs were capable of binding on both arms of the bispecific.

Table 6 – Bispecific antibody constructs and control monospecific antibodies

Full name	Alias	Native variable domain[1]	Additional Domain[2]
1D05/in-house anti-TIGIT	Bispecific 1	1D05 (anti-PD-L1)*	Kymab TIGIT
In-house anti-TIGIT/1D05	Bispecific 2	Kymab TIGIT	1D05 (anti-PD-L1)*
Tool anti-TIGIT/Tool anti-PD-L1	Bispecific 3	Tool anti-TIGIT	Tool anti-PD-L1
Tool anti-PD-L1/Tool anti-TIGIT	Bispecific 4	Tool anti-PD-L1	Tool anti-TIGIT
1D05	Antibody 1	In-house anti-PD-L1*	na
Kymab TIGIT	Antibody 2	In-house anti-TIGIT	na
Tool PD-L1	Antibody 3	Tool anti-PD-L1	na
Tool TIGIT	Antibody 4	Tool anti-TIGIT	na

* 1D05 has the V_H sequence of Seq ID No:33 and the V_L sequence of Seq ID No:43, and a heavy chain constant region of Seq ID No:205

[1] "Native Variable domain" corresponds to the antigen-binding site formed by VH_B and VL_B in Figure 1 of WO2015/103072

[2] "Additional domain" corresponds to the antigen binding site formed by VHA and VLA in Figure 1 of WO2015/103072

a) Kinetic analysis

An anti-human IgG capture surface was created by a mix of 3 anti-human Fc antibodies (Jackson Labs 109-005-008, 109-006-008 and 309-006-008) immobilised on a GLC chip by primary amine coupling. Control monospecific antibodies or Bispecific antibody constructs were captured on this surface and human PD-L1 or TIGIT was used as analyte at 512 nM, 128 nM, 32 nM, 8 nM and 2 nM with 0 nM (i.e. buffer alone) used to double reference the binding sensorgrams. The assay was run at 25 °C, using HBS-EP as running buffer. The sensorgrams were fitted to the 1:1 model inherent to the ProteOn analysis software.

Table 7 - TIGIT Binding

Full name	Alias	Ka	Kd	KD (nM)
1D05/in-house anti-TIGIT	Bispecific 1	2.38E+06	2.65E-03	1.11
In-house anti-TIGIT/1D05	Bispecific 2	1.12E+06	2.02E-03	1.8
Tool anti-TIGIT/Tool anti-PD-L1	Bispecific 3	2.10E+06	3.69E-03	1.75
Tool anti-PD-L1/Tool anti-TIGIT	Bispecific 4	3.22E+06	2.98E-03	0.93
1D05	Antibody 1	nbs	nbs	nbs
Kymab TIGIT	Antibody 2	1.58E+06	2.27E-03	1.44
Tool PD-L1	Antibody 3	nbs	nbs	nbs
Tool TIGIT	Antibody 4	3.16E+06	5.42E-03	1.72

Table 8 – PD-L1 Binding

Full name	Alias	Ka	Kd	KD (nM)
1D05/in-house anti-TIGIT	Bispecific 1	6.03E+05	1.61E-04	0.27
In-house anti-TIGIT/1D05	Bispecific 2	1.04E+06	2.14E-04	0.21
Tool anti-TIGIT/Tool anti-PD-L1	Bispecific 3	1.25E+06	1.22E-04	0.1
Tool anti-PD-L1/Tool anti-TIGIT	Bispecific 4	7.36E+05	1.57E-04	0.21
1D05	Antibody 1	9.71E+05	3.36E-04	0.35
Kymab TIGIT	Antibody 2	nbs	nbs	nbs
Tool PD-L1	Antibody 3	1.05E+06	2.08E-04	0.2
Tool TIGIT	Antibody 4	nbs	nbs	nbs

b) Bispecific Binding

Using the same anti-human IgG capture surface created for kinetic analysis, the bispecific antibody constructs were captured on this surface and recombinant PD-L1 or TIGIT was used as analyte at 512 nM, 128 nM, 32 nM, 8 nM and 2 nM with 0 nM (i.e. buffer alone) used to double reference the binding sensorgrams. The assay was carried out by injecting PD-L1 followed by TIGIT with no regeneration between analyte injections, and also with TIGIT followed by PD-L1. The sensorgrams for the double referenced 512 nM are shown in Figures 10 and 11.

c) Characterisation of bispecific FIT-Ig Molecules binding to PD-L1 and TIGIT by AlphaScreen®

An AlphaScreen® binding assay was developed to assess the bispecific binding of PD-L1/TIGIT FIT-Ig molecules. The assay was set up using biotinylated His-PD-L1 (SEQ ID No:3) and His-FLAG-TIGIT (SEQ ID No:539) detected respectively with streptavidin donor beads and anti-FLAG acceptor beads (both Perkin Elmer, 6760613). Human IgG1 (Sigma I5154) and parental monospecific antibodies alone or in combination were used as negative controls, while an anti-His antibody (Qiagen 34660) was used as positive control.

Two protocols were created to investigate the ability of FIT-Ig molecules to promote proximity of TIGIT and PD-L1 coated beads with a distinct stringency. Antibodies were either incubated with PD-L1 and TIGIT proteins before adding the AlphaScreen® detection beads (Method one), or incubated with the detection beads pre-coated with their respective TIGIT and PD-L1 proteins (Method two). Method two was designed to mimic the cell recruitment by bispecific antibodies.

i) Method one

Bispecific antibodies, parental monospecific antibodies and control antibodies were prepared in buffer (PBS pH 7.4 (Gibco) and 0.1% w/v BSA (Sigma)) at 150 nM and diluted as per 1:3 series, 8 points. 5 µL of each serial dilution of antibody were mixed in a 384-well AlphaLISA® assay plate (Perkin Elmer 6005350) to 5 µL of biotinylated His-PD-L1 and 5 µL of His-FLAG-TIGIT at 50 nM in buffer. Parental monospecific antibodies were also prepared as described above starting from 300 nM to be tested in combination. 2.5 µL of the first antibody was added to the same volume of the second antibody, then 5 µL of each combination of parental monospecific antibodies were mixed in assay plates to 5 µL of biotinylated His-PD-L1 and 5 µL of His-FLAG-TIGIT at 50 nM in buffer. Assay plates were incubated for 1 hour at room temperature before adding 5 µL of anti-FLAG acceptor beads at 0.1 g/L for an additional hour at room temperature in the dark. Finally, 5 µL of streptavidin donor beads at 0.1 g/L were added to assay plates for 2 hours and 30 minutes. Assay plates were read using an EnVision plate reader (Perkin Elmer) with excitation/emission wavelengths of 680/615 nm. The fluorescent counts measured (Alpha signal) were plotted in Prism against antibody titrations. Results are shown in Figure 25. Binding of FIT-Ig molecules to PD-L1 and TIGIT increases with the concentration of antibody up to 10 nM. No binding is observed for the monospecific parental antibodies and the isotype control.

ii) Method two

Streptavidin donor beads prepared at 0.05 g/L in buffer (PBS pH 7.4 (Gibco 14190169) and 0.1% w/v BSA (Sigma)) were coated with biotinylated His-PD-L1 (Seq ID No:3) at 25 nM, while His-FLAG-TIGIT (Seq ID No:539) at 25 nM was used to label anti-FLAG acceptor beads at 0.05 g/L in buffer. Both acceptor and donor beads were incubated for 1 hour at room temperature in the dark.

Bispecific antibodies, parental monospecific antibodies, alone and combined, and control antibodies were prepared in buffer at 300 nM and diluted as per 1:3 series, 8 points. 5 µL of each serial dilution of antibody were mixed in a 384-well AlphaLISA® assay plate (Perkin Elmer 6005350) to 10 µL of pre-coated donor beads and 10 µL of pre-coated acceptor beads. Assay plates were incubated at room temperature for 4 hours in the dark and then read as described for method one. The fluorescent counts measured (Alpha signal) were plotted in Prism against antibody titrations. Results are shown in Figure 26. Binding of FIT-Ig molecules to PD-L1 and TIGIT increases with the concentration of antibody up to 20 nM. No binding is observed for the monospecific parental antibodies and the isotype control.

d) Characterisation of bispecific FIT-Ig molecules binding to PD-L1 and TIGIT by flow cytometry

A flow cytometry protocol was developed to assess the ability of the FIT-Ig molecules to promote the recruitment of cells expressing TIGIT and PD-L1. For this purpose, CHO cells transfected with human PD-L1 were stained with CellTrace™ Far Red (Invitrogen C34572) which emits maximally at 661 nm while HEK cells transfected with human TIGIT were stained with CellTrace™ Violet (Invitrogen C34571) which emits maximally at 450 nm.

CHO human PD-L1 and HEK human TIGIT cells were harvested, counted, washed, and re-suspended in PBS (Gibco 14190169) at 1 million of cells per mL. CellTrace™ Far Red and CellTrace™ Violet dyes were diluted 1:2000 and incubated with cells for 20 min at 37 °C in the dark, according to manufacturer's recommendations. Buffer (PBS (Gibco 14190169), 1% BSA (Sigma) 0.1% Na azide (Severn Biotech 40-2010-01)) was then added in excess for an additional 5-minute incubation step. Cells were spun down, re-suspended in buffer at 0.5 million of cells per mL and incubated for at least 10 minutes at 37 °C before proceeding with binding protocol. Unstained cells were kept and used to set up the gating strategy.

Bispecific antibodies and human IgG1 were prepared in buffer at 150 nM and diluted as per 1:3 series, 8 points. 50 µL of each serial dilution of antibody, 50 µL of CHO human PD-L1 cells labelled with CellTrace™ Far Red and 50 µL of HEK human TIGIT labelled with CellTrace™ Violet were added to a 96-well, V-bottom PS plate (Greiner 651901). Assay plates were incubated at room temperature for 1 hour under gentle agitation (450 rpm) before being read using the Attune NxT flow cytometer (Thermo Fisher). CellTrace™ Violet was excited using the Violet laser and detected in the VL1 channel with a 440/50 bandpass filter. CellTrace™ Far Red was excited using the Red laser and detected in the RL1 channel with a 670/14 bandpass filter. Sample collection was performed without vortexing

samples. FCS files were analysed with FlowJo® software. Single cells and duplets were gated based on the forward and side scatter dot plot.

Data analysis resulted in the identification of four different gates: a double negative quadrant corresponding to unstained CHO human PD-L1 and unstained HEK human TIGIT; two quadrants positive for single staining (in VL1 or RL1 channel); and a quadrant positive for dual staining (in both VL1 and RL1 channels) composed of stained CHO human PD-L1 and stained HEK human TIGIT recruited by FIT-Ig molecules. Percentages of double positive cells were plotted into Prism against antibody titrations. Results are shown in Figure 27. Percentage of double positive cells increases with the concentration of FIT-Ig molecules up to 1 nM.

The monospecific binding of test molecules to target was confirmed on stained cells using monospecific antibodies labelled with R-Phycoerythrin (PE) which emits maximally at 590 nm. PE-labelled Antibody 1, Antibody 2 and human IgG1 were diluted in buffer at 150 nM. 50 μL of each antibody were mixed with 50 μL of stained CHO human PD-L1 and 50 μL of stained HEK human TIGIT in a 96-well, V-bottom PS plate (Greiner 651901). Following a 1 hour incubation at room temperature, cells were washed 3 times with 200 μL/well of PBS and re-suspended in 150 μL/well of buffer. Assay plates were read using the Attune NxT flow cytometer (Thermo Fisher) to record fluorescence. Cell Trace™ Violet and Far Red were detected as stated above. PE was excited using the Yellow laser and detected in the YL1 channel with a 585/16 bandpass filter. GeoMean values in the YL1 channel were used to determine monospecific binding to stained CHO human PD-L1 or stained HEK human TIGIT.

Example 11 – Generation and expression of anti-PD-L1-IL-2 immunocytokine constructs

Immunocytokines were generated by fusing wild type IL-2 (SEQ ID No:301), or IL-2 containing deletions in the first nine amino acids (see SEQ ID Nos:303 to 323, fused to Seq ID No:324), to the light chain of anti-PD-L1 antibody 1D05 (see Seq ID No:45). These were paired with an IgG1 effector-disabled variant of 1D05 heavy chain (Seq ID No:205). Wild type IL-2 fused to the heavy chain of 1D05 was generated for use as a control (SEQ ID No:302) and paired with the unmodified light chain of 1D05 (Seq ID No:45). Twenty-two immunocytokines were successfully expressed and characterised further. One light chain construct, 1D05 D1 did not express successfully.

Materials and Methods

The DNA sequences encoding the anti-PD-L1 (antibody 1D05) immunocytokine (C-terminal IL-2 fusion to light chain) were purchased as synthetic DNA strings and cloned into the pTT5 expression vector using the Golden Gate cloning strategy. The heavy chain sequence of 1D05, includes a constant region which is a disabled IgG1 variant with changes from wild-type shown in bold (Seq ID No:299). The light chain of antibody 1D05 has full length wild type IL-2 sequence (underlined) fused to the C-terminus of the Kappa constant region (Seq ID No:300). Overlap PCR using appropriate oligonucleotide primers were used to generate variants of N-terminal of IL-2 (see Seq ID No:300 where IL-2 the sequence is underlined and the region to be varied is shown in bold). Variant sequences

were cloned into the pTT5 expression vector using the Golden Gate method. The wild type and variant constructs were transfected to Expi293™ cells for expression.

Example 12 – Generation of IL-2R transfectant cells for screening

In order to differentiate between immunocytokine activity on the high affinity (αβγ) and intermediate affinity ( ) IL-2 receptors, IL-2R transfectants were generated. TF-1 cells, expressing endogenous common chain, were transfected with , or and receptor subunits, to impart responsiveness to IL-2. The proliferative response to immunocytokines was then analysed using these cells (see Example 13).

Materials and Methods

Two recombinant cell lines were generated to distinguish between signalling through high affinity ( ) IL-2R. The erythroleukemia cell line TF-1 (European Collection of Authenticated Cell Cultures) shows complete growth dependency on granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin-3 (IL-3). The first cell line generated was transfected with full length human IL-2Rβ (CD122) only. The second cell line was generated by transfecting the full length human IL-2R (CD25) into the first cell line.

The transfected sequences were codon optimized for mammalian expression and cloned into an expression vector under the CMV promoter flanked by 3′ and 5′ piggyBac specific terminal repeat sequences facilitating stable integration into the cell genome (see: "A hyperactive piggyBac transposase for mammalian applications"; Yusa K., , Proc. Natl. Acad. Sci. U S A., 108(4): 1531-6, 2011 Jan 25). Furthermore, the expression vector for each subunit contained a different selection cassette to facilitate stable cell line generation. The subunit was selected using puromycin (Sigma) and the subunit using geneticin (Gibco). The subunit was transfected into cells already expressing the subunit.

The expression plasmids were co-transfected with a plasmid encoding piggyBac transposase into the TF1 cell line by electroporation using the Lonza 4-D nucleofector transfection X kit system according to manufacturer instructions. 24 hours after transfection, complete media was supplemented with the appropriate selection and cells grown for at least 3 weeks to select a stable line, with media being exchanged every 3 to 4 days. The expression of the recombinant human subunits was assessed by flow cytometry using anti-human CD122 (IL-2R) APC conjugated antibody (eBioscience) and anti-human CD25 (IL-2R) PE conjugated antibody (eBioscience). Endogenous common chain expression was confirmed with anti-human CD132 (common chain) PE conjugated antibody (eBioscience). As expression was low, $CD122^+$ cells were sorted by fluorescence activated cell sorting (FACS) and further cultured under selection. There was uniform expression of chain after transfection, and therefore these cells were not sorted.

Complete TF1 media was made up of RPMI medium 1640 (Gibco) plus GM-CSF (2 ng/mL) and supplemented with 10% v/v heat inactivated fetal bovine serum (hiFBS, Gibco). Once responsiveness

to IL-2 was confirmed, transfected cell lines were maintained in RPMI 1640, 10% hiFBS and 5 ng/mL recombinant human IL-2 with ( ) or without ( ) geneticin.

Example 13 – Assessing ability of immunocytokine constructs to signal through IL-2R

Immunocytokines were assessed for their ability to induce proliferation of TF1 cell lines transfected with the subunit, or with both the and subunits of IL-2R. Cells were starved of cytokines overnight, then stimulated with titrations of each immunocytokine. CellTiter-Glo® was used to determine the number of viable cells in culture after 3 days, based on quantitation of the ATP present. There was a broad range of activities of the immunocytokines on IL-2R , with the largest IL-2 deletions having the greatest reduction on proliferation, compared with equimolar amounts of free IL-2. The effect on activity is not as pronounced, but again the greatest reduction in proliferation is seen with the largest IL-2 deletions. Deletions in the first few N-terminal amino acids of IL-2 allow for fine tuning of cytokine activity. A representative experiment is shown in Figures 12(a) and (b).

Materials and Methods

IL-2R transfected TF1 cells were routinely cultured in RPMI + 10% fetal bovine serum (culture medium) with the addition of IL-2 (Peprotech) at 5 ng/mL for the IL-2 at 5 ng/mL and Geneticin (Gibco) at 350 µg/mL for the transfected cell line. Prior to testing of immunocytokine constructs, the cells were harvested by centrifugation and aspirated to remove the supernatant. The cells were washed in PBS to remove cytokines and antibiotics. Cells were resuspended in fresh culture medium at 10^5 cells/mL, without supplements and returned to the incubator overnight.

The cells were harvested by centrifugation and aspirated to remove the supernatant. Cells were resuspended in complete medium and 30 µL of cell solution was added to the plate (white walled tissue culture treated 384-well plate) wells to achieve an initial cell concentration of 1250 cells/well.

The IL-2 ligand was prepared as serial four-fold dilutions from 300 ng/mL final assay concentration (FAC) (600 ng/mL working) in culture media. The immunocytokine constructs were titrated from 0.1 µg/mL (three-fold dilutions) for testing on the αβγ cell line and 10 µg/mL (three-fold µL of titrations were added to the cell plate. To control wells, 30 µL of culture media without IL-2 was added. To reduce evaporation effects, the outermost rows/columns of the plate were filled with 80 L of culture media. The plates were then incubated for 3 days at 37 °C, 5% CO_2. Following the culture period proliferation of TF-1 cells was assessed by addition of 30 µL of Cell Titre Glo (Promega) to all wells. The plate was incubated at room temperature for 10 minutes then read using ultrasensitive luminescence filter.

Equation 7: Calculation of fold over background from TF-1 proliferation assay

$$\text{fold over background} = \frac{\text{sample RLU}}{\text{mean over background RLU}}$$

RLU =relative luminescence units

Data expressed as fold over background. Background was defined as wells containing cells but no cytokine

Example 14 – Binding of immunocytokines to PD-L1

Surface plasmon resonance was used to confirm the ability of the immunocytokine constructs to bind PD-L1. The presence of the IL-2 on the light chain does not have any detrimental effect on binding (Table 9). Four constructs with a range of IL-2 activities were shortlisted for further characterisation – these were 1D05 D1-9 ICK, 1D05 D1-8 ICK, 1D05 D9-2 ICK and 1D05 D9-7 ICK.

Table 9: Affinity of 1D05 binding to PD-L1 is unaffected by the fusion of IL-2 to the antibody, as measured by surface plasmon resonance. Data shown is from a single experiment

Sample Name	KD (nM)
1D05	0.171
1D05 HC-IL2	0.240
1D05 LC-IL2	0.207
1D05 IC45 (D5-9)	0.203
1D05 IC46 (D1-9)	0.195
1D05 IC64 (D5-7)	0.214
1D05 D1-2	0.187
1D05 D1-3	0.199
1D05 D1-4	0.186
1D05 D1-5	0.203
1D05 D1-6	0.211
1D05 D1-7	0.178
1D05 D1-8	0.190
1D05 D9	0.205
1D05 D9-8	0.225
1D05 D9-7	0.200
1D05 D9-6	0.211
1D05 D9-4	0.175
1D05 D9-3	0.171
1D05 D9-2	0.189
1D05 D2-6	0.201
1D05 D3-7	0.203
1D05 D4-8	0.208
benchmark	0.099

Materials and Methods

Analysis of immunocytokines by surface plasmon resonance

Label-free surface plasmon resonance (SPR) analysis was carried out on the ProteOn XPR36 (BioRad) array SPR machine. An anti-human IgG capture surface was created on a GLC biosensor chip using amine coupling of an anti-human IgG from GE Healthcare. Test antibodies were captured on this surface and human PD-L1 (in-house) was used as the analyte at 64 nM, 16 nM, 4 nM, 1 nM and 0.25 nM. The assay was carried out at 25 °C using HBS-EP (Teknova H8022). Buffer alone was used to reference the binding sensorgrams. The data was analysed using the 1:1 model inherent to the ProteOn XPR36 analysis software.

Example 15 – Assessing capacity of immunocytokines to neutralise the interaction of PD-L1 and PD-1/CD80

To ensure that fusion of the IL-2 molecule to the antibody did not disrupt its neutralisation capacity, shortlisted immunocytokines were tested in a neutralisation ELISA. The shortlisted immunocytokines tested did not differ from wild type antibody in their ability to neutralise interactions between PD-L1 and PD-1, and PD-L1 and CD80. Results are shown in Figure 13 and Table 10. Values in the table are the means of three independent experiments.

Table 10: Summary of neutralisation ELISA data, expressed as mean of three independent experiments

Clone	PD1-PD-L1 Neutralisation IC_{50} (nM)	CD80-PD-L1 Neutralisation IC_{50} (nM)
1D05	1.41	0.882
1D05 LC-IL-2	0.833	0.505
1D05 IC46 (D1-9)	1.75	1.07
1D05 D1-8	1.16	0.745
1D05 D9-2	1.55	0.947
1D05 D9-7	1.15	0.70
Hybrid Control	N/A	N/A

Materials and Methods

a) PD-L1/PD-1 or PD-L1/CD80 neutralisation ELISA

CD80 (R&D Systems) or PD-1 (in house) diluted to 2.5 µg/mL were adsorbed to 96-well, low auto-fluorescent, high protein binding plates (Costar) overnight at 4 °C. Excess protein was removed by washing with PBS-Tween (0.1% v/v) and the wells were blocked with 1% w/v bovine serum albumin (BSA, Sigma) in PBS for 1 hour at room temperature, after which plates were washed as described previously. 60 µL of a titration (three-fold dilutions from 100 nM) of antibody was added to a 96-well, non-binding plate diluted in ELISA assay buffer (PBS + 0.1% BSA). 60 µL of biotinylated PD-L1 (in house, labelled with Lightning Link Biotinylation kit) at 16 nM working concentration (8 nM

FAC) was added to the plate excluding control wells where 60 µL ELISA assay buffer was added. The plate was incubated for 30 min before transferring 50 µL to the coated plates.

The coated plates were incubated for 1 hour at room temperature. Excess protein was removed by washing with PBS-Tween (0.1% v/v). PD-L1 binding was detected using streptavidin labelled Europium (Perkin Elmer) diluted 1/1000 in DELFIA assay buffer (Perkin Elmer). The plates were washed with TBS (Tris buffered saline)-Tween (0.1% v/v) and 50 µL/well of DELFIA Enhancement solution (Perkin Elmer) was added to the plate. The time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Percentage specific binding was calculated as defined in Equation 3.

IC_{50} values were determined using GraphPad Prism software by curve fitting using a four-parameter logistic equation (Equation 4) from the percentage specific binding (Equation 3).

Example 16 – De-immunisation of anti-PD-L1 antibody

To reduce the possibility of adverse immunological reactions based around the anti-PD-L1-immunocytokine, a series of 1D05 antibody mutants (Seq ID Nos:47 to 51) was created with anticipated lower potential of immunogenicity, as determined by T-cell epitope analysis software. The mutations can be single or in combination. Mutants were assessed for their ability to bind PD-L1 with the same affinity as the wild-type molecule by SPR as described in Example 14, with the addition of human PD-L1 analyte at 256 nM. Mutations under investigation are included as Seq ID Nos:47 to 51, indicated by underlined and bold text. The V_H framework mutations (Seq ID Nos:47 and 48) do not have any detrimental effects on binding. The V to A mutation in CDRH2 (Seq ID No:50) was detrimental to binding, and so an alternative mutation will be analysed (V to Y, Seq ID No:298). Results are shown in Table 11.

Example 17 – Inhibition of tumour growth by an anti-PD-L1 antibody in NOD/SCID: xenograft T-cell model

Inhibition of melanoma tumour growth by lead antibody 1D05 in the hIgG1 LAGA (Seq ID No: 205) format was demonstrated in a NOD/SCID:xenograft T-cell model. T-cells were expanded in the presence of A375, a melanoma cell line, for 20 days in the presence of IL-2 and IL-7. T-cells were co-implanted subcutaneously with fresh A375 cells, then the antibody administered intraperitoneally after 1 hour. Tumour size and animal survival were monitored. Tumours in mice treated with antibody 1D05 were smaller than in animals treated with isotype control. Survival time in 1D05-treated mice was also increased.

Materials and Methods

Efficacy studies were performed using a T-cell/Xenograft model in NOD/SCID mice employing a refinement of the methods outlined in Stewart R . (Cancer Immunol. Res., 2015 Sep;3(9):1052-62). Leukoreduction system chambers were obtained from NHSBT. HLA-A2 positive donors were selected by staining unfractionated blood using a PE-labelled anti-human HLA-A2 (Biolegend, Clone:

Table 11: Deimmunisation mutations to lead 1D05 antibody

Heavy Chain	Light Chain	KD (nM)
1D05 – IgG1 disabled (LAGA) Seq ID No:299	1D05 kappa (Seq ID No:45)	0.29
1D05 V to A change in V_H (Seq ID No:47), IgG1 disabled (LAGA, Seq ID No:205)	1D05 kappa (Seq ID No:45)	0.33
1D05 F to S change in V_H (Seq ID No:48), IgG1 disabled (LAGA, Seq ID No:205)	1D05 kappa (Seq ID No:45)	0.23
1D05 V to A & F to S change in V_H (Seq ID No:342), IgG1 disabled (LAGA, Seq ID No:205)	1D05 kappa (Seq ID No:45)	0.23
1D05 – IgG1 disabled (LAGA) Seq ID No:299	1D05 kappa, V to A change (Seq ID No:50)	2.66
1D05 V to A change in V_H (Seq ID No:47), IgG1 disabled (LAGA, Seq ID No:205)	1D05 kappa, V to A change (Seq ID No:50)	2.8
1D05 F to S change in V_H (Seq ID No:48), IgG1 disabled (LAGA, Seq ID No:205)	1D05 kappa, V to A change (Seq ID No:50)	1.94
1D05 V to A & F to S change in V_H (Seq ID No:342), IgG1 disabled (LAGA, Seq ID No:205)	1D05 kappa, V to A change (Seq ID No:50)	1.94

BB7.2), the red blood cells were then lysed, followed by fixation with 4% PFA, prior to acquisition on the Attune flow cytometer. PBMCs were isolated by density gradient centrifugation over Ficoll. Primary human $CD4^+$ and $CD8^+$ T-cells were then isolated using an EasySep human $CD4^+$ and $CD8^+$ T-cell enrichment kit (Stemcell Technologies, Cat 19052 and 19053). The $CD4^+$ and $CD8^+$ T-cells were then cultured separately for 20 days on a monolayer of mitomycin C treated A375 cells (at day 10, T-cells were re-plated on a fresh A375 monolayer) in the presence of recombinant human IL-2 and IL-7 (Peprotech). On day 20 the cells were frozen in 90% hiFBS/10% DMSO at -80°C in a "Mr Frosty" (Nalgene) and stored in liquid nitrogen until required. The day before starting an experiment the cells were thawed and placed in culture.

On the day of implantation, the $CD4^+$ and $CD8^+$ T-cells were counted and mixed together in a 1:1 ratio. The $CD4^+/CD8^+$ mixture was then added to A375 tumour cells and injected subcutaneously into mice on the rear right flank. Treated groups received their first dose of antibody or isotype control (all dosed intraperitoneally at 10 mg/kg) one-hour post implantation of the cells. The animals received further doses 3, 6, 8 and 10 days post-implantation. Tumour development was monitored three times a week using digital callipers measuring in two dimensions until end of the study. Tumour volumes (mm^3) were estimated using a standard formula $(L \times W^2)/2$ (with L being the larger diameter, and W the smaller diameter of the tumour). Mice were kept on studies until their tumours developed to a mean diameter of 12mm or they reached one of the humane endpoints outlined in the study protocol. The humane endpoint survival statistics were calculated using the Kaplan-Meier method with Prism. This approach was used to determine if PD-L1 treatment was associated with improved survival.

Table 12: Treatment Groups

Groups	Number of animals	Cell Line
1	9	$2x10^6$ A375 Cells
2	9	1:6 ratio T-cells: A375 Cells ($2x10^6$ A375 Cells)
3	8	10 mg/kg isotype control hIgG1 1:6 ratio T-cells: A375 Cells ($2x10^6$ A375 Cells)
4	8	10 mg/kg anti-PD-L1 1D05 hIgG1 LAGA (Seq ID No: 205) 1:6 ratio T-cells: A375 Cells ($2x10^6$ A375 Cells)

Treatment with the isotype control had no effect on tumour development when compared to the group where the $CD4^+/8^+$ T-cells are co-injected with the tumour cells. Whilst treatment with the anti-PDL1 antibody 1D05 delayed the tumour development when compared to the Isotype Control. This is shown in Figure 14.

All groups with T-cells co-injected with the tumours showed an increase in time on study when compared to the tumour alone group. Treatment with the isotype control had no effect on time on study, whilst treatment with the anti-PDL1 antibody 1D05 increased time on study when compared to all the other groups including the isotype control groups. Results are shown in Figure 15.

Example 18: Single dose study of immunocytokines in cynomolgus monkeys

To assess pharmacodynamic and pharmacokinetic (PK) parameters in the most relevant animal model, male cynomolgus monkeys received a single dose of immunocytokine (ICK) at 1 mg/kg. Animals were observed for clinical manifestations of toxicity, and blood samples were taken over the course of 7 days for the analysis of PK, production of cytokines and characterisation of leukocyte subsets. The in-life phase of the study, and haematology, flow cytometry and cytokine analysis was performed at Envigo UK (study number GF13YC). Pharmacokinetic analysis was performed in-house.

Materials and Methods

Male cynomolgus monkeys of at least 2 years of age were used for the study and body weights were recorded at 7 days and 4 days before the start of the study. Immunocytokine constructs were formulated in 50 mM sodium acetate pH 5.5, at 1 mg/mL and were diluted to 0.2 mg/mL in physiological saline for intravenous infusion at a rate of 5 mL/kg/hour. Blood pressure and body temperature were monitored pre-treatment, 1 hour and 4 hours post end-of-dose. Animals were observed twice daily for signs of ill-health. The study was performed in two phases – initial doses of 1D05 HC IL-2 ICK and 1D05 LC D9-7 ICK to ensure dose level and PK timepoints were suitable, then dosing of 1D05 LC D9-7 ICK was repeated, alongside four further constructs (see Table 1). Phase 2 dosing of 1D05 LC D9-7 ICK is indicated by a (2) next to the construct name.

Table 13: Treatment groups and animal numbers

Phase	Animal	Test Item
1	134	1D05 HC IL-2 ICK
1	135	1D05 LC D9-7 ICK
2	136	1D05 LC IL-2 ICK
2	137	1D05 LC D9-7 ICK (2)
2	138	1D05 LC D9-2 ICK
2	139	1D05 LC D1-8 ICK
2	140	1D05 LC D1-9 ICK

For haematological analysis, fasting blood samples were taken into EDTA treated tubes pre-treatment, and 2, 5 and 7 days post-treatment. Routine haematology parameters were measured by the Bayer Advia 120. Results are shown in Figures 16 and 17.

For analysis of cytokines and soluble CD25, blood samples were taken into EDTA-treated tubes pre-treatment and 3 days post-treatment, and plasma extracted by centrifugation at 2000 g for 10 minutes. Samples were frozen until analysis by multiplex MSD (cytokines) or commercial ELISA (soluble CD25). Results are shown in Figure 18 and 19.

For immunophenotyping, blood samples were taken into EDTA-treated tubes pre-treatment and 5 days post-treatment. Blood samples were stained with cocktails of directly conjugated monoclonal antibodies, then red blood cells were lysed and the samples fixed by re-suspension in phosphate buffered saline containing 1% formaldehyde prior to analysis. Results are shown in Figure 20.

For PK analysis, blood samples were taken into untreated tubes pre-treatment, end of infusion (EOI), 2, 4, 8, 16, 24, 32, 40 and 48 hours after EOI, extended to 72 hours and 96 hours for Phase 2) and serum prepared by allowing the blood to clot, then centrifugation at 2000 g for 10 min. Serum samples were frozen on dry ice for shipment to Kymab. Results are shown in Figure 21.

Pharmacokinetic analysis of serum samples

a) PK assay for detection of anti-PD-L1 antibody

50 µL/well of human PD-L1 Flag His (Seq ID No:505, in house) diluted to 2 µg/mL in PBS (Sigma, P3813-10PAK) was adsorbed to 96-well, high protein binding fluorescent plates (Greiner) overnight at 4 °C. Excess protein was removed by washing 3× with 300 µL/well PBS-Tween (0.1% v/v) and the wells were blocked with 1% w/v bovine serum albumin (BSA, Sigma) in PBS for 1 hour at room temperature, after which plates were washed as described previously. Antibodies were diluted from 10,000 ng/mL to 9.77 ng/mL (1/2 dilution) in pooled cynomolgus serum (Seralab, CYNSRM) to give 12 standards including a blank. Standards, quality controls and samples were diluted at 1 in 50 MRD (minimum required dilution) in ELISA assay buffer (PBS + 0.1% BSA) and were added to the coated 96-well high-binding plates at 50 µL/well. The plate was incubated for 1 hour at room temperature, after which plates were washed 3× with PBS-Tween. 50 µL biotinylated goat anti-human IgG (Southern Biotech) at 1 µg/mL was added to the plate. The plate was incubated for 1 hour at

room temperature, after which plates were washed 3× with PBS-Tween. PD-L1 binding was detected using streptavidin labelled Europium (Perkin Elmer) diluted 1/1000 in DELFIA assay buffer (Perkin Elmer). Plates were washed with TBS (Tris buffered saline)-Tween (0.1% v/v) and 50 µL/well of DELFIA Enhancement solution (Perkin Elmer) was added to the plate. Time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Concentrations were determined using GraphPad Prism software by interpolating from a standard curve fitted using a four-parameter logistic equation (Equation 4). Results are shown in Figures 21a and 21b.

b) PK assay for detection of intact immunocytokine (antibody fused to IL-2)

50 µL/well of human PD-L1 Flag His (Seq ID No:505 in house) diluted to 3 µg/mL in PBS (Sigma, P3813-10PAK) was adsorbed to 96-well, low auto-fluorescent, high protein binding plates (Costar) overnight at 4 °C. Excess protein was removed by washing 3× with 300 µL/well PBS-Tween (0.1% v/v) and the wells were blocked with 1% w/v bovine serum albumin (BSA, Sigma) in PBS for 1 hour at room temperature, after which plates were washed 3× with PBS-Tween. Antibodies were diluted from 50,000 ng/mL to 617.3 ng/mL in pooled cynomolgus serum (Seralab, CYNSRM) to give 10 standards including a blank. Standards, quality controls and samples were diluted at 1 in 20 MRD in ELISA assay buffer (PBS + 0.1% BSA) and were added to the coated 96-well high-binding plates at 50 µL/well. The plate was incubated for 1 hour at room temperature, after which plates were washed 3× with PBS-Tween. 50 µL biotinylated anti-human IL-2 (Peprotech) at 2 µg/mL was added to the plate. The plate was incubated for 1 hour at room temperature, after which plates were washed as described previously. Binding was detected using streptavidin labelled Europium (Perkin Elmer) diluted 1/1000 in DELFIA assay buffer (Perkin Elmer). Plates were washed with TBS (Tris buffered saline)-Tween (0.1% v/v) and 50 µL/well of DELFIA Enhancement solution (Perkin Elmer) was added to the plate. Time-resolved fluorescence was measured at 615 nm on an Envision plate reader (PerkinElmer). Concentrations were determined using GraphPad Prism software by interpolating from a standard curve fitted using a four-parameter logistic equation. Results are shown in Figures 21c and 21d.

Results summary

No signs of overt IL-2 mediated toxicity (fever, vascular leak, diarrhoea) were observed after dosing. Lymphocyte numbers increased over the duration of the study with the different immunocytokine constructs. The constructs with the greatest truncations induced the lowest levels of lymphocyte expansion; little expansion was observed with 1D05 LC D1-9 ICK or 1D05 LC D1-8 ICK over the seven-day period, whereas 1D05 LC D9-7 ICK and the full-length IL-2 induced significant expansion. The lymphopenia observed at day 2 with some constructs is indicative of lymphocyte margination out of the circulation. This is followed by a rebound lymphocytosis which can be seen at day 5 (Figure 16).

Administration of immunocytokine constructs did not cause significant anaemia (Figure 17). Around a 20% reduction in haemoglobin, haematocrit and red blood cell levels was observed at day

7 with the most active constructs (1D05 HC IL-2 ICK, 1D05 LC IL2 ICK and 1D05 LC D9-7 ICK), and around a 10% reduction with the other constructs. This agrees with anecdotal evidence from studies with IL-2 heavy chain immunocytokines. Thrombocytopenia (reduced platelet count) was not observed.

IL-2 was strongly increased 3 days post-dosing, indicative of production by activated T-cells. However, there is a possibility that the assay is cross-reactive for human IL-2 and so could also detect the immunocytokine. There was no clear up- or down-regulation of any of the other cytokines post-dosing, although there was a trend for down-regulation of IL-8 levels (Figure 18). Levels of soluble CD25, which is a biomarker of T-cell activation, were strongly increased 3 days after dosing with immunocytokines (Figure 19). Levels of soluble CD25 correlated with the stimulatory activity of the immunocytokines described in Example 13.

Dosing with immunocytokines increases the number of activated T-cells in the blood (Figure 20). When dosed with 1D05 LC IL-2 ICK, total $CD4^+$ and $CD8^+$ cell numbers are increased, but $CD69^+$ (early activation) and $CD25^+$ (later activation) subsets are greatly increased, compared with pre-treatment levels. The increase in cell numbers is less striking for the truncated constructs. No significant changes in B-cell, NK cell or neutrophil numbers were observed, with a moderate increase in monocyte numbers. Data for the animal dosed with 1D05 LC D9-7 ICK is not available, due to clotting of the sample.

The light chain (LC) fusions have a longer half-life than the heavy chain (HC) fusion, which agrees with previous data in mouse (Gillies SD, Protein Engineering, Design and Selection, 26:10: 561-569, 2013). The half-life of 1D05 LC IL-2 ICK was around 8 hours, and the half-life of the truncated IL-2 constructs was around two-fold longer (Figure 21a and 21b). The increased half-life of immunocytokines with truncated IL-2, compared with full-length IL-2, may reflect reduced binding to IL-2 receptors.

A modified assay was used to detect intact immunocytokine i.e. antibody fused to IL-2 (Figure 21c and 21d). This result shows that the IL-2 part of the molecule remains fused and is not cleaved.

Example 19 - Extended single dose study in cynomolgus monkeys

To determine the duration of lymphocytosis, and obtain more detailed analysis of T-cell subsets, an extended single dose study will be performed (study number HQ52PV). Female cynomolgus monkeys are dosed with 1 mg/kg immunocytokine as per Example 18 and monitored over at least 14 days. Cytokines will be analysed on days 1, 3, 7, 10 and 14, and pre-treatment. Haematology measurements will be performed on days 2, 5, 7, 10 and 14, and pre-treatment. Detection of soluble CD25 will be performed on days 3, 7 and 10, and pre-treatment. CD127 will be added to the immunophenotyping panel, to allow for detection of regulatory T-cells ($CD3^+$ $CD4^+$ $CD25^{hi}$

CD127^{lo}), and analysis will be performed on days 1, 5, 7, 10 and 14, and pre-treatment. PK analysis will be performed as before. Treatment groups are shown in Table 14.

Table 14: Treatment groups and animal numbers

Phase	Animal	Test Item
3	378	1D05 LC IL-2 ICK
3	379	1D05 LC D9-7 ICK
3	380	1D05 LC D9-2 ICK
3	381	1D05 LC D1-8 ICK
3	382	1D05 LC D5-9 ICK

No signs of overt IL-2 mediated toxicity (fever, vascular leak, diarrhoea) were observed after dosing. Lymphocyte numbers peaked at day 7 with all immunocytokine constructs. The constructs with the greatest truncations induced the lowest levels of lymphocyte expansion; the least expansion was observed with 1D05 LC D1-8 ICK, whereas 1D05 LC D9-7 ICK and the full-length IL-2 induced the greatest expansion. The lymphopenia observed at day 2 with some constructs is indicative of lymphocyte margination out of the circulation. This is followed by a rebound lymphocytosis (Figure 28). Levels of soluble CD25, which is a biomarker of T-cell activation, peaked 3 days after dosing with immunocytokines (Figure 29). Levels of soluble CD25 correlated with the stimulatory activity of the immunocytokines described in Example 13.

Administration of immunocytokine constructs did not cause significant anaemia (Figure 30). A 10-20% reduction in haemoglobin, haematocrit and red blood cell levels was observed with the immunocytokine constructs. Haemoglobin levels remained lower over the entire time course in the animal dosed with 1D05 LC D1-8 ICK. Mild thrombocytopenia was observed with the two most active constructs at day 5, but levels recovered after this timepoint.IL-2 was strongly increased 3 days post-dosing, indicative of production by activated T-cells. However, there is a possibility that the assay is cross-reactive for human IL-2 and so these levels reflect the presence of the immunocytokine. There was no clear up- or down-regulation of any of the other cytokines post-dosing (Figure 31).

As observed previously in Example 18, the half-life of 1D05 LC IL-2 ICK was around 8 hours, and the half-life of the truncated IL-2 constructs correlated with the size of the truncation (Figure 32). The immunocytokine construct containing the longest truncation, D1-8, had the longest half-life, of approximately 24 hours. The increased half-life of immunocytokines with truncated IL-2, compared with full-length IL-2, may reflect reduced binding to IL-2 receptors.

Expansion of $CD4^+$ and $CD8^+$ T-cells is shown in Figure 33. As observed for the automated cell counts, the degree of expansion correlates well with the size of the IL-2 truncation, the greatest expansion of both T-cell subsets observed in the animal dosed with 1D05 LC ICK D9-7.

Example 20 – Binding to cell endogenously expressed hPD-L1 and neutralisation of hPD-L1 binding to PD-1 and CD80

Lead antibodies are tested for ability to bind to ES2 cells endogenously expressing hPD-L1 as well as the neutralisation of PD-L1/PD-1 interaction and PD-L1/CD80 interactions. ES2 cells endogenously expressing hPD-L1 (ATCC) are diluted in FACS buffer (PBS 1% BSA 0.1% sodium azide) and distributed to three 96-well, V-bottom plate (Greiner) at a density of 0.5-1×10^5 cells per well. Cells are washed with 150 µL PBS and centrifuged at 300 g for 3 minutes. Supernatant is aspirated and 150 µL PBS added. This wash step is repeated.

To plate 1 (PD-L1 binding), 25 µL lead antibody, reference antibody or control antibody diluted in FACS buffer is added to the washed cells. 25 µL FACS buffer is added and cells are incubated at 4 °C for 60 minutes. 150 µL FACS buffer is added and cells washed as described above. To detect anti-PD-L1 antibody binding, anti-human PE (Jackson ImmunoResearch) is diluted 1/500 in FACS buffer and 50 µL of this mixture added to cells. Cells are incubated 4 °C for 60 minutes. Cells are washed twice with 150 µL FACS buffer, centrifuging at 300 g for 3 minutes after each wash step and aspirating supernatant. Cells are fixed by addition of 50 µL 4% paraformaldehyde and overnight incubation at 4 °C. Cells are washed once as above and resuspended in FACS buffer for analysis. PE signal intensity (geometric mean) is measured by flow cytometry using a Beckman Coulter Cytoflex instrument. Data is plotted as geometric mean values without further calculation.

To plate 2 (PD-1 neutralisation) 25 µL lead antibody, reference antibody or control antibody diluted in FACS buffer is added to the washed cells. 25 µL of biotinylated human PD-1 (in-house, Fc-tagged, SEQ ID No:6) is added and cells are incubated at 4 °C for 60 minutes. Biotinylation is performed in-house using Lightning Link conjugation kit (Innova Biosciences) according to manufacturer's instructions. 150 µL FACS buffer is added and cells washed as described above. To detect biotinylated PD-1, Streptavidin-Alexa Fluor 647 (AF647, Jackson ImmunoResearch) is diluted 1/500 in FACS buffer and 50 µL of this mixture added to cells. Cells are incubated at 4 °C for 60 minutes. Cells are washed twice with 150 µL FACS buffer, centrifuging at 300 g for 3 minutes after each wash step and aspirating supernatant. Cells are fixed, washed and resuspended for analysis as above. APC signal intensity (geometric mean) is measured by flow cytometry. Data is plotted as geometric mean values without further calculation.

To plate 3 (CD80 neutralisation) 25 µL lead antibody, reference antibody or control antibody diluted in FACS buffer is added to the washed cells. 25 µL biotinylated human CD80 (Fc tagged, R&D Systems, 140-B1) is added and cells are incubated at 4 °C for 60 minutes. All other steps are performed as per plate 2.

Alternatively, to simultaneously detect binding and neutralisation, ES2 cells expressing hPD-L1 are diluted in FACS buffer and are distributed to two 96-well, V-bottom plate (Greiner) at a density of 0.5-1×10^5 cells per well. Cells are washed with 150 µL PBS and centrifuged at 300 g for 3 minutes. Supernatant is aspirated and 150 µL PBS added. This wash step is repeated.

25 µL lead antibody, reference antibody or control antibody diluted in FACS buffer is added to the washed cells. 25 µL biotinylated human PD-1 (R&D Systems, 8986-PD-100, his-tagged) or CD80 (R&D Systems, 9050-B1-100, his-tagged) is added and cells are incubated at 4 °C for 60 minutes. 150 µL FACS buffer is added and cells washed as described above. To detect biotinylated PD-1 or CD80 and anti-PD-L1 antibody binding, streptavidin-AF647 and anti-human PE are each diluted 1:500 in FACS buffer and 50 µL of this mixture added to cells. Cells are incubated at 4 °C for 60 minutes. Cells are washed twice with 150 µL FACS buffer, centrifuging at 300 g for 3 minutes after each wash step and aspirating supernatant. Cells are fixed, washed and resuspended for analysis as above. PE and APC signal intensity (geometric mean) are measured by flow cytometry. Data is plotted as geometric mean values without further calculation. Alternatively, an anti-his tag antibody conjugated to APC (R&D Systems) may be used to detect PD-1 or CD80, or PD-1 and CD80 may be directly labelled with AF647.

Example 21 – Testing of lead anti-PD-L1 antibodies in reporter cell bioassay

The ability of anti-PDL1 antibodies to neutralise PD-L1/PD-1 interaction on cells will be determined using a bioluminescence cell based assay (Promega®). PD-L1 aAPC/CHO-K1 cells, transfected with PD-L1 and a cell surface protein designed to promote TCR activation, are co-cultured with PD-1 expressing Jurkat cells. These cells also present a NFAT induced luciferase responsive element. Co-culture of the two cell types in the presence of an antibody able to block PD-1-PD-L1 interaction activates TCR signaling and NFAT-mediated luciferase activity.

The assay is run according to manufacturer's recommendations. Briefly, PD-L1 aAPC/CHO-K1 cells are cultured overnight in Hams F12 medium supplemented with 10% hiFBS. The next day, media is removed, effector PD-1 Jurkat cells and anti-PD-L1 antibodies are added to assay plates for 6 hours at 37 °C in RPMI 1640 supplemented with 1% hiFBS. Plates are read following 10 minutes of incubation with Bio-Glo™ on the Envision plate reader using luminescence settings. Antibody-induced luciferase activity is represented as fold induction compared to assay signal of wells showing background levels of response as defined by Equation 8. EC_{50} values are calculated using a 4-parameter logistic fit (Equation 4).

Equation 8

$$\text{Fold induction} = \text{sample well/basal luciferase response}$$

Basal luciferase response = value from wells containing PD-L1 CHO-K1 cells and PD-1 Jurkat cells

Example 22 – Pharmacokinetic study of lead antibodies in hPD-L1 expressing mice

Lead antibodies, in human IgG1 effector enabled format (i.e. having a constant region of wild type IgG1, Seq ID No:341), are dosed intra-peritoneally at 10 mg/kg in mice expressing human PD-L1, eight mice per antibody. Blood samples are taken pre-treatment and at 2, 4, 8, 12, 24, 48, 72, 96,

192, 336, 508 and 672 hours. Serum is prepared and samples frozen until analysis. Samples will be analysed according to the method described for detection of antibody in Example 18 with the following exception: serum from C57BL/6 mice will be used as the vehicle in which to prepare standard curves and blanks. Minimum required dilution will differ from Example 18 due to the larger dose administered; this will be determined empirically.

Example 23 - Pharmacokinetic study of lead antibodies in non-human primates

Lead antibodies, in human IgG1 effector enabled format (i.e. having a constant region of wild type IgG1, Seq ID No:341), are dosed intravenously at 10 mg/kg in male cynomolgus monkeys, three animals per antibody. Blood samples are taken pre-treatment and at 2, 4, 8, 12, 24, 48, 72, 96, 192, 336, 508 and 672 hours. Serum is prepared and samples frozen until analysis. Samples will be analysed according to the method described for detection of antibody in Example 18. Minimum required dilution will differ from Example 18 due to the larger dose administered; this will be determined empirically.

Example 24: Lead antibody activity in a mouse B cell:T-cell hybridoma assay.

Antibodies were tested in a murine B cell:T-cell hybridoma co-culture assay to assess induction of IL-2. 50 µL of human PD-L1 (SEQ ID No:1) transfected LK35.2 mouse B-lymphocyte hybridoma cells (ATCC) prepared in DMEM (Gibco) supplemented with 1% Foetal Bovine Serum (Gibco) were treated with 10 µM $Ovalbumin_{323-329}$ peptide (Thermo Scientific) and dispensed at a density of 2×10^4 cells/well in a 96-well tissue culture treated plate (Costar). Ovalbumin peptide loaded cells were then mixed with 50 µL 1:3 titration series of anti-PD-L1 antibodies or anti- ICOS/PD-L1 bi-specific antibodies in a mAb^2 ™ format from 30 nM for 9 concentration points in DMEM supplemented with 1% Foetal Bovine Serum.

Following 1 hour incubation at 37 °C 5% CO_2, 100 µL of murine T-helper hybridoma cell line DO-11-10 (National Jewish Health) cultured overnight in DMEM (Gibco) supplemented with 1% Foetal Bovine Serum (Gibco) were added to assay plate at 2×10^4 cells/well. LK35.2/DO-11-10 co-culture was incubated overnight at 37 °C 5% CO_2 before supernatant was collected to assess production of mouse IL-2. Cells treated with 1 or 0.1× working stock of cell stimulation cocktail (eBioscience) were used as positive control for murine IL-2 production.

Mouse IL-2 quantification was performed using the mouse IL-2 Duoset ELISA kit (R&D Systems) following manufacturer's protocol, modified to include streptavidin-Europium as the detection reagent (DELFIA®). Briefly, assay plates were coated overnight at 4 °C with provided capture antibody prepared in PBS at 1 µg/mL. Plates were washed three times with PBS-Tween (0.1% v/v) before adding 200 µL of 1% w/v bovine serum albumin (BSA, Sigma) in PBS for 1 hour at room temperature. 50 µL cell supernatants were added to assay plates following a washing step performed as described previously. Following one hour incubation, 50 µL of provided detection antibody at 200 µg/mL prepared in 0.1% w/v BSA in PBS was added and plates were incubated for a further hour. Plates were washed as described above and 50 µL of DELFIA® Eu-N1 streptavidin diluted 1:500 from

stock solution in DELFIA® assay buffer (Perkin Elmer) were added to all wells for 1 hour. An additional washing step was performed using DELFIA wash buffer (0.5 M Tris HCL (Gibco), 1% Tween v/v (Sigma) ® Enhancement Solution (Perkin Elmer). The plate was incubated for 5 minutes at room temperature protected from the light and read at 615 nm using appropriate settings for DELFIA® time resolved fluorescence on an Envision plate reader (Perkin Elmer). The concentration of mouse IL-2 was interpolated from a standard curve run alongside test samples. Final plotted values were calculated using Equation 9, where background signal was calculated using assay signal of co-culture cells treated with 50 µL of media only. Results are shown in Figure 23. All antibodies potently enhance production of IL-2 in this co-culture system.

Equation 9 = Mouse IL-2 (pg/mL) – Background

Table 15: EC_{50} values for induction of IL-2 by of PD-L1 antibodies in a murine T cell hybridoma assay

Antibody name	EC_{50} (nM)		
	n=1	n=2	n=3
1D05	0.33	0.21	0.21
84G09	0.24	0.14	0.17
413G05	0.29	0.11	0.29
414B06	0.59	0.30	0.18
416E01	0.19	0.15	0.14
benchmark 2	0.26	0.13	0.13

Table 16: EC_{50} values for induction of IL-2 by ICOS/PD-L1 bi-specific mAb^2 ™ antibodies in a murine T cell hybridoma assay

Bispecific antibody name	EC_{50} (nM)		
	n=1	n=2	n=3
ICOS/PD-L1 bispecific 1	0.386	n/a	0.888
Hybrid Control/PD-L1 bispecific	0.247	0.311	0.162
ICOS/PD-L1 bispecific 2	0.338	0.217	0.229
PD-L1 benchmark	0.122	0.128	0.123

Example 25 – Testing of lead antibodies in an activated DC – T-cell mixed lymphocyte reaction

Monocytes were isolated from cryopreserved PBMCs by negative selection methods using a Monocyte Isolation Kit and the MACS™ magnetic separation system (Miltenyi Biotec). Monocytes were resuspended in RPMI 1640 medium containing 10% hiFBS and 100 ng/mL GM-CSF and IL-4 (both Peprotech). Cells were cultured for 5 days in non-TC treated 6-well plates (Greiner) to induce differentiation of DCs, before addition of 100 ng/mL lipopolysaccharide from O55:B5 (Sigma) to activate the DCs. Cells were harvested after 24 hours of activation, and washed once with PBS to remove LPS, and resuspended at 10^6/mL in RPMI 10% hiFBS. Allogeneic $CD3^+$ T-cells were isolated

from cryopreserved PBMC using a Pan T-Cell Isolation kit and the MACS system as above, and resuspended at 2×10^6/mL in RPMI 10% hiFBS. Serial dilutions of selected antibodies (1:3) from 10 nM were prepared in RPMI 10% hiFBS and 50 µL added to 96-well, flat-bottomed TC plates plates in triplicate. DCs (100 µL) and T-cells (50 µL) were added to plates and incubated at 37 °C, 5% CO_2 for five days. Supernatants were removed after three days for measurement of IL-2, and five days for measurement of IFN . Supernatants were stored at -20 °C until use. Cytokine production was measured with the R&D Systems and IL-2 Duoset® ELISA, using DELFIA® Eu-N1 Streptavidin detection. Results are shown in Figure 24.

Example 26 – Multi-dose study of immunocytokines in cynomolgus monkeys

Pharmacology and toxicity of two immunocytokines, 1D05 D9-7 ICK and 1D05 D1-8 ICK (as described in Example 14), will be assessed in a multi-dose study in cynomolgus monkeys. Male juvenile monkeys are dosed with 1 mg/kg/dose according to two different regimens: Regimen 1 – animals dosed on day 0 and day 14; regimen 2 – animals dosed on day 0, 2, 14 and 16. Two animals will be dosed per group and monitored for 28 days. Treatment groups are shown in Table 17.

Table 17: Treatment groups for multi-dose study

Treatment group	Construct	Regimen	Animals per group
1	1D05 D9-7 ICK	1	2
2	1D05 D9-7 ICK	2	2
3	1D05 D1-8 ICK	1	2
4	1D05 D1-8 ICK	2	2

Heart rate, body temperature, respiration rate and blood pressure will be measured 1 hour and 4 hours after dosing. Body weight will be monitored daily. Cytokines will be analysed on days 2, 5, 7, 10, 14, 16, 19, 21, 24 and 28, and pre-treatment. Haematology measurements will be performed on days 2, 5, 7, 10, 14, 16, 19, 21, 24 and 28, and pre-treatment. Detection of soluble CD25 will be performed on days 3, 7 and 10, 17, 21, 24, and pre-treatment. Immunophenotyping will be performed on days 7, 10, 14, 24 and 28, and pre-treatment, according to the panel described in Example 19. Samples for pharmacokinetic (PK) analysis will be taken at the following timepoints at each infusion: pre-treatment, end of infusion, and at 8, 16, 24, 32, 40, 48, 72, and 96 hours.

Example 27: Immunocytokine efficacy study in a syngeneic tumour model

An efficacy study will be performed using a CT-26 mouse tumour model, to compare surrogate immunocytokine activity with unmodified antibody, and to assess the role of effector function. On the day of implantation, BALB/c mice are injected subcutaneously into mice on the rear right flank with 1×10^5 CT-26 cells/animal. Treated groups will receive their first dose of antibody or relevant control (all dosed intraperitoneally at 10 mg/kg) 6 days post implantation of the tumour cells and will be dosed three times a week for a total of two weeks. Tumour development will be monitored three times a week using digital callipers measuring in two dimensions until end of the study. Tumour volumes

(mm^3) will be estimated using a standard formula (L x W^2)/2 (with L being the larger diameter, and W the smaller diameter of the tumour). Mice are kept on studies until their tumours developed to a mean diameter of 12mm or they reached the one humane endpoints outlined in the study protocol. The humane endpoint survival statistics will be calculated using the Kaplan-Meier method with Prism.

Table 18: Treatment groups for efficacy study

Groups	Number of animals	Treatment
1	10	10 mg/kg hybrid control huIgG1$_{LAGA}$ (constant region SEQ ID No:205)
2	10	10 mg/kg hybrid control huIgG1$_{LAGA}$ IL-2
3	10	10 mg/kg anti-PD-L1 huIgG1$_{LAGA}$
4	10	10 mg/kg anti-PD-L1 huIgG1$_{LAGA}$ IL-2
5	10	10 mg/kg anti-PD-L1 huIgG1 (constant region SEQ ID No:340)
6	10	10 mg/kg anti-PD-L1 huIgG1 IL-2

Example 28: Immunocytokine efficacy study in a T-cell: melanoma cell line xenograft model

An efficacy study will be performed using a T-cell: A375 cell line xenograft model in NOD/SCID mice employing a refinement of the methods outlined in R. Stewart *et al.* Briefly HLA-A2 positive donors are selected by staining whole blood using a PE labelled anti-human HLA-A2 antibody (Biolegend), followed by red blood cell lysis and analysis by flow cytometry. Primary human $CD4^+$ and $CD8^+$ T-cells will then be isolated, using an EasySep human $CD4^+$ or $CD8^+$ T-cell enrichment kit, Stemcell Technologies, Cat 19052/3). The $CD4^+$ and $CD8^+$ cells are then cultured separately for 20 days on a monolayer of mitomycin C treated A375 cells in the presence of IL-2 and IL-7. T-cells are plated on a fresh feeder layer of A375 at day 10. On day 20, the cells are cryopreserved and stored in liquid nitrogen till required. The day before implantation, T-cells are thawed and cultured in medium plus cytokines overnight. On the day of implantation, the $CD4^+$ and $CD8^+$ cells are counted and mixed together in a 1:1 ratio. The T-cells are mixed with fresh A375 tumour cells at 1:6 ratio and injected subcutaneously into mice on the rear right flank. Treated groups will receive their dose of antibody, immunocytokine or relevant control (all dosed intraperitoneally at 10 mg/kg) one-hour post implantation of the T-cells and tumour cells. Tumour development will be monitored three times a week using digital callipers measuring in two dimensions until end of the study. Tumour volumes (mm^3) will be estimated using a standard formula (L x W^2)/2 (with L being the larger diameter, and W the smaller diameter of the tumour). Mice are kept on studies until their tumours developed to a mean diameter of 12mm or they reached the one humane endpoints outlined in the study protocol. The humane endpoint survival statistics will be calculated using the Kaplan-Meier method with Prism. This approach will be used to determine which treatment is/are associated with improved survival. Subsequent studies will compare the immunocytokine constructs with different IL-2 activities.

Table 19: Treatment groups for efficacy study

Groups	Number of animals	Treatment
1	10	$2x10^6$ A375 Cells
2	10	$CD4^+/CD8^+$ T cells: A375 Cells
3	10	10 mg/kg hybrid control $CD4^+/CD8^+$ T cells: A375 Cells
4	10	10 mg/kg hybrid control IL-2 $CD4^+/CD8^+$ T cells: A375 Cells
5	10	200,000 IU recombinant human IL-2 $CD4^+/CD8^+$ T cells: A375 Cells ($2x10^6$ A375 Cells)
6	10	10 mg/kg 1D05 $CD4^+/CD8^+$ T cells: A375 Cells ($2x10^6$ A375 Cells)
7	10	10 mg/kg 1D05 LC IL-2 $CD4^+/CD8^+$ T cells: A375 Cells ($2x10^6$ A375 Cells)

Example 29: Activity of lead antibodies in a reporter assay of effector function

The antibody-dependent cell-mediated cytotoxicity (ADCC) activity of selected antibodies was evaluated using an ADCC Reporter Bioassay. ES2 cells (ATCC CRL-1978) endogenously expressing human PD-L1 were co-incubated with effector cells (engineered Jurkat cells stably expressing human – V158, Promega) that produce luciferase in a concentration-dependent manner in the presence of an ADCC-enabled antibody. The soluble luciferase activity is assessed by measuring the luminescence produced as the luciferase transformed a luminogenic substrate into a luminescent product.

Immediately prior to the assay, target cells (ES2) were centrifuged and resuspended in RPMI 1640 + 10% Ultra low IgG FBS (Thermo Fisher Scientific) and plated at 30,000 cells/well (10 µL/well) in 384-well white bottom plates. Jurkat NFAT luciferase reporter (effector) cells were resuspended in RPMI 1640 + 10% Ultra low IgG FBS and added to the target cells at 10,000 cells per well (10µL/well). Eleven three-fold serial dilutions of antibodies were prepared from 2.2nM in RPMI 1640 + 10% Ultra low IgG FBS and added to the target cells (10 µL/well). The plates were incubated overnight at 37 °C, 5% CO_2, after which a luminogenic BioGlo substrate was added directly to the wells (30 µL/well) and luminescence quantified on an Envision (Perkin Elmer) plate reader.

Relative light unit (RLU) values from the raw data (Envision reads) were normalised to 'Fold of induction using the following equation:

Equation 10:

$$\text{fold of induction} = \frac{(\text{RLU (induced)} - \text{RLU (background)})}{\text{RLU (background)}}$$

Data was plotted in GraphPad Prism, using a 4-parameter logistic fit, and a representative experiment is shown in Figure 34. Results are summarised in Table 20. All antibodies tested induced

luminescence, suggesting that all have the capacity to induce killing of target cells by ADCC. Although EC_{50} values are generally similar, 416E01 induces a highest maximum level of luminescence.

Table 20: Summary of data from reporter cell assay

Antibody name	EC_{50} (pM)			max fold induction		
	n=1	n=2	n=3	n=1	n=2	n=3
1D05	24.14	21.53	34.71	13.70	16.69	25.04
84G09	24.95	15.30	25.90	16.33	22.21	33.82
413G05	21.92	20.87	27.52	13.22	16.41	23.45
414B06	19.08	15.02	24.24	10.94	20.15	31.51
416E01	79.98	10.58	22.86	32.11	33.76	60.16
benchmark 2	24.81	10.56	24.93	19.55	31.88	43.23

Example 30: Binding of lead antibodies to cell-expressed cynomolgus PD-L1

CHO-S cells transfected with cynomolgus PD-L1 were diluted in FACS buffer (PBS + 1% w/v BSA + 0.1% w/v sodium azide) and were distributed to a 96-well V-bottom plate (Greiner) at a density of 1×10^5 cells per well. Antibody titrations were prepared from 133 nM working concentration as a 1/3 dilution series in FACS buffer. Plates were centrifuged at 300 x for 3 minutes and supernatant aspirated. 50 µL per well of antibody titrations were added to cells and incubated at 4 °C for 1 hour. Cells were washed with 150 µL of PBS and centrifuged at 300 g for 3 minutes. Supernatant was aspirated and 150 µL PBS added per well. This wash step was repeated. Presence of bound antibody was detected by addition of 50 µL per well of anti-Human IgG AlexaFluor 647 (Jackson ImmunoResearch) diluted 1/500 in FACS buffer. Cells were incubated for 1 hour at 4 °C in the dark. Cells were washed as previously described. To fix cells, 50 µL per well of 4% v/v paraformaldehyde was added and cells incubated for 20 minutes at 4 °C, cells were pelleted by centrifugation at 300 x and the plates resuspended in 75 µL PBS. Geometric mean was measured by flow cytometry using a Beckman Coulter CytoFLEX instrument. Alexa Fluor 647 was excited by a 637nm laser and detected in the Red channel with a 660/20 bandpass filter. Data was analysed using FlowJo software and is shown in Figure 35. All antibodies bind to cynomolgus PD-L1 expressed on cells.

Example 31: Binding to CHO-expressed hPD-L1 and neutralisation of hPD-L1 binding to PD-1 and CD80

CHO cells untransfected (referred to as WT) or transfected with hPD-L1 expressing recombinant human PD-L1 were diluted in FACS buffer (PBS 1% BSA 0.1% sodium azide) and distributed to three 96-well, V-bottom plate (Greiner) at a density of 1×10^5 cells per well. Cells are washed with 150 µL PBS and centrifuged at 300 g for 3 minutes. Supernatant is aspirated and 150 µL PBS added. This wash step is repeated.

To plate 1 (PD-L1 binding), lead antibody, reference antibody or control antibody titrations were prepared from 150 nM working concentration as a 1/3 dilution series in FACS buffer. 50 µL of antibody diluted in FACS buffer is added to the washed cells and incubated at 4 °C for 60 minutes.

150 µL FACS buffer is added and cells washed as described above. To detect anti-PD-L1 antibody binding, anti-human PE (Jackson ImmunoResearch) is diluted 1/500 in FACS buffer and 50 µL of this mixture added to cells. Cells are incubated 4 °C for 60 minutes. Cells are washed twice with 150 µL FACS buffer, centrifuging at 300 for 3 minutes after each wash step and aspirating supernatant. Cells are fixed by addition of 100 µL 4% paraformaldehyde and 30 mins at 4 °C. Cells are washed once as above and resuspended in 100 µL FACS buffer for analysis. PE signal intensity (geometric mean) is measured by flow cytometry using a Beckman Coulter Cytoflex instrument. Data is plotted as geometric mean values without further calculation.

To plate 2 (PD-1 neutralisation), biotinylated human PD-1-Fc (in-house expressed, Seq ID No:6) were prepared as a titration from 1 µM final assay concentration (FAC), 1/2 dilution series in FACS buffer. Lead antibody, reference antibody or control antibody titrations were prepared from 300 nM working concentration, 150 nM FAC, as a 1/3 dilution series in FACS buffer. Biotinylated PD-1 were diluted in FACS buffer to 60 nM working concentration, 30 nM FAC. 25 µL PD-1 and 25 µL antibody solution (or 50 µL of PD1 titration) were added to cells and incubated at 4 °C for 1 hour. Biotinylation is performed in-house using Lightning Link conjugation kit (Innova Biosciences) according to manufacturer's instructions. 150 µL FACS buffer is added and cells washed as described above. To detect biotinylated PD-1, Streptavidin-Alexa Fluor 647 (AF647, Jackson ImmunoResearch) is diluted 1/500 in FACS buffer and 50 µL of this mixture added to cells. Cells are incubated at 4 °C for 60 minutes. Cells are washed twice with 150 µL FACS buffer, centrifuging at 300 g for 3 minutes after each wash step and aspirating supernatant. Cells are fixed, washed and resuspended for analysis as above. APC signal intensity (geometric mean) is measured by flow cytometry using a Beckman Coulter CYTOFLEX instrument. Data is plotted as percentage of receptor binding.

To plate 3 (CD80 neutralisation) Biotinylated human CD80 (Fc tagged, R&D Systems, 140-B1) were prepared as a titration from 1 µM final assay concentration (FAC), 1/2 dilution series in FACS buffer. Lead antibody, reference antibody or control antibody titrations were prepared from 300 nM working concentration, 150 nM FAC, as a 1/3 dilution series in FACS buffer. Biotinylated CD80 were diluted in FACS buffer to 60 nM working concentration, 30 nM FAC. 25 µL CD80 and 25 µL antibody solution (or 50 µL of CD80 titration) were added to cells and incubated at 4 °C for 1 hour. All other steps are performed as per plate 2.

Equation 11: Percentage of receptor binding (flow cytometry)

Based on geometric mean fluorescence

$$\% \text{ of specific binding} = \frac{\text{sample value - non-specific binding}}{\text{total binding - non-specific binding}} \times 100$$

Total binding = biotinylated PD-1 or CD80 only (Hybrid Control at 150nM FAC)

Non-specific binding = no PDL1 binding, (benchmark 2 at 150nM FAC)

Results are shown in Figure 36 and in Table 21. All lead antibodies neutralise interactions of PD-L1 with both PD-1 and CD80.

Table 21: Summary of neutralisation of PD-1 and CD80 interactions with PD-L1

Antibody name	PD-1 IC_{50} (nM)		CD80 IC_{50} (nM)	
	n=1	n=2	n=1	n=2
1D05	1.27	1.46	1.15	1.46
84G09	0.89	1.41	1.11	1.41
413G05	1.07	1.17	1.09	1.17
414B06	0.95	1.22	1.26	1.22
416E01	0.81	0.89	1.04	0.89
benchmark 2	1.36	1.46	1.27	1.46

Example 32: Effector function of lead antibodies in a primary NK cell ADCC assay

Activity of antibodies to kill PD-L1 expressing target cells via ADCC (antibody-dependent cell-mediated cytotoxicity) is measured by DELFIA cytotoxicity assay (Perkin Elmer) using human primary NK cells as effectors and ES2 as PD-L1$^+$ target cells.

This method is based on loading target cells with an acetoxymethyl ester of fluorescence enhancing ligand (BATDA) which quickly penetrates the cell membrane. Within the cell the ester bonds are hydrolysed to form a hydrophilic ligand (TDA) which no longer passes the membrane. After cytolysis the ligand is released and can be detected by addition of Europium which forms with the BATDA a highly fluorescent and stable chelate (EuTDA). The measured signal correlates directly with the degree of cell lysis.

ES2 cells are resuspended at 10^6/mL in assay medium (RPMI +10% ultra-low IgG FBS, from Gibco) and loaded with 5 L/mL of BATDA reagent (Perkin Elmer) for 30 min at 37 °C. Cells were then washed 3 times with 50 mL PBS (300 x g for 5 min) and resuspended at $8x10^5$/mL in assay medium supplemented with 2 mM Probenecid (Life technologies) to reduce BATDA spontaneous release from the cells. Supernatant from ES2 cells immediately after final resuspension in assay medium is used as background control.

Seven serial three-fold dilutions of PD-L1 antibodies and isotype controls are prepared in assay media + × final concentration). NK cells are negatively isolated from fresh PBMC using Human NK Cell Isolation Kit (Miltenyi Biotec) as per manufacturer's instructions and resuspended at $4x10^6$/mL in assay medium + 2 mM Probenecid. 50 L of diluted Ab, 50 L of BATDA L L of assay medium +2 mM Probenecid (final volume of L/well) are added in each well to give an effector: target ratio of 5:1. Wells containing ES cells only or ES2 cells + DELFIA lysis buffer (Perkin Elmer) are used to determine spontaneous and maximum release, respectively.

Cells are incubated at 37 °C, 5% CO2 for 4 hours before centrifugation of plates for 5 min at 500 ×g, and transfer of 50 L of cell-free supernatant into a DELFIA microtitration Plates (Perkin

L of DELFIA Europium solution (Perkin Elmer) was added to the supernatants and incubated for 15 min at Room Temperature. Fluorescent signal was then quantified with an EnVision plate reader (PerkinElmer).

Background counts are subtracted from all experimental counts. Specific release is calculated according to the following equation:

Equation 12:

$$\% \text{ specific release} = \frac{(\text{experimental release} - \text{spontaneous release})}{(\text{maximum release} - \text{spontaneous release})} \times 100$$

All references cited herein, including patents, patent applications, papers, text books and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated herein by reference in their entirety.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The foregoing description and Examples detail certain preferred embodiments of the invention. It will be appreciated, however, that the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

It will be understood that particular configurations, aspects, examples, clauses and embodiments described herein are shown by way of illustration and not as limitations of the invention. Any part of this disclosure may be read in combination with any other part of the disclosure, unless otherwise apparent from the context.

		NCBI number: NP_054862.1	**FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAA LIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQI TDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSE HELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRIN TTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERT**
		NCBI number: XP_014973154.1	MGWSCIILFLVATATGVHSM**FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDL TSLIVYWEMEDKNIIQFVHGEEDLKVQHSNYRQRAQLLKDQLSLGNAAL RITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVT SEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLLNVTSTLR INTTANEIFYCIFRRLDPEENHTAELVIPELPLALPPNERT**
			MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYW EMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYR CMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSS DHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPE
			MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYW EMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYR CMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSS DHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPE **CPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**
			MGWSCIILFLVATATGVHSMFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLTSLIV YWEMEDKNIIQFVHGEEDLKVQHSNYRQRAQLLKDQLSLGNAALRITDVKLQDAG VYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQAEGYPKAEVI WTSSDHQVLSGKTTTTNSKREEKLLNVTSTLRINTTANEIFYCIFRRLDPEENHTAE

		sequence derived from cDNA as	MGWSCIILFLVATATGVHSLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSE SFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARR NDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQ_____ **EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT** **PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS** **VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP** **SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG** **SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP**
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	
			EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ IGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFD
		Nucleic acid sequence of V	CAaGAAAAAGCTTGCCGCCACCATGGAGTTTGGGCTGAGCTGGATTTTCCTTTT GGCTATTTTAAAAGGTGTCCAGTGTGAAGTACAATTGGTGGAGTCCGGGGGAG GCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCA CCTTTGATGATTATGCCATGCACTGGGTCCGACAAACTCCAGGGAAGGGCCTGG AGTGGGTCTCAGGTATAAGTTGGAAGAGTAATATCATAGGC TGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGC AAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTATTGTGCAAGAGATA TAACGGGTTCGGGGAGTTATGGCTGGTTCGACCCCTGGGGCCAGGGAACCCTG GTCACCGTCTCCTCAGCCAAAACGACACCCCCATCTGTCTATCCACTGGCCCCTG AATCTGCTAAAACTCAGCCTCCG
		Amino acid sequence of 84G09 heavy chain (mutations from	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWVSGISWK SNIIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFD PWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG

		ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESK YGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSL	
		GAAGTGCAGCTGGTGGAATCTGGGCGGCGGACTGGTGCAGCCTGGCAGATCCCT GAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCGACGACTACGCTATGCACTG GGTGCGACAGACCCCTGGCAAGGGCCTGGAATGGGTGTCCGGCATCTCCTGGA AGTCCAACATCATCGGCTACGCCGACTCCGTGAAGGGCCGGTTCACCATCTCCC GGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACAGCC ACACCGCCCTGTACTACTGCGCCAGAGACATCACCGGCTCCGGCTCCTACGGAT GGTTCGATCCTTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCTGCCAGCACCA AGGGCCCCTCTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAA CAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGT CCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGC AGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCT GGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGT GGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTG TCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCC ATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGA TGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGA AGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCG GGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGT ACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCT CCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGCA GGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCT ACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACT ACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAA GCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGT GATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCC		
			Amino acid sequence of CDRL1	
			Amino acid sequence of CDRL2	

	Amino acid sequence of CDRL3		
	Amino acid sequence of CDRL1		
	Amino acid sequence of CDRL2		
	Amino acid sequence of CDRL3		
		DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKPLIYVASSLQS GVPSSFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSNPITFGQGTRLEIK	
	Nucleic acid sequence of V	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCCCCTGATCTATGTTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACT CTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGA GTTACAGTAATCCGATCACCTTCGGCCAAGGGACACGACTGGAGATCAAA	
	Amino acid sequence of 84G09	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKPLIYVASSLQS GVPSSFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSNPITFGQGTRLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
	Nucleic acid sequence of 84G09	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCCCCTGATCTATGTTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGTTTCAGTGGCAGTGGA CTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGA GTTACAGTAATCCGATCACCTTCGGCCAAGGGACACGACTGGAGATCAAACGTA CGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGT CCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCA AGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAATCCG TGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCC TGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACC AGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT	
	Amino acid sequence of CDRH1		
	Amino acid sequence of CDRH2		

	Amino acid sequence of CDRH3	
	Amino acid sequence of CDRH1	
	Amino acid sequence of CDRH2	
	Amino acid sequence of CDRH3	
	1D05 (mutations from germline	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ RDNAKNSLYLQMNSLRAEDTALYYCAKDMKGSGTYGG
		AAGCTTGCCGCCACCATGGAGTTTGGGCTGAGCTGGATTTTCCTTTTGGCTATT TTAAAAGGTGTCCAGTGTGAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGT GCAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGA TGATTATGCCATGCACTGGGTCCGGCAAGTTCCAGGGAAGGGCCTGGAATGGG TCTCAGGCATTAGTTGGATTCGTACTGGCATAGGCTATGCGGACTCTGTGAAGG GCCGATTCACCATTTTCAGAGACAACGCCAAGAATTCCCTGTATCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGATATGAAGGG TTCGGGGACTTATGGGGGGTGGTTCGACACCTGGGGCCAGGGAACCCTGGTCA CCGTCTCCTCAGCCAAAACAACAGCCCCATCGGTCTATCCACTGGCCCCTGC
	Amino acid sequence of 1D05	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWVSGISWI RTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYCAKDMKGSGTYGGW FDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
	Nucleic acid sequence of 1D05	GAAGTGCAGCTGGTGGAATCTGGGGGCGGACTGGTGCAGCCTGGCAGATCCCT GAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCGACGACTACGCTATGCACTG GGTGCGACAGGTGCCAGGCAAGGGCCTGGAATGGGTGTCCGGCATCTCTTGGA TCCGGACCGGCATCGGCTACGCCGACTCTGTGAAGGGCCGGTTCACCATCTTCC GGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACAGCC ACACCGCCCTGTACTACTGCGCCAAGGACATGAAGGGCTCCGGCACCTACGGCG GATGGTTCGATACTTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCTGCCAGCA

		CCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCG GAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCG TGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGC TGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCT CTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAA GGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCC TTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAA CTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGT GGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGT GGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTA CCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAG AGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCA TCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTA GCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCT TCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACA ACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAG CAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAA CGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAG
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL2	
	Amino acid sequence of CDRL3	
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL2	
	Amino acid sequence of CDRL3	
	1D05(mutations from germline	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGTRLEIK
	Nucleic acid sequence of V	AAAGCTTGCCGCCACCATGAGGCTCCCTGCTCAGCTTCTGGGGCTCCTGCTACT CTGGCTCCGAGGTGCCAGATGTGACATCCAGATGACCCAGTCTCCATCCTCCCT

		AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCAT TAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAACTCCT GATCTATGTTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAG TGGATCTGGGACAGATTTCACTCTCACTATCAGCAGTCTGCAACCTGAAGATTTT GCAACTTACTACTGTCAACAGAGTTACAGTACCCCGATCACCTTCGGCCAAGGG ACACGTCTGGAGATCAAACGTACGGATGCTGCACCAACT	
	Amino acid sequence of 1D05	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYVASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGTRLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
		GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCTGCTTCCGTGGGCGACAGA GTGACCATCACCTGTCGGGCCTCCCAGTCCATCTCCTCCTACCTGAACTGGTATC AGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGTGGCCAGCTCTCTGC AGTCCGGCGTGCCCTCTAGATTCTCCGGCTCTGGCTCTGGCACCGACTTTACCC GACCATCAGCTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGT CCTACTCCACCCCTATCACCTTCGGCCAGGGCACCCGGCTGGAAATCAAACGTA CGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGT CCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCA AGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAAC TGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCC TGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACC AGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT		
	Amino acid sequence of 1D05 heavy chain with V to A back mutation in framework region to germline highlighted with IgG1 disabled (LAGA) constant region	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ_ RTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYCAKDMKGSGTYGGW FDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV _____PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF _____EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS	
	Amino acid sequence of 1D05 heavy chain with F to S back germline highlighted with IgG1 disabled (LAGA) constant region	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWVSGISWI _RDNAKNSLYLQMNSLRAEDTALYYCAKDMKGSGTYGGW FDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV _____PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP	

			SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCS
		Amino acid sequence of 1D05 region to germline highlighted	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWVSGISWI RTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYCAKDMKGSGTYGGW FDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV - SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
		Amino acid sequence of 1D05	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY_ GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGTRLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
		Amino acid sequence of 1D05 kappa light chain with L to F	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKL_ GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGTRLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH3	
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH3	
			EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKED GSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYCARNRLYSDFLDNW

	Nucleic acid sequence of V	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT CTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTATTGGATGAGTTG GGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATCAAGAAG ATGGAAGTGAGAAATACTATGTCGACTCTGTGAAGGGCCGATTCACCATCTCCA GAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGG ACACGTCTGTGTATTACTGTGCGAGAAATCGACTCTACAGTGACT CTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
	Amino acid sequence of 411B08	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKED GSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYCARNRLYSDFLDNW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
		GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTATTGGATGAGTTG GGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATCAAGAAG ATGGAAGTGAGAAATACTATGTCGACTCTGTGAAGGGCCGATTCACCATCTCCA GAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGG ACACGTCTGTGTATTACTGTGCGAGAAATCGACTCTACAGTGACTTCCTTGACAA CTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCACCAAGGGCCCCTC TGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCT GGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTC TCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGG CCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCCA GACCTACATCTGCAACGTGAACCACACAAGCCCTCCAACACCAAGGTGGACAAGAA GGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCC TGAACTGCTGGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCC CCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCA CGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAA CGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTC CGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAA GGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAA GGGCCAGCCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCT GACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGA

			TATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCAC CCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGT GCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGA GGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG
		Amino acid sequence of CDRL1	
		Amino acid sequence of CDRL2	
		Amino acid sequence of CDRL3	
		Amino acid sequence of CDRL1	
		Amino acid sequence of CDRL2	
		Amino acid sequence of CDRL3	
			DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLIYGASSLQ SGVPSRFSGSGSGTEFILTISSLQPEDFATYYCQQANSIPFTFGPGTKVDIK
		Nucleic acid sequence of V	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGCTGGTTAGCCTGGTAT CAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAGAGTTCATT CTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTT CTAACAGTATCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAAC
		Amino acid sequence of 411B08	DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLIYGASSLQ SGVPSRFSGSGSGTEFILTISSLQPEDFATYYCQQANSIPFTFGPGTKVDIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
		Nucleic acid sequence of 411B08	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGCTGGTTAGCCTGGTAT CAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAGAGTT CTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGG CTAACAGTATCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGTAC GGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTC CGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAA

			GGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAATCCGT GACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCCT GTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCA GGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	
			EVQLVDSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKED GSEKYYVDSLKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYCARVRLYSDFLDYWG
		Nucleic acid sequence of V	GAGGTGCAGCTGGTGGACTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTATTGGATGAGTTG GGTCCGCCAGGCTCCAGGGAAAGGGGCTGGAGTGGGTGGCCAACATAAAGAAG ATGGAAGTGAGAAATACTATGTAGACTCTTTGAAGGGCCGATTCACCATCTCCA GAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGG ACACGTCTGTGTATTACTGTGCGAGAGTTCGACTCTACAGTGACTTCCTTGACTA CTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
		Amino acid sequence of 411C04	EVQLVDSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKED GSEKYYVDSLKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYCARVRLYSDFLDYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS

	Amino acid sequence of CDRL1	GAGGTGCAGCTGGTGGACTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTATTGGATGAGTTG GGTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGGGTGGCCAACATAAAGAAG ATGGAAGTGAGAAATACTATGTAGACTCTTTGAAGGGCCGATTCACCATCTCCA GAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGG ACACGTCTGTGTATTACTGTGCGAGAGTTCGACTCTACAGTGACTTCCTTGACTA CTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCTC TGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCT GGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTC TCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGG CCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCCA GACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAA GGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCC TGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCC CCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCA CGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAA CGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTC CGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAA GGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAA GGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCT GACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGA TATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCAC CCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGT GCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGA GGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG
	Amino acid sequence of CDRL2	
	Amino acid sequence of CDRL3	
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL2	
	Amino acid sequence of CDRL3	

			DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLIYGASSLQ SGVPSRFSGSGSGTEFILSISSLQPEDFATYYCQQANSIPFTFGPGTKVDIK
		Nucleic acid sequence of V	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGTTGGTTAGCCTGGTAT CAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCCTCCAGTTTG CAAAGTGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAGAGTTCATT CTCAGCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTT CTAACAGTATCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAAC
		Amino acid sequence of 411C04	DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLIYGASSLQ SGVPSRFSGSGSGTEFILSISSLQPEDFATYYCQQANSIPFTFGPGTKVDIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
		Nucleic acid sequence of 411C04	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGTTGGTTAGCCTGGTAT CAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCCTCCAGTTTG CAAAGTGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAGAGTT CTCAGCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGG CTAACAGTATCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGTAC GGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTC CGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAA GGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAATCCGT GACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCCT GTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCA GGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	

			QVQLQESGPGLVKPSGTLSLTCIVSGGSIISSDWWNWVRQPPGKGLEWIGEIFHS GRTNYNPSLKSRVTISIDKSKNQFSLRLSSVTAADTAVYYCARDGSGSYWGQGTLV
		Nucleic acid sequence of V	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGG GTCCCTCACCTGCATTGTCTCTGGTGGCTCCATCATCAGTAGTGACTGGTGGAA TTGGGTCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGAGAAATCTTTC ATAGTGGGAGGACCAACTACAACCCGTCCCTCAAGAGTCGAGTCACCATATCAA TAGACAAGTCCAAGAATCAGTTCTCCCTGAGGCTGAGCTCTGTGACCGCCGCGG ACACGGCCGTGTATTACTGTGCGAGAGATGGTTCG GGAACCCTGGTCACCGTCTCCTCAG
		Amino acid sequence of 411D07	QVQLQESGPGLVKPSGTLSLTCIVSGGSIISSDWWNWVRQPPGKGLEWIGEIFHS GRTNYNPSLKSRVTISIDKSKNQFSLRLSSVTAADTAVYYCARDGSGSYWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
			CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGGGACCCT GTCCCTCACCTGCATTGTCTCTGGTGGCTCCATCATCAGTAGTGACTGGTGGAA TTGGGTCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGAGAAATCTTTC ATAGTGGGAGGACCAACTACAACCCGTCCCTCAAGAGTCGAGTCACCATATCAA TAGACAAGTCCAAGAATCAGTTCTCCCTGAGGCTGAGCTCTGTGACCGCCGCGG ACACGGCCGTGTATTACTGTGCGAGAGATGGTTCGGGGGAGTTACTGGGGCCAG GGAACCCTGGTCACCGTCTCCTCAGCCACCAAGGGCCCCTCTGTGTTCCCT CTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTC GTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTG GCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGCCTGTACTCC CTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATC TGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCC AAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTG GGCGGACCTTCCGTGTTCCTGTTCCCCCCAAGCCCAAGGACACCCTGATG TCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCT GAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACC AAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTCCGTGCTGACC GTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAAC AAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCA

		Amino acid sequence of CDRL1	CGGGAACCCCAGGTGTACACACTGCCCCCCTAGCAGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTG GAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTG CTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAGTCC CGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCAC AACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG
		Amino acid sequence of CDRL2	
		Amino acid sequence of CDRL3	
		Amino acid sequence of CDRL1	
		Amino acid sequence of CDRL2	
		Amino acid sequence of CDRL3	
			DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKSGQPPKLLIYW ASTRESGVPDRFSGSGSGTDFTLTISSLQTEDVAVYYCQQYYSNRSFGQGTKLEIK
		Nucleic acid sequence of V	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGG GCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAGA ATTACTTAGCTTGGTACCAGCAGAAATCAGGACAGCCTCCTAAGTTGCTCATTTA CTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGT CTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGA TTTATTACTGTCAGCAATATTATAGTAATCGCAGTTTTGGCCAGGGGACCAAGCT
		Amino acid sequence of 411D07	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKSGQPPKLLIYW ASTRESGVPDRFSGSGSGTDFTLTISSLQTEDVAVYYCQQYYSNRSFGQGTKLEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
			GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGG GCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAGA ATTACTTAGCTTGGTACCAGCAGAAATCAGGACAGCCTCCTAAGTTGCTCATTTA CTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATT CTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGACTGAAGATGTGGCAG

		Amino acid sequence of CDRH1	TTTATTACTGTCAGCAATATTATAGTAATCGCAGTTTTGGCCAGGGGACCAAGCT GGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGA CGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTA CCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCA ACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGT CCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCT GCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGG
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	
			EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKED GSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYCARNRLYSDFLDNW
		Nucleic acid sequence of V	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTATTGGATGAGTTG GGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATCAAAGAAG ATGGAAGTGAGAAATACTATGTCGACTCTGTGAAGGGCCGATTCACCATCTCCA GAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCC ACACGTCTGTGTATTACTGTGCGAGAAATCGACTCTACAGTGACTTCCTTGACAA CTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
		Amino acid sequence of 385F01	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKED GSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYCARNRLYSDFLDNW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP

		IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL	
		GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTATTGGATGAGTTG GGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATCAAAGAAG ATGGAAGTGAGAAATACTATGTCGACTCTGTGAAGGGCCGATTCACCATCTCCA GAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGG ACACGTCTGTGTATTACTGTGCGAGAAATCGACTCTACAGTGACTTCCTTGACAA CTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCACCAAGGGCCCCTC TGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCT GGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTC CTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGG CCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCCA GACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAA GGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCC TGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCC CCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCA CGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAA CGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTC CGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAA GGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAA GGGCCAGCCCCCGGGAACCCCAGGTGTACACACTGCCCCCCTAGCAGGGACGAGCT GACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGA TATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCAC CCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGT AGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGA GGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCCGGCAAG	
		Amino acid sequence of CDRL1	
		Amino acid sequence of CDRL2	
		Amino acid sequence of CDRL3	
		Amino acid sequence of CDRL1	

	Amino acid sequence of CDRL2		DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLIYGASSLQ SGVPSRFSGSGSGTEFILTISSLQPEDFATYYCQQANSIPFTFGPGTKVDIK		
	Amino acid sequence of CDRL3				
	Nucleic acid sequence of V		GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGCTGGTTAGCCTGGTAT CAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAGAGTTCATT CTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTT CTAACAGTATCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAAC		
	Amino acid sequence of 385F01		DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLIYGASSLQ SGVPSRFSGSGSGTEFILTISSLQPEDFATYYCQQANSIPFTFGPGTKVDIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC		
	Nucleic acid sequence of 385F01		GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGCTGGTTAGCCTGGTAT CAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAGAGTT CTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGG CTAACAGTATCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGTAC GGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTC CGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAA GGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAATCCGT GACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCCT GTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCA GGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT		
	Amino acid sequence of CDRH1				
	Amino acid sequence of CDRH2				
	Amino acid sequence of CDRH3				
	Amino acid sequence of CDRH1				

	Amino acid sequence of CDRH2		QVQLVESGGGVVQPGRSLRLSCAASGFTFRIYGMHWVRQAPGKGLEWVAVIWYD GSNKYYADSVKGRFTISRDNSDNTLYLQMNSLRAEDTAVYYCARDMDYFGMDVW	
	Amino acid sequence of CDRH3			
	Nucleic acid sequence of V		CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCCGTATTTATGGCATGCACTG GGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATG ATGGAAGTAATAAATACTATGCTGACTCCGTGAAGGGCCGATTCACCATCTCCA GAGACAATTCCGACAACACGCTGTATCTGCAAATGAACAGCC ACACGGCTGTGTATTACTGTGCGAGAGATATGGACTACTTCGGTATGGACGTCT GGGGCCAAGGGACCACGGTCACCGTCTCCTCAG	
	Amino acid sequence of 413D08		QVQLVESGGGVVQPGRSLRLSCAASGFTFRIYGMHWVRQAPGKGLEWVAVIWYD NSDNTLYLQMNSLRAEDTAVYYCARDMDYFGMDVW GQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL	
			CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCCGTATTTATGGCATGCACTG GGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGTATG ATGGAAGTAATAAATACTATGCTGACTCCGTGAAGGGCCGATTCACCATCTCCA GAGACAATTCCGACAACACGCTGTATCTGCAAATGAACAGCC ACACGGCTGTGTATTACTGTGCGAGAGATATGGACTACTTCGGTATGGACGTCT GGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCACCAAGGGCCCCTCTG TGTTCCCTCTGGCCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGG GCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTG GCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGCC TGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCCAGA CCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGG TGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGA ACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCT	

		ACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGA GGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGC CAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTCCGT GCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGT GTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGG CCAGCCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGAC CAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATAT CGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCC CCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGA CAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTC CCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL2	
	Amino acid sequence of CDRL3	
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL2	
	Amino acid sequence of CDRL3	
		DLQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKRLIYAASSLQS GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPRTFGQGTKVEIK
	Nucleic acid sequence of V	GACCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACT CTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTT ATAATAGTTACCCTCGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAAC
	Amino acid sequence of 413D08	DLQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKRLIYAASSLQS GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPRTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

		GACCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATT CTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGC ATAATAGTTACCCTCGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTA CGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGT CCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCA AGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCC TGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCC TGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACC AGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
	Amino acid sequence of CDRH1	
	Amino acid sequence of CDRH2	
	Amino acid sequence of CDRH3	
	Amino acid sequence of CDRH1	
	Amino acid sequence of CDRH2	
	Amino acid sequence of CDRH3	
		QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSDWWSWVRQPPGKGLEWIGEIFHS GNTNYNPSLKSRVTISVDKSKNQISLRLNSVTAADTAVYYCVRDGSGSYWGQGTL
	Nucleic acid sequence of V	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGGGACCCT GTCCCTCACCTGCGCTGTCTCTGGTGGCTCCATCAGCAGTAGTGACTGGTGGAG TTGGGTCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGGGAAATCTTTC ATAGTGGGAACACCAACTACAACCCGTCCCTCAAGAGTCGAGTCACCATATCAGT AGACAAGTCCAAGAACCAGATCTCCCTGAGGCTGAACTCTG CACGGCCGTGTATTACTGTGTGAGAGATGGTTCGGGGAGTTACTGGGGCCAGG GAACCCTGGTCACCGTCTCCTCAG
	Amino acid sequence of 386H03	QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSDWWSWVRQPPGKGLEWIGEIFHS GNTNYNPSLKSRVTISVDKSKNQISLRLNSVTAADTAVYYCVRDGSGSYWGQGTL

			VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
		CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGGGACCCT GTCCCTCACCTGCGCTGTCTCTGGTGGCTCCATCAGCAGTAGTGACTGGTGGAG TTGGGTCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGGGAAATCTTTC ATAGTGGGAACACCAACTACAACCCGTCCCTCAAGAGTCGAGTCACCATATCAGT AGACAAGTCCAAGAACCAGATCTCCCTGAGGCTGAACTCTGTGACCGCCGCGGA CACGGCCGTGTATTACTGTGTGAGAGATGGTTCGGGGAGTTACTGGGGCCAGG GAACCCTGGTCACCGTCTCCTCAGCCACCAAGGGCCCCTCTGTGTTCCCTC TGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCG TGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGA GCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGCCTGTACTCCC TGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCT GCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCCA AGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGG GCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATG CCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCT GAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACC AAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTCCGTGCTGACC GTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAAC AAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCA CGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTG GAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTG CTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAGTCC CGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCAC AACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG	
	Amino acid sequence of CDRL1		
	Amino acid sequence of CDRL2		
	Amino acid sequence of CDRL3		

	Amino acid sequence of CDRL1						
	Amino acid sequence of CDRL2						
	Amino acid sequence of CDRL3						
			DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYW ASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTRSFGQGTKLEIK				
	Nucleic acid sequence of V		GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGG GCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAGA ACTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAACTGCTCATTTA CTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGT CTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGG TTTATTACTGTCAGCAATATTATAGTACTCGCAGTTTTGGCCAGGGGACCAAGCT				
	Amino acid sequence of 386H03		DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYW ASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTRSFGQGTKLEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC				
			GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGG GCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAGA ACTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAACTGCTCATTTA CTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATT CTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGATGTGGCAG TTTATTACTGTCAGCAATATTATAGTACTCGCAGTTTTTGGCCAGGGGACCAAGCT GGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGA CGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTA CCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCA ACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGT CCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCT GCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGG				
				Amino acid sequence of CDRH1			
				Amino acid sequence of CDRH2			

		Amino acid sequence of CDRH3				
				QLQESGPGLVKPSETLSLTCTVSGGSISSSSYYCGWIRQPPGKGLDWIGSIYSTGYT YYNPSLKSRVTISIDTSKNQFSCLILTSVTAADTAVYYCAISTAAGPEYFHRWGQGT		
		Amino acid sequence of CDRH2				
		Amino acid sequence of CDRH3				
				CAGCTGCAGGAGTCGGGCCCAGGCCTGGTGAAGCCTTCGGAGACCCTGTCCCTC ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTAGTAGTTATTACTGCGGCTGG ATCCGCCAGCCCCCTGGGAAGGGGCTGGACTGGATTGGGAGTATCTATTCTACT GGGTACACCTACTACAACCCGTCCCTCAAGAGTCGAGTCACCATTTCCATAGACA CGTCCAAGAACCAGTTCTCATGCCTGATACTGACCTCTG CGGCTGTGTATTACTGTGCGATAAGTACAGCAGCTGGCCCTGAATACTTCCATC GCTGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAG		
		Nucleic acid sequence of V				
				QLQESGPGLVKPSETLSLTCTVSGGSISSSSYYCGWIRQPPGKGLDWIGSIYSTGYT YYNPSLKSRVTISIDTSKNQFSCLILTSVTAADTAVYYCAISTAAGPEYFHRWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK		
		Amino acid sequence of 389A03				
				CAGCTGCAGGAGTCGGGCCCAGGCCTGGTGAAGCCTTCGGAGACCCTGTCCCTC ACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTAGTAGTTATTACTGCGGCTGG ATCCGCCAGCCCCCTGGGAAGGGGCTGGACTGGATTGGGAGTATCTATTCTACT GGGTACACCTACTACAACCCGTCCCTCAAGAGTCGAGTCACCATTTCCATAGACA CTCATGCCTGATACTGACCTCTGTGACCGCCGCAGACA CGGCTGTGTATTACTGTGCGATAAGTACAGCAGCTGGCCCTGAATACTTCCATC GCTGGGGCCAGGGCACCCTGGTCACCGTCTCCTCAGCCACCAAGGGCCCCT CTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTC TGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACT GGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCG		

			GCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCC AGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGA AGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCC CTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAA CCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCC ACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACA ACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGT CCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCA AGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCA AGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCCTAGCAGGGACGAGC TGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCG ATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCA CCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAG TGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACG AGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG
	Amino acid sequence of CDRL1		
	Amino acid sequence of CDRL2		
	Amino acid sequence of CDRL3		
	Amino acid sequence of CDRL1		
	Amino acid sequence of CDRL2		
	Amino acid sequence of CDRL3		
			DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNSKNFLAWYQQKPGQPPKLFIYW ASTRGSGVPDRISGSGSGTDFNLTISSLQAEDVAVYYCQQYYSTPRTFGQGTKVEI
		Nucleic acid sequence of V	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGG GCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAGTAAGA ACTTCTTAGCTTGGTACCAGCAGAAACCGGGACAGCCTCCTAAGCTGTTCATTTA CTGGGCATCTACCCGGGGATCCGGGGTCCCTGACCGAATCAGTGGCAGCGGGT CTGGGACAGATTTCAATCTCACCATCAGCAGCCTGCAGG

			TTTATTACTGTCAACAATATTATAGTACTCCTCGGACGTTCGGCCAAGGGACCAA
	Amino acid sequence of 389A03		DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNSKNFLAWYQQKPGQPPKLFIYW ASTRGSGVPDRISGSGSGTDFNLTISSLQAEDVAVYYCQQYYSTPRTFGQGTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	Nucleic acid sequence of 389A03		GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGG GCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAGTAAGA ACTTCTTAGCTTGGTACCAGCAGAAACCGGGACAGCCTCCTAAGCTGTTCATTTA CTGGGCATCTACCCGGGGATCCGGGTCCCTGACCGAAT CTGGGACAGATTTCAATCTCACCATCAGCAGCCTGCAGGCTGAAGATGTGGCAG TTTATTACTGTCAACAATATTATAGTACTCCTCGGACGTTCGGCCAAGGGACCAA GGTGGAGATCAAACGTACGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTC CGACGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTT CTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCG GCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCC TGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACG CCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACC
		Heavy Chain Constant Region	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccg ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactcta gaagaccccgaggttccagttcaactggtacgtggatggcgtggagg tgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctca ccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgt cctccatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccctgcccc cccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctaccccagcg acatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg gactccgacggctccttcttcctctacagcaggctaaccgtggacaagagcaggtggcaggaggggaat gtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaa

		Heavy Chain Constant Region	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEF LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
		Heavy Chain Constant Region	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccg ccctgggctgcctggtcaaggactacttccccgaaccggtgacgtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaagg tggacaagagagttgagtccaaatatggtccccctgcccatcatgcccagcacctgagttcctgggggg accatcagtcttcctgttccccccaaaacccaaggacactctcatgatctccccggacccctgaggtcacgtg cgtggtggtggacgtgagccaggaagacccgaggtccagttcaactggtacgtggatggcgtggagg gcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctca ccgtctgtgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccg tcctccatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccctgccc ccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctaccccagc atcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgct ggactccgacggctccttcttcctctacagcaggctaaccgtggacaagagcaggtggcaggagggga atgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctct
		Heavy Chain Constant Region	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEF LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
		Heavy Chain Constant Region	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccg ccctgggctgcctggtcaaggactacttccccgaaccggtgacgtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaagg tggacaagagagttgagtccaaatatggtccccctgcccatcatgcccagcacctgagttcctgggggg accatcagtcttcctgttccccccaaaacccaaggacactctcatgatctccccggacccctgaggtcacgtg cgtggtggtggacgtgagccaggaagacccgaggtccagttcaactggtacgtggatggcgtggagg gcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctca ccgtctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgt cctccatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccctgcccc

				catcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctaccccagcg atcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctg gactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcaggaggggaac gtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctctg
		Heavy Chain Constant Region		ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEF LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
		Heavy Chain Constant Region		gcctccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacggccg ccctgggctgcctggtcaaggactacttcccgaaccagtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaagg tggacaagagagttgagtccaaatatggtcccccatgcccaccatgcccagcgcctgaatttgagggggg gaccatcagtcttcctgttcccccaaaacccaaggacactctcatgatctcccggaccccctgaggtcacgt gcgtggtggtggacgtgagccaggaagaccccgaggttccagttcaactggtacgtggatggcgtggag gcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctccc gtcatcgatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccctgc cccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctacccca atcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgt gctggactccgacggatccttcttcctctacagcaggctaaccgtggacaagagcaggtggcaggaggg gaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcctctccctgtc
		Heavy Chain Constant Region Encoded by Synthetic Version A,		ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
		Heavy Chain Constant Region		Gcctccaccaagggacctagcgtgttcctctgccccctgttccaggtccacaagcgagtccaccgctgc cctcggctgtctggtgaaagactacttcccgagcccgtgaccgtctcctggaatagcggagccctgac ccggcgtgcacacatttcccgccgtgctgcagagcagcggactgtatagcctgagcagcgtggtgaccgt gcccagctccagcctcggcaccaaaacctacacctgcaacgtggaccacaagcccttccaacaccaaggt ggacaagcgggtggagagcaagtacgggccccccttgtcctcctgtcctgccctgagttcgagggagg

			accctccgttcctgttcccccaaacccaaggacaccctgatgatctcccggacacccgaggtgacct gtgtggtcgtggacgtcagccaggaggaccccgaggtgcagttcaactggtatgtggacggcgtggag gtgcacaatgccaaaaccaagcccagggaggagcagttcaattccacctacagggtggtgagcgtgct gaccgtcctgcatcaggattggctgaacggcaaggagtacaagtgcaaggtctccaacaagggactgc ccagctccatcgagaaagaccatcagcaaggctaagggccagccgagggagccccaggtgtataccctg cctcctagccaggaagagatgaccaagaaccaagtgtcctgacctgcctggtgaaggattctaccct ccgacatcgccgtggagtgggagagcaatggccagcccgagaacaactacaaaacaaccctcccgtg ctcgatagcgacggcagcttcttctctacagccggctgacagtggacaagagcaggtggcaggagggc ctcctgttccgtgatgcacgaggccctgcacaatcactacacccagaaagagcctctccctgtcc
	Heavy Chain Constant Region		gccagcaccaagggcccttccgtgttccccctggccccttgcagcaggagcacctccgaatccacagctg ccctgggctgtctggtgaaggactacttcccgagcccgtgaccgtgagctggaacagcggcgctctgac atccggcgtccacacctttccctgccgtcctgcagtcctccggcctctactcccctgtcctccgtggtgaccgtg cctagctcctcccctcggcaccaagacctacacctgtaacgtggaccacaaacccctccaacaccaaggtgg acaaacgggtcgagagcaagtacggccctcccctcccctgtcctgccccgagttcgaaggcggacc cagcgttcctgttcctcctaagcccaaggacaccctcatgatcagccggacacccgaggtgacctgc gtggtggtggatgtgagccaggaggaccctgaggttccagttcaactggtatgtggatggcgtggaggtg ccgggaagagcagttcaactccacctacagggtggtcagcgtgctgac cgtgctgcatcaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggactgccca gcagcatcgagaaaaccatctccaaggctaaagggcagccccgggaacctcaggtgtacaccctgcctc ccagccaggaggagatgaccaagaaccaggtgagcctgacctgcctggtgaaagggattctacccttccg atcgccgtggagtgggagtccaacgggcagccgagaacaattataagaccacccctcccgtcctcg acagcgacggatccttcttctttctgtactccaggctgaccgtggataagtccaggtggcaggaaggcaacgt gttcagctgctccgtgatgcacgaggccctgcacaatcactacacccagaagtccctgagcctgtccctgg
	Heavy Chain Constant Region		gcctccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacggccg ccctgggctgcctggtcaaggactacttccccgaaccagtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccc tgccctccagcagcttgggcacgaagacctacacctgcaacgtagatcacaagcccagcaacaccaagg tggacaagagagttgagtccaaatatggtcccccatgcccaccatgcccagcgcctccagttgcgggggg gaccatcagtcttcctgttcccccaaaacccaaggacactctcatgatctcccggaccccctgaggtcacgt gcgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtggatggcgtggag gtgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctccc gtcatcgatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccctgc gaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctacccca gcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgt

				gctggactccgacggatccttcttcctctacagcaggctaaccgtggacaagagcaggtggcaggagggg gaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcc
			Heavy Chain Constant Region (inactivating mutations from human WT IgG4 shown in bold)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
			Heavy Chain Constant Region	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaagg tggacaagaaagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaac tcgcgggggcaccgtcagtcttcctcttccccccaaaacccaaggacaccctcatgatctcccggaccccct tggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggac ggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtgg tcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaaca aagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccaca tacaccctgcccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggct tctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccac gcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggc agcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcct
			Heavy Chain Constant Region residues that differ from the	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
			Ck Light Chain Constant Region	cgtacggtggccgctcccttcgtgttcatcttcccaccttccgacgagcagctgaagtccggcaccgcttct gtcgtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaaggtggacaacgccctg cagtccggcaactcccaggaatccgtgaccgagcaggactccaaggacagcacctactccctgtcctcca ccctgaccctgtccaaggccgactacgagaagcacaaggtgtacg ctgtctagcccccgtgaccaagtctttcaaccggggcgagtgt
			Ck Light Chain Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

			Cκ Light Chain Constant Region	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctg ttgtgtgcctgctgaataaacttctatcccagagaggccaaagtacagtggaaggtggataacgccctcca atcgggtaactcccaggagagtgtcacagagcaggagagcaaggaca accctgacgctgagcaaagcagactacgagaaacacaaagtctacgcccgcgaagtcacccatcaggg cctgagctcgcccgtcacaaagagcttcaacaggggagagtgt
			Cκ Light Chain Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQESKDSTYSLSSTLTLSKADYEKHKVYAGEVTHQGLSSPVTKSFNRGEC
			Cκ Light Chain Constant Region	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctg ttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctcca atcgggtaactcccaggagagtgtcacagagcaggagagcaaggacagcacctacagcctcagcagc accctgacgctgagcaaagcagactacgagaaacacaaagtctacg cctgagctcgcccgtcacaaagagcttcaacaggggagagtgt
			Cκ Light Chain Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQRKVDNALQSGNSQESV TEQESKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
			Cκ Light Chain Constant Region	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctg ttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctcca atcgggtaactcccaggagagtgtcacagagcaggacgcaaggaca accctgacgctgagcaaagcagactacgagaaacacaaactctacgcctgcgaagtcacccatcaggg cctgagctcgcccgtcacaaagagcttcaacaggggagagtgt
			Cκ Light Chain Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKLYACEVTHQGLSSPVTKSFNRGEC
			Cκ Light Chain Constant Region	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctg ttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctcca atcgggtaactcccaggagagtgtcacagagcaggacgcaaggacagcacctacagcctcagcaac accctgacgctgagcaaagcagactacgagaaacacaaagtctacg cctgagctcgcccgtcacaaagagcttcaacaggggagagtgc
			Cκ Light Chain Constant Region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSNTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
			Cλ Light Chain Constant Region	cccaaggccaaccccacggtcactctgttcccgccctcctctgaggagctccaagccaacaaggccacac tagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcttggaaggcagatggcagccccgt caaggcgggagtggagacgaccaaaccctccaaacagagcaacaacaag cctgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccaggtcacgcatgaaggga gcaccgtggagaagacagtggccctacagaatgttca
			Cλ Light Chain Constant Region	PKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPS KQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

			Cλ Light Chain Constant Region	ggtcagcccaaggccaacccactgtcactctgttcccgccctcctctgaggagctccaagccaacaagg ccacactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcctggaaggcagatggcag cccgtcaaggcgggagtggagaccaccaaaccctccaaacagagcaacaactacgcggccagc agctacctgagcctgacgcccgagcagtggaagtcccacagaagctaca agggagcaccgtggagaagacagtggccctacagaatgttca
			Cλ Light Chain Constant Region	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
			Cλ Light Chain Constant Region	ggtcagcccaaggccaacccactgtcactctgttcccgccctcctctgaggagctccaagccaacaagg ccacactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcctggaaggcagatggcag ccccgtcaaggcgggagtggagaccaccaaaccctccaaacagagc agctacctgagcctgacgcccgagcagtggaagtcccacagaagctacagctgccaggtcacgcatga agggagcaccgtggagaagacagtggccctacagaatgttca
			Cλ Light Chain Constant Region	ggccagcctaaggccgctccttctgtgaccctgttcccccatcctccgaggaactgcaggctaacaaggc caccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctggaaggctgatagctctc ctgtgaaggccggcgtggaaaccaccaccctttccaagcagtccaacaacaaatacgccgcctcctccta cctgtccctgaccctgagcagtggaagtcccaccggtcctacagctgccaagtgacccacgagggctcc accgtggaaaagaccgtggctcctaccgagtgctcc
			Cλ Light Chain Constant Region	ggccagcctaaagctgccccaggcgtcaccctgtttcctcctcccagcgaggagctccaggccaacaagg ccaccctcgtgtgcctgatctccgacttctatcccggcgctgtgaccgtggcttggaaagccgactccagcc ctgtcaaagccggcgtggagaccaccacaccctccaagcagtccaacaacaagtacgccgcctccagct atctctcctgaccctgagcagtggaagtcccaccggtcctactcctgtcaggtgacccacgagggctcc accgtggaaaagaccgtcgccccaccgagtgctcc
			Cλ Light Chain Constant Region	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
			Cλ Light Chain Constant Region	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatagcag cccgtcaaggcgggagtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagc agctatctgagcctgacgcctgagcagtggaagtcccacagaagctaca gggagcaccgtggagaagacagtggccctacagaatgttca
			Cλ Light Chain Constant Region	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETT PSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
			Cλ Light Chain Constant Region	cccaaggctgccccctcggtcactctgttcccacccctcctctgaggagcttcaagccaacaaggccacact ggtgtgtctcataagtgacttctacccgggagccgtgacagttgcctggaaggcagatagcagccccgtc aaggcgggggtggagaccaccacaccctccaaacaaagcaacaacaag

				tgagcctgacgcctgagcagtggaagtcccacaaagctacagctgccaggtcacgcatgaagggagc accgtggagaagacagttgcccctacggaatgttca	
			Cλ Light Chain Constant Region	PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPS KQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS	
			Cλ Light Chain Constant Region	ggtcagcccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcataagtgacttctacccgggccagtgacagttgcctggaaggcagatagcagc cccgtcaaggcgggggtggagaccacacacccctccaaacaaagcaacacaagtacgcggccagca gctacctgagcctgacgcctgagcagtggaagtcccacaaaagctaca		
			Cλ Light Chain Constant Region	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGPVTVAWKADSSPVKAGVETTT PSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS	
			Cλ Light Chain Constant Region	ggtcagcccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatagcag ccccgtcaaggcgggagtggagaccacacacccctccaaacaaagcaac agctacctgagcctgacgcctgagcagtggaagtcccacaaaagctacagctgccaggtcacgcatgaa gggagcaccgtggagaagacagtggccctacagaatgttca		
			Cλ Light Chain Constant Region	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT PSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS	
			Cλ Light Chain Constant Region	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatagcag ccccgtcaaggcgggagtggagaccacacacccctccaaacaaagcaacacaagtacgcggccagc agctacctgagcctgacgcctgagcagtggaagtcccacagaagctaca gggagcaccgtggagaagacagtggccctacagaatgttca		
			Cλ Light Chain Constant Region	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT PSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	
			Cλ Light Chain Constant Region	ggtcagcccaaggctgccccatcggtcactctgttcccgccctcctctgaggagcttcaagccaacaaggc cacactggtgtgcctgatcagtgactcttacccgggagctgtgaaagtggcctggaaggcagatggcag ccccgtcaacacgcgggagtggagaccacacacccctccaaacagagcaac agctacctgagcctgacgcctgagcagtggaagtcccacagaagctacagctgccaggtcacgcatgaa gggagcaccgtggagaagacagtggccctgcagaatgttca		
			Cλ Light Chain Constant Region	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGVETT TPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECS	
			Cλ Light Chain Constant Region	ggtcagcccaaggctgccccatcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggc cacactggtgtgtctcgtaagtgacttctacccgggagccgtgacagtggcctggaaggcagatggcag ccccgtcaaggtgggagtggagaccaccaaaccctccaaacaaagcaacacaagtatgcggccagc		

				agctacctgagcctgacgcccgagcagtggaagtcccacagaagctaca agggagcaccgtggagaagacagtggccccctgcagaatgctct
			Cλ Light Chain Constant Region	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFYPGAVTVAWKADGSPVKVGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECS
. .			Amino acid sequence of CDRH1	.
			Amino acid sequence of CDRH2	
			Amino acid sequence of CDRH3	
			Amino acid sequence of CDRH1	
			Amino acid sequence of CDRH2	
			Amino acid sequence of CDRH3	
				QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQVPGKGLEWVSYISTSG STIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDAAVYHCARGITGTNFYHYGLG
			Nucleic acid sequence of V	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCTG GATCCGCCAGGTTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTACTAG TGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCT GGACAACGCCAAGAACTCACTGTATCTACAAATGAACAGCCTGAGAGCCGAGGA CGCGGCCGTGTATCACTGTGCGAGAGGTATAACTGGAACTAACTTCTACCACTA CGGTTTGGGCGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG
			Amino acid sequence of 413G05	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQVPGKGLEWVSYISTSG STIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDAAVYHCARGITGTNFYHYGLG VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL

		CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACATGAGCTG GATCCGCCAGGTTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTACTAG TGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAG AAGAACTCACTGTATCTACAAATGAACAGCCTGAGAGCCGAGGA CGCGGCCGTGTATCACTGTGCGAGAGGTATAACTGGAACTAACTTCTACCACTA CGGTTTGGGCGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCAGCAC CAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGG AACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGA GTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCT GCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTC TCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAG GTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCT TGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGT CCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTG GATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTG GAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTAC CGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGA GTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCAT CTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAG CAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTT CTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAA CTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGC CAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCC GTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGC			
	Amino acid sequence of CDRL1			
	Amino acid sequence of CDRL2			
	Amino acid sequence of CDRL3			
	Amino acid sequence of CDRL1			

	Amino acid sequence of CDRL3		DIQMTQSPSSVSASVGDRVTITCRASQGINSWLAWYQQKPGKAPKLLIYAASTLQS GVPSRFSGSGSGADFTLTISSLQPEDFATYYCQQVNSFPLTFGGGTKVEIK
		Nucleic acid sequence of V	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGA TCGGGCGAGTCAGGGTATTAACAGCTGGTTAGCCTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCACTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGGTCTGGGGCAGATTTCACT CTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGG TTAACAGTTTCCCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAAC
		Amino acid sequence of 413G05	DIQMTQSPSSVSASVGDRVTITCRASQGINSWLAWYQQKPGKAPKLLIYAASTLQS GVPSRFSGSGSGADFTLTISSLQPEDFATYYCQQVNSFPLTFGGGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
			GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTATTAACAGCTGGTTAGCCTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCACTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGGTCTGGGGCAGATTTCACT CTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTT TTAACAGTTTCCCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGTA CGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGT CCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCA AGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAATCCG TGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCC TGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACC AGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH3	
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH2	

	Amino acid sequence of CDRH3		EVPLVESGGGLVQPGGSLRLSCAASGFTFSYYAMSWVRQAPGKGLDWVSTISGGG GNTHYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAVYYCAKDRMKQLVRAYYF
	Nucleic acid sequence of V		GAGGTGCCGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGTCCC GAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGCTACTATGCCATGAGCTG GGTCCGTCAGGCTCCAGGGAAGGGGCTGGACTGGGTCTCAACTATTAGTGGTG GTGGTGGTAACACACACTACGCAGACTCCGTGAAGGGCCGATTCACTATATCCA GAGACAATTCCAAGAACACGCTGTATCTGCACATGAACAGCCTGAGAGCCGAAG ACACGGCCGTCTATTACTGTGCGAAGGATCGGATGAAACA ACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
	Amino acid sequence of 413F09		EVPLVESGGGLVQPGGSLRLSCAASGFTFSYYAMSWVRQAPGKGLDWVSTISGGG GNTHYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAVYYCAKDRMKQLVRAYYF DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
			GAGGTGCCGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGCTACTATGCCATGAGCTG GGTCCGTCAGGCTCCAGGGAAGGGGCTGGACTGGGTCTCAACTATTAGTGGTG GTGGTGGTAACACACACTACGCAGACTCCGTGAAGGGCCGATTCACTATATCCA CACGCTGTATCTGCACATGAACAGCCTGAGAGCCGAAG ACACGGCCGTCTATTACTGTGCGAAGGATCGGATGAAACACGCTCGTCCGGGCCT ACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCAGCA CCAAGGGCCCCTCTGTTCCCCTGGCCCCTTCCAGCAAGTCCACCTCTGGCG GAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCG TCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGC TGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCT CTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAA GGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCC TTGTCCTGCCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCC GCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGT GGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGT

		Amino acid sequence of CDRL1	GGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTA CCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAG AGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCA TCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTA GCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCT TCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACA ACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAG GACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTC CGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAG
		Amino acid sequence of CDRL2	
		Amino acid sequence of CDRL3	
		Amino acid sequence of CDRL1	
		Amino acid sequence of CDRL2	
		Amino acid sequence of CDRL3	
			DIQLTQSPSFLSASVGDRVTITCWASQDISTYLGWYQQKPGKAPKLLIYGTSSLQS GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLHTDPITFGQGTRLEIK
		Nucleic acid sequence of V	GACATCCAGTTGACCCAGTCTCCATCCTTCCTGTCTGCATCTGTAGGAGACAGA CTGGGCCAGTCAGGACATTAGCACTTATTTAGGCTGGTAT CAGCAAAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTACATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACT CTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCAACAGC TTCATACTGACCCGATCACCTTCGGCCAAGGGACACGACTGGAGATCAAAC
		Amino acid sequence of 413F09	DIQLTQSPSFLSASVGDRVTITCWASQDISTYLGWYQQKPGKAPKLLIYGTSSLQS GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLHTDPITFGQGTRLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
		ucleic acid sequence of 413F09	GACATCCAGTTGACCCAGTCTCCATCCTTCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCTGGGCCAGTCAGGACATTAGCACTTATTTAGGCTGGTAT

		Amino acid sequence of CDRH1	CAGCAAAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTACATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTC CTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCAACAGC TTCATACTGACCCGATCACCTTCGGCCAAGGGACACGACTGGAGATCAAACGTA CGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGT CCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCA AGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCG TGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCC TGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACC AGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH2	
		Amino acid sequence of CDRH3	
			EVHLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLEWVANIKQD GSEKYYVDSVKGRFTVSRDNAKNSLYLQMNSLRAEDTAVYYCARVRQWSDYSDY
		Nucleic acid sequence of V	GAGGTGCACCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTATTGGATGAACTG GGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCAAG ATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGCTTCACCGTCTCCA GAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCC ACACGGCTGTGTATTACTGTGCGAGAGTTCGACAATGGTCCGACTACTCTGACT ACTGGGGCCAGGGAACCCCGGTCACCGTCTCCTCAG
		Amino acid sequence of 414B06	EVHLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLEWVANIKQD GSEKYYVDSVKGRFTVSRDNAKNSLYLQMNSLRAEDTAVYYCARVRQWSDYSDY WGQGTPVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS

		CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL	
		GAGGTGCACCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTATTGGATGAACTG GGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCAAG ATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGCTTCACCGTCTCCA GAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGG ACACGGCTGTGTATTACTGTGCGAGAGTTCGACAATGGTCCGACTACTCTGACT ACTGGGGCCAGGGAACCCCGGTCACCGTCTCCTCAGCCACCAAGGGCCCCT CTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTC TGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACT CTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCG GCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCC AGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGA AGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCC CTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCC CCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCC ACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACA ACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGT CCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCA AGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCA AGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGC TGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCG ATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCA CCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAG AGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACG AGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG	
	Amino acid sequence of CDRL1		
	Amino acid sequence of CDRL2		
	Amino acid sequence of CDRL3		

	Amino acid sequence of CDRL1					
	Amino acid sequence of CDRL2					
	Amino acid sequence of CDRL3					
			DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPFTFGPGTKVDIK			
		Nucleic acid sequence of V	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGCTGGTTAGCCTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACT CTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTT CTAACAGTTTCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAAC			
		Amino acid sequence of 414B06	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPFTFGPGTKVDIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC			
		ucleic acid sequence of 414B06	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGCTGGTTAGCCTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTC CTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGG CTAACAGTTTCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGTAC GGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTC CGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAA GGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCG GACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCCT GTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCA GGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT			
		Amino acid sequence of 1D05 mutation in CDRL2 highlighted	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY_ GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGTRLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC			
		Amino acid sequence of IgG1	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWVSGISWI RTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYCAKDMKGSGTYGGW			

		FDTWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT		
	1D05 Light chain sequence sequence is underlined and region to be varied is shown in	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYVASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGTRLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITF		
	Full length amino acid sequence	**APTSSSTKKTQLQLEHLLLLD**LQMILNGINNYKNPKLTRMLTFKFYMPKKATELK HLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETA	
	Heavy chain 1D05 IgG1 variant	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWVSGISWI RTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYCAKDMKGSGTYGGW FDTWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE LFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGKAPTSSSTKKTQLQLEHLLLLDLQMILNGINNYKNPKLTRMLTFKFYMP TELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMC EYADETATIVEFLNRWITFCQSIISTLT		

PTSSSTKKTQLQLEHLLLD								APTSSSTKTQLQLEHLLLD									

	Amino acids 21 to 133 of hIL	LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKN FHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT **FTITAPKDLYVVEYGSNVTMECRFPVERELDLLAL** **VVYWEKEDEQVIQFVAGEEDLKPQHSNFRGRASLPKDQLLKGNAALQIT** **DVKLQDAGVYCCIISYGGADYKRITLKVNAPYRKINQRISVDPATSEHEL** **ICQAEGYPEAEVIWTNSDHQPVSGKRSVTTSRTEGMLLNVTSSLRVNAT** **ANDVFYCTFWRSQPGQNHTAELIIPELPATHPPQNRT**_____ STVLLFLRKQVRMLDVEKCGVEDTSSKNRNDTQFEET
		FTITAPKDLYVVEYGSNVTMECRFPVERELDLLALVVYWEKEDEQVIQFVAGEEDLK PQHSNFRGRASLPKDQLLKGNAALQITDVKLQDAGVYCCIISYGGADYKRITLKVN APYRKINQRISVDPATSEHELICQAEGYPEAEVIWTNSDHQPVSGKRSVTTSRTEG MLLNVTSSLRVNATANDVFYCTFWRSQPGQNHTAELIIPELPATHPPQNRT_____ ___
		ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSSW DNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPP WENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLIC TGEMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAATMETSIFTTEYQ VAVAGCVFLLISVLLLSGLTWQRRQRKSRRTI
		AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDRRRWNQTCELLPVS QASWACNLILGAPDSQKLTTVDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPI SLQVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQE WICLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRT LLVGLSGAFGFIILVYLLINCRNTGPWLKKVLKCNTPDPSKFFSQLSSEHGGDVQKW LSSPFPSSSFSPGGLAPEISPLEVLERDKVTQLLLQQDKVPEPASLSSNHSLTSCFTN QGYFFFHLPDALEIEACQVYFTYDPYSEEDPDEGVAGAPTGSSPQPLQPLSGEDDA YCTFPSRDDLLLFSPSLLGGPSPPSTAPGGSGAGEERMPPSLQERVPRDWDPQPLG PPELVLREAGEEVPDAGPREGVSFPWSRPPGQGEFRALNARL PLNTDAYLSLQELQGQDPTHLV
		LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFNVEYMNCTWNSSS EPQPTNLTLHYWYKNSDNDKVQKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQD LVIPWAPENLTLHKLSESQLELNWNNRFLNHCLEHLVQY RTDWDHSWTEQSVDYRHKFSLPSVDGQKRYTFRVRSRFNPLCGSAQHWSEWSH PIHWGSNTSKENPFLFALEAVVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLEDLV TEYHGNFSAWSGVSKGLAESLQPDYSERLCLVSEIPPKGGALGEGPGASPCNQHSP

			DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGMFL FRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQPTKS LEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEH
			GIHVFILGCFSAGLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVT AMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNI
			QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQL KSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFK SLLQKMIHQHLSSRTHGSEDS
			APARSPSPSTQPWEHVNAIQEARRLLNLSRDTAAEMNETVEVISEMFDLQEPTCLQ TRLELYKQGLRGSLTKLKGPLTMMASHYKQHCPPTPETSCATQIITFESFKENLKDF
			CDLPQNHGLLSRNTLVLLHQMRRISPFLCLKDRRDFRFPQEMVKGSQLQKAHVMS VLHEMLQQIFSLFHTERSSAAWNMTLLDQLHTELHQQLQHLETCLLQVVGEGESA GAISSPALTLRRYFQGIRVYLKEKKYSDCAWEVVRMEIMKSLFLSTNMQERLRSKD
		Extracellular portion of human	GPQREEFPRDLSLISPLAQAVRSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANAL LANGVELRDNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTHTISRIAVSYQTKVNL LSAIKSPCQRETPEGAEAKPWYEPIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQV
			RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDK TSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQ VEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKT KIKLCILLHAFRIRAVTIDRVMSYLNAS
			IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTI QVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEA KNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDNKEYE YSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPL KNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR KNASISVRAQDRYYSSSWSEWASVPCS
			TPVVRKGRCSCISTNQGTIHLQSLKDLKQFAPSPSCEKIEIIATLKNGVQTCLNPDSA DVKELIKKWEKQVSQKKKQKNGKKHQKKKVLKVRKSQRSRQKKTT
			VPLSRTVRCTCISISNQPVNPRSLEKLEIIPASQFCPRVEIIATMKKKGEKRCLNPESK
		WT human IgG1 amino acid	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP

				APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
			WT human IgG1 nucleic acid	GCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCCTTCCAGCAAGTCCACC TCTGGCGGAACAGCCGCTCTGGGCTCGCCTCGTGAAGGACTACTTCCCCGAGCCT GTGACCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCT GCTGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCT TCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGA ACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCT GTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCC CCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCG TGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGG ACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACT CCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACG GCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAA AGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGC CCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGA CCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTG AGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCT GTACAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTC CTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTC CCTGAGCCCCGGCAAGTGATGA
			Amino acid sequence of 1D05 heavy chain with V to A and F to region to germline highlighted	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ_ SLRAEDTALYYCAKDMKGSGTYGGW FDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
			Amino acid sequence of CDRH1	

	Amino acid sequence of CDRH2		
	Amino acid sequence of CDRH3		
	Amino acid sequence of CDRH1		
	Amino acid sequence of CDRH3		
		ESGGGLVQPGGSLRLSCAASGFTFS TYYADSVKGRFTISRDNSKNTLYL	
	Nucleic acid sequence of V	GAAGTGCAACTGGCGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAACTATGCCATGAGTTG GGTCCGCCAGACTCCAGGAAAGGGGCTGGAGTGGGTCTCAGCTATTAGTTTTAG TGGTGGTACTACATACTACGCTGACTCCGTGAAGGGCCGGTTCACCATCTCCAG AGACAATTCCAAGAACACGCTGTATTTGCACATGAACAGCC CACGGCCGTATATTACTGTGCGAAAGATGAGGCACCAGCTGGCGCAACCTTCTT TGACTCCTGGGGCCAGGGAACGCTGGTCACCGTCTCCTCAG
	Amino acid sequence of 416E01	EVQLAESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQTPGKGLEWVSAISFSG GTTYYADSVKGRFTISRDNSKNTLYLHMNSLRADDTAVYYCAKDEAPAGATFFDS WGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
		GAAGTGCAACTGGCGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAACTATGCCATGAGTTG GGTCCGCCAGACTCCAGGAAAGGGGCTGGAGTGGGTCTCAGCTATTAGTTTTAG TGGTGGTACTACATACTACGCTGACTCCGTGAAGGGCCGGTTCACCATCTCCAG AGACAATTCCAAGAACACGCTGTATTTGCACATGAACAGCCTGAGAGCCGATGA CACGGCCGTATATTACTGTGCGAAAGATGAGGCACCAGCTGGCGCAACCTTCTT

		TGACTCCTGGGGCCAGGGAACGCTGGTCACCGTCTCCTCAGCCAGCACCAAGGG CCCTTCCGTGTTCCCCCTGGCCCCTTGCAGCAGGAGCACCTCCGAATCCACAGC TGCCCTGGGCTGTCTGGTGAAGGACTACTTTCCCGAGCCCGTGACCGTGAGCTG CGGCGCTCTGACATCCGGCGTCCACACCTTTCCTGCCGTCCTGCAGTC CTCCGGCCTCTACTCCCTGTCCTCCGTGGTGACCGTGCCTAGCTCCTCCCTCGG CACCAAGACCTACACCTGTAACGTGGACCACAAACCCTCCAACACCAAGGTGGAC AAACGGGTCGAGAGCAAGTACGGCCCTCCCTGCCCTCCTTGTCCTGCCCCCGAG TTCGAAGGCGGACCCAGCGTGTTCCTGTTCCCTCCTAAGCCCAAG ATGATCAGCCGGACACCCGAGGTGACCTGCGTGGTGGTGGATGTGAGCCAGGA GGACCCTGAGGTCCAGTTCAACTGGTATGTGGATGGCGTGGAGGTGCACAACG CCAAGACAAAGCCCCGGGAAGAGCAGTTCAACTCCACCTACAGGGTGGTCAGCG TGCTGACCGTGCTGCATCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAG GTCAGCAATAAGGGACTGCCCAGCAGCATCGAGAAGACCATCTCCAAGGCTAAA GGCCAGCCCCGGGAACCTCAGGTGTACACCCTGCCTCCCAGCCAGGAGGAGATG ACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGATTCTACCCTTCCGAC ATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAACAATTATAAGACCACC CCTCCCGTCCTCGACAGCGACGGATCCTTCTTCTTTCTGTACTCCAGGCTGACCGTG GATAAGTCCAGGTGGCAGGAAGGCAACGTGTTCAGCTGCTCCGTGATGCACGAG GCCCTGCACAATCACTACACCCAGAAGTCCCTGAGCCTGTCCCTGGGAAAG
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL2	
	Amino acid sequence of CDRL3	
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL2	
	Amino acid sequence of CDRL3	
		DIQMTQSPSSVSASVGDRVTITCRASQGI SLQPEDFATYYCQQANSFPITFGQGTRLEIK

	Nucleic acid sequence of V	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGA TCGGGCGAGTCAGGGTATTAGGAGGTGGTTAGCCTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAACTCCTGATCTCTGGTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACT CTCATCATTACCAGTCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGG CTAACAGTTTCCCGATCACCTTCGGCCAAGGGACACGACTGGAGATCAAAC
	Amino acid sequence of 416E01	DIQMTQSPSSVSASVGDRVTITCRASQGIRRWLAWYQQKPGKAPKLLISGASSLQS GVPSRFSGSGSGTDFTLIITSLQPEDFATYYCQQANSFPITFGQGTRLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
	ucleic acid sequence of 416E01	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGGAGGTGGTTAGCCTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAACTCCTGATCTCTGGTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTC CTCATCATTACCAGTCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGG CTAACAGTTTCCCGATCACCTTCGGCCAAGGGACACGACTGGAGATCAAACGTA CGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGT CCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCA AGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCG TGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCC TGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACC AGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
	Amino acid sequence of CDRH1	
	Amino acid sequence of CDRH2	
	Amino acid sequence of CDRH3	
		QVQVVQSGAEVKKPGASVKVSCKASGYTFSTFGITWVRQAPGQGLEWMGWISAY NGDTNYAQNLQGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARSSGHYYYYGM
	Nucleic acid sequence of V	CAGGTTCAGGTGGTGCAGTCTGGAGCTGAGGTGAAGAAGC GAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTTCCACC GTGCGACAGGCCCCTGGACAAGGGCTTGAATGGATGGGAT CAATGGTGACACAAACTATGCACAGAATCTCCAGGGCAGA AGACACATCCACGAGCACAGCCTACATGGAGCTGAGGAGC

		CACGGCCGTTTATTACTGTGCGAGGAGCAGTGGCCACTA
		GGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
		QVQVVQSGAEVKKPGASVKVSCKASGYTFSTFGITWVRQAPGQGLEWMGWISAY
		NGDTNYAQNLQGRVIMTTDTSTSTAYMELRSLRSDDTAVYYCARSSGHYYYYGM
		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
		SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE
		PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
		KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
		LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
		GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
		CAGGTTCAGGTGGTGCAGTCTGGAGCTGAGGTGAAGAAGC
		GAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTTCCACC
		GTGCGACAGGCCCCTGGACAAGGGCTTGAATGGATGGGAT
		CAATGGTGACACAAACTATGCACAGAATCTCCAGGGCAGA
		CACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGA
		CACGGCCGTTTATTACTGTGCGAGGAGCAGTGGCCACTAC
		GGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
		CCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGC
		CGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTG
		AACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTC
		CTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGG
		CACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGAC
		AAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCT
		GCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCC
		GACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTG
		TCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTG
		CACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTG
		GTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAG
		TGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAG
		GCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCCTAGCAGGGAC
		GAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCC
		TCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAG
		ACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTG
		TCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATG
		CACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGC

		Amino acid sequence of CDRL1
		Amino acid sequence of CDRL2
		Amino acid sequence of CDRL3
		DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNEYNYLDWYLQKPGQSPQLLIFLGS NRASGVPDRFSGSGSGTDFTLKITRVEAEDVGIYYCMQSLQTPLTFGGGTKVEIK
		Nucleic acid sequence of V
		Amino acid sequence of CDRH1
		Amino acid sequence of CDRH3

		QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLEWMGWISAY NGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARSTYFYGSGTLY	
	Nucleic acid sequence of V	CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGC GAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGC GGTGCGACAGGCCCCTGGACAAGGACTAGAGTGGATGGGA ACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAG CAGACACATCCACGAGCACAGCCTACATGGAGCTGAGGAG ACACGGCCGTGTATTACTGT TCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCAC	
		QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLEWMGWISAY NGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARSTYFYGSGTLY ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY	
		CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGC GAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGC GGTGCGACAGGCCCCTGGACAAGGACTAGAGTGGATGGGA ACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAG CACGAGCACAGCCTACATGGAGCTGAGGAGCTTGAGATCT ACACGGCCGTGTATTACTGTGCGAGATCTACGTATTTCTA TCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCAC GCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACC TCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCC GTGACCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCT GCTGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCT TCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCA ACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCT GTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCT CCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCCGAAGTGACCTGCG TGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGG ACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACT CCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACG	

			GCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAA AGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGC CCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGA AAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTG AGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCT GCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTC CTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTC CCTGAGCCCCGGCAAGTGATGA
	Amino acid sequence of CDRL1		
	Amino acid sequence of CDRL2		
	Amino acid sequence of CDRL3		
			DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNYLDWYLQKPGQSPQLLIYLGS TRASGFPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLSFGQGTKLEIK
	Nucleic acid sequence of V		GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCA TCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTGATGG TGTTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCAC TTGGGTTCTACTCGGGCCTCCGGGTTCCCTGACAGGTTCA GGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTG TATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTTTG
			DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNYLDWYLQKPGQSPQLLIYLGS TRASGFPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLSFGQGTKLEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
			GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCA GCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATA TGTTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCAC TTGGGTTCTACTCGGGCCTCCGGGTTCCCTGACAGGTTCA GGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTG TATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTTTG cgtacggtggccgctccctccgtgttcatcttcccaccttccgacgagcagctgaa gtccggcaccgcttctgtcgtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaag gtggacaacgccctgcagtccggcaactcccaggaatccgtgaccgagca

			ctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaa gtgacccaccagggcctgtctagccccgtgaccaagtctttcaaccgggggcgagtgt
	Amino acid sequence of CDRH1		
	Amino acid sequence of CDRH2		
	Amino acid sequence of CDRH3		
			QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLEWMGWISAY NGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARSTYFYGSGTLY
	Nucleic acid sequence of V		CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGC GAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGC GGTGCGACAGGCCCCTGGACAAGGACTAGAGTGGATGGGA ACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAG CAGACACATCCACGAGCACAGCCTACATGGAGCTGAGGAG ACACGGCCGTGTATTACTGTGCGAGATCTACGTATTTCTA TCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCAC
			QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLEWMGWISAY NGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARSTYFYGSGTLY ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
			CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGC GAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGC GGTGCGACAGGCCCCTGGACAAGGACTAGAGTGGATGGGA ACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAG CCACGAGCACAGCCTACATGGAGCTGAGGAGCTTGAGATC ACACGGCCGTGTATTACTGTGCGAGATCTACGTATTTCTA TCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCAC GCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTG GCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCC

		CCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTG TGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCA GCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACAC CAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCC CCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCC AAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGT GGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACG GCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCA CCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCA AAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGA CCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCC CTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAG GCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGA ACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTA GCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTG CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCT GAGCCCCGGCAAGTGATGA
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL3	
		DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNCLDWYLQKPGQSPQLLIYLGS TRASGFPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPCSFGQGTKLEIK
	Nucleic acid sequence of V	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCA TCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTG TGTTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCAC TTGGGTTCTACTCGGGCCTCCGGGTTCCCTGACAGGTTCA GGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTG TATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTTTG
		DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNCLDWYLQKPGQSPQLLIYLGS TRASGFPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPCSFGQGTKLEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

		GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCA GCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATA TGTTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCAC TTGGGTTCTACTCGGGCCTCCGGGTTCCCTGACAGGTTCA GGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTG TATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTTTG cgtacggtggccgctcccttccgtgttcatcttcccaccttccgacgagcagctgaa gtccggcaccgcttctgtcgtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaag gtggacaacgccctgcagtccggcaactcccaggaatccgtgaccgagca ctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaa gtgacccaccagggcctgtctagcccgtgaccaagtctttcaaccggggcgagtgt
	Amino acid sequence of CDRH1	
	Amino acid sequence of CDRH3	
		EVQLVESGGGVVRPGGSLRLSCVASGVTFDDYGMSWVRQAPGKGLEWVSGINWN GGDTDYSDSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDFYGSGSYYHV
	Nucleic acid sequence of V	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGC GAGACTCTCCTGTGTAGCCTCTGGAGTCACCTTTGATGAT GGTCCGCCAAGCTCCAGGGAAGGGGCTGGARTGGGTCTCT ATGGTGGCGACACAGATTATTCAGACTCTGTGAAGGGCCG GAGACAACGCCAAGAACTCCCTGTATCTACAAATGAATAG ACACGGCCTTGTATTACTGTGCGAGGGATTTCTATGGTTC ACGTTCCTTTTGACTACTGGGGCCAGGGAATCCTGGTCAC
		EVQLVESGGGVVRPGGSLRLSCVASGVTFDDYGMSWVRQAPGKGLEWVSGINWN GDTDYSDSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDFYGSGSYYHV ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT

		GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGC GAGACTCTCCTGTGTAGCCTCTGGAGTCACCTTTGATGAT GGTCCGCCAAGCTCCAGGGAAGGGGCTGGARTGGGTCTCT ATGGTGGCGACACAGATTATTCAGACTCTGTGAAGGGCCG GAGACAACGCCAAGAACTCCCTGTATCTACAAATGAATAG ACACGGCCTTGTATTACTGTGCGAGGGATTTTCTATGGTTC ACGTTCCTTTTGACTACTGGGGCCAGGGAATCCTGGTCAC GCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTG GCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGA CCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTG TGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCA GCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACAC CAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCC CCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCC ACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGT GGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACG GCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCA CCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCA AAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGA CCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCC CTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAG GCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGA ACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTA CAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGG CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCT GAGCCCCGGCAAGTGATGA
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL2	
	Amino acid sequence of CDRL3	
		EIVLTQSPGTLSLSPGERATLSCRASQSVSRSYLAWYQQKRGQAPRLLIYGASSRAT GIPDRFSGDGSGTDFTLSISRLEPEDFAVYYCHQYDMSPFTFGPGTKVDIK
	Nucleic acid sequence of V	GAAATTGTGTTGACGCAGTCTCCAGGGACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGAA TACCAGCAGAAACGTGGCCAGGCTCCCAGGCTCCTCATCT

			AGGGCCACTGGCATCCCAGACAGGTTCAGTGGCGATGGGT ACTCTCTCCATCAGCAGACTGGAGCCTGAAGATTTTGCAG AGTATGATATGTCACCATTCACTTTCGGCCCTGGGACCAA	
			EIVLTQSPGTLSLSPGERATLSCRASQSVSRSYLAWYQQKRGQAPRLLIYGASSRAT GIPDRFSGDGSGTDFTLSISRLEPEDFAVYYCHQYDMSPFTFGPGTKVDIK SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	
			GAAATTGTGTTGACGCAGTCTCCAGGGACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGAA TACCAGCAGAAACGTGGCCAGGCTCCCAGGCTCCTCATCT AGGGCCACTGGCATCCCAGACAGGTTCAGTGGCGATGGGT ACTCTCTCCATCAGCAGACTGGAGCCTGAAGATTTTGCAG AGTATGATATGTCACCATTCACTTTCGGCCCTGGGACCAA tacggtggccgctccctccgtgttcatcttcccaccttccgacgagcagctgaagtccggcaccgcttctgtc gtgtgcctgctgaacaacttctaccccgcgaggccaaggtgcagtggaaggtggacaacgccctgcag tccggcaactcccaggaatccgtgaccgagcaggactccaaggacagcacctactccctgtcctccaccc tgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgt ctagccccgtgaccaagtctttcaaccggggcgagtgt	
		Amino acid sequence of CDRH1		
		Amino acid sequence of CDRH3		
			EVQLVESGGGVVRPGGSLRLSCAASGLTFDDYGMSWVRQVPGKGLEWVSGINWN GDNTDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDYYGSGSYYNV	
		Nucleic acid sequence of V	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGC GAGACTCTCCTGTGCAGCCTCTGGACTCACCTTTGATGAT GGTCCGCCAAGTTCCAGGGAAGGGGCTGGAGTGGGTCTCT ATGGTGATAACACAGATTATGCAGACTCTGTGAAGGGCCG GAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAACAG ACACGGCCTTGTATTACTGT ACGTTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCAC	
			EVQLVESGGGVVRPGGSLRLSCAASGLTFDDYGMSWVRQVPGKGLEWVSGINWN DNTDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDYYGSGSYYNV	

		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT		
		GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGC GAGACTCTCCTGTGCAGCCTCTGGACTCACCTTTGATGAT GGTCCGCCAAGTTCCAGGGAAGGGGCTGGAGTGGGTCTCT ATGGTGATAACACAGATTATGCAGACTCTGTGAAGGGCCG GAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAACAG ACACGGCCTTGTATTACTGTGCGAGGGATTACTATGGTTC ACGTTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCAC GCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTG GCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGA CCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTG TGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCA GCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACAC CAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCC CCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCC ACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGT GGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACG GCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCA CCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCA AAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGA CCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCC CTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAG GCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGGCCAGCCTGAGA ACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTA CAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGG CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCT GAGCCCCGGCAAGTGATGA		
			Amino acid sequence of CDRL1	
			Amino acid sequence of CDRL2	

	Amino acid sequence of CDRL3	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQYGSSPFFGPGTKVDIK
		GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCA TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATAT AGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGT ACTCTCACCATCAGAAGACTGGAGCCTGAAGATTTTGCAG CAGTATGGTAGTTCACCATTCTTCGGCCCTGGGACCAAAG
	Nucleic acid sequence of V	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCA TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATAT AGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGT ACTCTCACCATCAGAAGACTGGAGCCTGAAGATTTTGCAG CAGTATGGTAGTTCACCATTCACTTCGGCCCTGGGACCAA
		EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQYG VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
		GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCA TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATAT AGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGT ACTCTCACCATCAGAAGACTGGAGCCTGAAGATTTTGCAG CAGTATGGTAGTTCACCATTCTTCGGCCCTGGGACCAAAG cggtggccgctcctccgtgttcatcttccacctccgacgagcagctgaagtccggcaccgcttctgtcg tgtgcctgctgaacaacttctaccccgcgaggccaaggtgcagtggaaggtggacaacgccctgcagt ccggcaactcccaggaatccgtgaccgagcaggactccaaggacag gaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgt ctagccccgtgaccaagtctttcaaccgggggcgagtgt
		GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCA TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATAT AGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGT ACTCTCACCATCAGAAGACTGGAGCCTGAAGATTTTGCAG

		CAGTATGGTAGTTCACCATTCACTTCGGCCCTGGGACCAA tacggtggccgctcccctccgtgttcatcttcccaccttccgacgagcagctgaagtccggcaccgcttctgtc gtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaaggtggacaacgccctgcag tccggcaactcccaggaatccgtgaccgagcaggactccaaggac tgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgt ctagccccgtgaccaagtctttcaaccggggcgagtgt
	Amino acid sequence of CDRH1	
	Amino acid sequence of CDRH3	
		QVQLVQSGAEVKKPGASVKVSCKASGYTFNSYGIIWVRQAPGQGLEWMGWISVH NGNTNCAQKLQGRVTMTTDTSTSTAYMELRSLRTDDTAVYYCARAGYDILTDFSD
	Nucleic acid sequence of V	CAGGTTCAGTTGGTGCAGTCTGGAGCTGAGGTGAAGAAGC GAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTAATAGT GGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGA ACAATGGTAACACAAACTGTGCACAGAAGCTCCAGGGTAG CAGACACATCCACGAGCACAGCCTACATGGAGCTGAGGAG ACACGGCCGTGTATTACTGTGCGAGAGCGGGTTACGATAT CCGATGCTTTTGATATCTGGGGCCACGGGACAATGGTCAC
		QVQLVQSGAEVKKPGASVKVSCKASGYTFNSYGIIWVRQAPGQGLEWMGWISVH GNTNCAQKLQGRVTMTTDTSTSTAYMELRSLRTDDTAVYYCARAGYDILTDFSD ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
		CAGGTTCAGTTGGTGCAGTC TGAGGTGAAGAAGCCTGGGG GAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTAATAGT GGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGA ACAATGGTAACACAAACTGTGCACAGAAGCTCCAGGGTAG CAGACACATCCACGAGCACAGCCTACATGGAGCTGAGGAG

TACTGTGCGAGAGCGGGTTACGATATTTTGACTGATTTTT CCGATGCTTTTGATATCTGGGGCCACGGGACAATGGTCAC GCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACC TCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCT GTGACCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCT GTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCT TCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCA ACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCT GTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCC CCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCG TGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGG ACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACT CCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACG GCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAA AGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGC CCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGA AAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTG AGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCT GTACAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTC CACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTC CCTGAGCCCCGGCAAGTGATGA			
	Amino acid sequence of CDRL1		
	Amino acid sequence of CDRL2		
		DIQMTQSPSSLSASVGDRVTITCRASQNINNFLNWYQQKEGKGPKLLIYAASSLQR GIPSTFSGSGSGTDFTLTISSLQPEDFATYICQQSYGIPWVGQGTKVEIK	
	Nucleic acid sequence of V	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGGCAAGTCAGAACATTAATAACTTTTTAAATTGGTATC AGCAGAAAGAAGGGAAAGGCCCTAAGCTCCTGATCTATGCAGCATCCAGTTTGC AAAGAGGGATACCATCAACGTTCAGTGGCAGTGGATCTGGGACAGACTTCACTC TCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTT CTACGGTATCCCGTGGGTCGGCCAAGGGACCAAGGTGGAAATCAAA	
		DIQMTQSPSSLSASVGDRVTITCRASQNINNFLNWYQQKEGKGPKLLIYAASSLQR GIPSTFSGSGSGTDFTLTISSLQPEDFATYICQQSYGIPWVGQGTKVEIK	

			RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
			GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGCAAGTCAGAACATTAATAACTTTTTAAATTGGTATC AGCAGAAAGAAGGGAAAGGCCCTAAGCTCCTGATCTATGCAGCATCCAGTTTGC AAAGAGGGATACCATCAACGTTCAGTGGCAGTGGATCTGGGACAGACTTCACTC TCACCATCAGCAGTCTGCAACCTGAAGATTTTTGCAACTT CTACGGTATCCCGTGGGTCGGCCAAGGGACCAAGGTGGAAATCAAA ccgctcctccgtgttcatcttccacctttccgacgagcagctgaagtccggcaccgcttctgtcgtgtgcct gctgaacaacttctaccccgcgaggccaaggtgcagtggaaggtggacaacgccctgcagtccggca actcccaggaatccgtgaccgagcaggactccaaggacagcacctactccctgtcctcaccctgaccct gtccaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgtctagcc ccgtgaccaagtctttcaaccggggcgagtgt
		Amino acid sequence of CDRH1	
		Amino acid sequence of CDRH3	ARDHYDGSGIYPLYYYYGLD
			QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYFMSWIRQAPGKGLEWISYISSSGS TIYYADSVRGRFTISRDNAKYSLYLQMNSLRSEDTAVYYCARDHYDGSGIYPLYYYY
		Nucleic acid sequence of V	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGC GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGAC GATCCGCCAGGCGCCCAGGGAAGGGGCTGGAGTGGATTTCA TGGTAGTACCATATACTACGCAGACTCTGTGAGGGGCCGA GGACAACGCCAAGTACTCACTGTATCTGCAAATGAACAGC CACGGCCGTGTATTACTGTGCGAGAGATCACTACGATGGT CCTCTACTACTATTACGGTTTGGACGTCTGGGGCCAGGGG
			QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYFMSWIRQAPGK TIYYADSVRGRFTISRDNAKYSLYLQMNSLRSEDTAVYYCARDHYDGSGIYPLYYYY ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN

			KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
			CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGC GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGAC GATCCGCCAGGCGCCAGGGAAGGGGCTGGAGTGGATTTCA TGGTAGTACCATATACTACGCAGACTCTGTGAGGGGCCGA GGACAACGCCAAGTACTCACTGTATCTGCAAATGAACAGC CACGGCCGTGTATTACTGTGCGAGAGATCACTACGATGGT CCTCTACTATTACGGTTTGGACGTCTGGGGCCAGGGG GCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAA GTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCC CGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACAC CTTCCCTGCTGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGAC CGTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAA GCCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGAC CCACACCTGTCCCCCTTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTT AAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGT GACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTG GTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAAC AGTACAACTCCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATT GGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCC CCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGT ACACACTGCCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCT GTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACG GCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCT CATTCTTCCTGTACAGCAAGCTGACAGTGGACAAGTCCCG ACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGA AGTCCCTGTCCCTGAGCCCCGGCAAGTGATGA	
		Amino acid sequence of CDRL1	
		Amino acid sequence of CDRL2	
		Amino acid sequence of CDRL3	
			IVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDYYLQKPGQSPQLLIYLGSY RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPRSFGQGTTLEIK

	Nucleic acid sequence of V	ATTGTGATGACTCAGTCTCCACTCTCCCTACCCGTCACCC TCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTA TGGATTATTACCTGCAGAAGCCAGGGCAGTCTCCACAGCT GTTCTTATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGG CAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGG ACTGCATGCAAGCTCTACAAACTCCTCGCAGTTTTGGCCA
		IVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDYYLQKPGQSPQLLIYLGSY RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPRSFGQGTTLEIK VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
		ATTGTGATGACTCAGTCTCCACTCTCCCTACCCGTCACCC TCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTA TGGATTATTACCTGCAGAAGCCAGGGCAGTCTCCACAGCT GTTCTTATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGG CAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGA ACTGCATGCAAGCTCTACAAACTCCTCGCAGTTTTGGCCA cgtacggtggccgctcctccctcgttcatcttcccaccttccgacgagcagctgaagtccg gcaccgcttctgtcgtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaaggtgg caacgccctgcagtccggcaactcccaggaatccgtgaccgagcaggactccaaggacagcacctactc cctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacc caccagggcctgtctagccccgtgaccaagtctttcaaccggggcgagtgt
	Amino acid sequence of CDRH1	
	Amino acid sequence of CDRH2	
	Amino acid sequence of CDRH3	
		QITLKESGPTLVKPTQTLTLTCTFSGFSLSTTGVGVGWIRQPPGKALEWLAVIYWD DDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYFCTHGYGSASYYHYGM
	Nucleic acid sequence of V	CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAAC ACGCTGACCTGCACCTTCTCTGGGTTCTCACTCAGCACTA GGCTGGATCCGTCAGCCCCCAGGAAAGGCCCTGGAGTGGC TGGGATGATGATAAGCGCTACAGCCCATCTCTGAAGAGCA AAGGACACCTCCAAAAACCAGGTGGTCCTTACAATGACCA

GACACAGCCACACATATTTCTGTACACACGGATATGGTTCGG ACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGT	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTTGVGVGWIRQPPGKALEWLAVIYWD DDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYFCTHGYGSASYYHYGM ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ	
	CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAAC ACGCTGACCTGCACCTTCTCTGGGTTCTCACTCAGCACTA GGCTGGATCCGTCAGCCCCCAGGAAAGGCCCTGGAGTGGC TGGGATGATGATAAGCGCTACAGCCCATCTCTGAAGAGCA CAAAACCAGGTGGTCCTTACAATGACCAACATGGACCCT GACACAGCCACACATATTTCTGTACACACGGATATGGTTCGG ACGGTATGGACGTCTGGGGC ACCACGGTCACCGTCTCCTC GCCAGCACCAAGGGCCCCTCTGTGTTCCCCTCTGGCCCCCTTCCAGCAAGTCCACC TCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCT GACCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCT GCTGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCT TCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCA ACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCT GTCCCCCTTGTCCTGCCCCCTGAACTGCTGGGCGGACCTTCC CCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCG TGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGG ACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACT CCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACG GCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAA AGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGC CCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGA AAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTG AGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCT GACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTC CTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTC CCTGAGCCCCGGCAAGTGATGA	

	Amino acid sequence of CDRL1						
	Amino acid sequence of CDRL2						
	Amino acid sequence of CDRL3						
			EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRLLIYDASNRAT GIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHRSNWPLTFGGGTKVEIK				
			GAAATTGTATTGACACAGTCTCCAGCCACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCAACT CAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG GCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTG CTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTT GTAGCAACTGGCCTCTCACTTTCGGCGGAGGGACCAAGGT				
			EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRLLIYDASNRAT GIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHRSNWPLTFGGGTKVEIK SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC				
			GAAATTGTATTGACACAGTCTCCAGCCACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCAACT CAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG GCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTG CTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTT GTAGCAACTGGCCTCTCACTTTCGGCGGAGGGACCAAGGT cggtggccgctccctccgtgttcatcttcccaccttccgacgagcagctgaagtccggcaccgcttctgtcg tgtgcctgctgaacaacttctaccccgcgaggccaaggtgcagtggaaggtggacaacgccctgcagt ccggcaactcccaggaatccgtgaccgagcaggactccaaggaca gaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgt ctagccccgtgaccaagtctttcaaccggggcgagtgt				
				Amino acid sequence of CDRH1			
						Amino acid sequence of CDRH3	

		QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWIRQPPGKALEWLAVIYWD DDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYFCTHGYGSASYYHYGM	
	Nucleic acid sequence of V	CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAAC ACGCTGACCTGCACCTTCTCTGGGTTCTCACTCAGCACTA GGCTGGATCCGTCAGCCCCCAGGAAAGGCCCTGGAGTGGC TGGGATGATGATAAGCGCTACAGCCCATCTCTGAAGAGCA AAGGACACCTCCAAAAACCAGGTGGTCCTTACAATGACCA GACACAGCCACATATTTCTGTACACACGGATATGGTTCGG ACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGT	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWIRQPPGKALEWLAVIYWD DDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYFCTHGYGSASYYHYGM ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ	
		CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAAC ACGCTGACCTGCACCTTCTCTGGGTTCTCACTCAGCACTA GGCTGGATCCGTCAGCCCCCAGGAAAGGCCCTGGAGTGGC TGGGATGATGATAAGCGCTACAGCCCATCTCTGAAGAGCA CCAAAAACCAGGTGGTCCTTACAATGACCAACATGGACCC GACACAGCCACATATTTCTGTACACACGGATATGGTTCGG ACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGT CCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCG GAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGT TGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGC TGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCT CTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAA GGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCC TTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAA GCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGT GGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGT GGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTA CCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAG	

			AGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCA TCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTA GCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCT TCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACA ACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAG GACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTC CGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAG
	Amino acid sequence of CDRL1		
	Amino acid sequence of CDRL2		
	Amino acid sequence of CDRL3		
			EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRLLIYDASNRAT GIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGGGTKVEIK
		Nucleic acid sequence of V	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCAACT CAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG GCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTG CTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTT GTAGCAACTGGCCTCTCACTTTCGGCGGAGGGACCAAGGT
			EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRLLIYDASNRAT GIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGGGTKVEIK SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
			GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGT GCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCAACT CAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG GCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTG CTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTT GTAGCAACTGGCCTCTCACTTTCGGCGGAGGGACCAAGGT ggtggccgctcccctccgtgttcatcttcccaccttccgacgagcagctgaagtccggcaccgcttctgtcgt gtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaaggtggacaacgccctgcagtc cggcaactcccaggaatccgtgaccgagcaggactccaaggacag

					accctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcctgtct agcccctgaccaagtctttcaaccgggggcgagtgt		
	Amino acid sequence of CDRH1						
	Amino acid sequence of CDRH3		ARDFYDILTDSPYFYYGVDV				
					QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISSSGS TIYYADSVKGRFTISRDNAKNSLYLQINSLRAEDTAVYYCARDFYDILTDSPYFYYG		
					CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCTG GATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAGTA GTGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCA GGGACAACGCCAAGAACTCACTGTATCTGCAAATTAACAGCC ACACGGCCGTGTATTACTGTGCGAGAGATTTTTACGATATTTTGACTGATAGTC CGTACTTCTACTACGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT		
					QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISSSGS TIYYADSVKGRFTISRDNAKNSLYLQINSLRAEDTAVYYCARDFYDILTDSPYFYYG ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT		
					CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCTG GATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAGTA GTGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCA CCAAGAACTCACTGTATCTGCAAATTAACAGCCTGAGAGCCGAGG ACACGGCCGTGTATTACTGTGCGAGAGATTTTTTACGATATTTTGACTGATAGTC CGTACTTCTACTACGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT GCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCCTTCCAGCAAGT		

		CCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTT AGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCT TCCCTGCTGTGCTGCAGTCCTCCGGCCTGTACTCCCTCTGTCCTCCGTCGTGACCG TGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCC CTCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCA CACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCT GTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGAC CTGCGTGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTA CGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGT ACAACTCCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGC TGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCA TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACA CACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTC TCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCC AGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCAT GTACAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACG TGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGT CCCTGTCCCTGAGCCCCGGCAAGTGATGA
	Amino acid sequence of CDRL1	
	Amino acid sequence of CDRL3	
		DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGS NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPRTFGQGTKVEIK
	Nucleic acid sequence of V	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCA GCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATA ATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACA TGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAG GGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTG TATTACTGCATGCAAGCTCTACAAACTCCTCGGACGTTCG
		DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGS NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPRTFGQGTKVEIK TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

		GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCA GCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATA ATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACA TGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAG GGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTG TATTACTGCATGCAAGCTCTACAAACTCCTCGGACGTTCG cgtacggtggccgctccctccgtgttcatcttcccaccttccgacgagcagctgaa gtccggcaccgcttctgtcgtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaag gtggacaacgccctgcagtccggcaactcccaggaatccgtgaccgagca ctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaa gtgacccaccagggcctgtctagcccgtgaccaagtctttcaaccggggcgagtgt
	———	VQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCM HELTCQAEGYPKAEVIWTSS —	
		———	
	Mature amino acid sequence of	EINGSANYEMFIFHNGGVQILCKYPDIVQQFKMQLLKGGQILCDLTKTKGSGNTVSI KSLKFCHSQLSNNSVSFFLYNLDHSHANYYFCNLSIFDPPPFKVTLTGGYLHIYESQL CCQLKFWLPIGCAAFVVVCILGCILICWLTKKKYSSSVHDPNGEYMFMRAVNTAKK	
	Amino acid sequence of human	EINGSANYEMFIFHNGGVQILCKYPDIVQQFKMQLLKGGQILCDLTKTKGSGNTVSI KSLKFCHSQLSNNSVSFFLYNLDHSHANYYFCNLSIFDPPPFKVTLTGGYLHIYESQL	
		_____EINGSANYEMFIFHNGGVQILCKYPDIVQQFKMQLLK GGQILCDLTKTKGSGNTVSIKSLKFCHSQLSNNSVSFFLYNLDHSHANYYFCNLSIF DPPPFKVTLTGGYLHIYESQLCCQLKFWLPIGCAAFVVVCILGCILICWLTKKKYSSS VHDPNGEYMFMRAVNTAKKSRLTDV	
		The sequence of this isoform differs from the canonical sequence in its cytoplasmic domain as follows: 168 KYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTLM	
	Amino acid sequence of mature	EINGSADHRMFSFHNGGVQISCKYPETVQQLKMRLFRREVLCELTKTKGSGNAVS IKNPMLCLYHLSNNSVSFFLNNPDSSQGSYYFCSLSIFDPPPFQERNLSGGYLHIYES	
	Amino acid sequence of the	EINGSADHRMFSFHNGGVQISCKYPETVQQLKMRLFRREVLCELTKTKGSGNAVS IKNPMLCLYHLSNNSVSFFLNNPDSSQGSYYFCSLSIFDPPPFQERNLSGGYLHIYES	

		Amino acid sequence of mouse	_____EINGSADHRMFSFHNGGVQISCKYPETVQQLKMRLFR EREVLCELTKTKGSGNAVSIKNPMLCLYHLSNNSVSFFLNNPDSSQGSYYFCSLSIF DPPPFQERNLSGGYLHIYESQLCCQLKIVVQVTE
			_____ FKMQLLKGGQILCDLTKTKG STVHDPNGEYMFMRAVNTAK
		cynomolgus ICOS extracellular	LCKYPDIVQQFKMQLLKGGQ
		Amino acid sequence of human	DTQEKEVRAMVGSDVELSCACPEGSRFDLNDVYVYWQTSESKTVVTYHIPQNSSL ENVDSRYRNRALMSPAGMLRGDFSLRLFNVTPQDEQKFHCLVLSQSLGFQEVLSVE VTLHVAANFSVPVVSAPHSPSQDELTFTCTSINGYPRPNVYWINKTDNSLLDQALQ NDTVFLNMRGLYDVVSVLRIARTPSVNIGCCIENVLLQQNLTVGSQTGNDIGERDK
			MRLGSPGLLFLLFSSLRADTQEKEVRAMVGSDVELSCACPEGSRFDLNDVYVYWQT SESKTVVTYHIPQNSSLENVDSRYRNRALMSPAGMLRGDFSLRLFNVTPQDEQKFH CLVLSQSLGFQEVLSVEVTLHVAANFSVPVVSAPHSPSQDELTFTCTSINGYPRPNV YWINKTDNSLLDQALQNDTVFLNMRGLYDVVSVLRIARTPSVNIGCCIENVLLQQN LTVGSQTGNDIGERDKITENPVSTGEKNAATWSILAVLCLLVVVAVAIGWVCRDRC LQHSYAGAWAVSPETELTGHV
		Amino acids 21 to 133 of hIL _____	_MLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKN FHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
		Amino acids 21 to 133 of hIL _____	_MLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKN FHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
			GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCA GCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATA TATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCAC TTGGGTTCTACTCGGGCCTCCGGGTTCCCTGACAGGTTCA GGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTG TATTACTGCATGCAAGCTCTACAAACTCCGCTCAGTTTTG

	corrected STIM002 light chain	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCA GCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATA TATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCAC TTGGGTTCTACTCGGGCCTCCGGGTTCCCTGACAGGTTCA GGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTG TATTACTGCATGCAAGCTCTACAAACTCCGCTCAGTTTTG cgtacggtggccgctcccctccgtgttcatcttcccaccttccgacgagcagctgaa gtccggcaccgcttctgtcgtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaag gtggacaacgccctgcagtccggcaactcccaggaatccgtgaccgagca ctactccctgtcctccacccctgaccctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaa gtgacccaccagggcctgtctagcccgtgaccaagtctttcaaccggggcgagtgt
		GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGC GAGACTCTCCTGTGTAGCCTCTGGAGTCACCTTTGATGAT GGTCCGCCAAGCTCCAGGGAAGGGGCTGGAGTGGGTCTCT ATGGTGGCGACACAGATTATTCAGACTCTGTGAAGGGCCG GAGACAACGCCAAGAACTCCCTGTATCTACAAATGAATAG ACACGGCCTTGTATTACTGTGCGAGGGATTTCTATGGTTC ACGTTCCTTTTGACTACTGGGGCCAGGGAATCCTGGTCAC
	corrected STIM003 heavy chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGC GAGACTCTCCTGTGTAGCCTCTGGAGTCACCTTTGATGAT GGTCCGCCAAGCTCCAGGGAAGGGGCTGGAGTGGGTCTCT ATGGTGGCGACACAGATTATTCAGACTCTGTGAAGGGCCG GAGACAACGCCAAGAACTCCCTGTATCTACAAATGAATAG ACACGGCCTTGTATTACTGTGCGAGGGATTTCTATGGTTC ACGTTCCTTTTGACTACTGGGGCCAGGGAATCCTGGTCAC GCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAG GCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTT CCGTGTCCTGGAACTCTGGC CAGCGGAGTGCACACCTTCC TGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGT GCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCA CAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAG CCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTG ACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGG GGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAAT GCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGA CCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGA AAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGC

			CCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGT CTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGAC GCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAA ACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGG CAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGG CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAG GAGCCCCGGCAAGTGATGA
		Human Heavy Chain Constant	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaagg tggacaagagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaact cctgggggaccgtcagtcttcttcttcccccaaaacccaaggacaccctcatgatctcccggaccccctg aggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacg gacaaagccgcgcgggaggagcagtacaacagcacgtaccgtgtggt cagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaa agccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgt acaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggct cccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccac gcctcccgtgctggactccgacggctccttcttcctctatagcaagctcaccgtggacaagagcaggtggc agcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcct
		Human Heavy Chain Constant Region (IGHG1*03) Protein	A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K
		Human Heavy Chain Constant Region (IGHG1*04) Nucleotide	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact tgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaagg tggacaagaaagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaact

			cctgggggacgtcagtcttcctcttccccccaaaacccaaggacaccctcatgatctcccggaccctg aggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacg gcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtggt cagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaa agccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgt ccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggctt ctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacg cctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggca gcaggggaacatcttctcatgctccgtgatgcatgaggctctgcacaaccactaca
		Human Heavy Chain Constant Region (IGHG1*04) Protein	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNHYTQKSLSLSPGK
		Human Heavy Chain Constant Region (IGHG2*01) Nucleotide	gcctccaccaagggcccatcggtcttccccctggcgccctgctccaggagcacctccgagagcacagccg ccctgggctgcctggtcaaggactacttccccgaaccggtgacgttgtcgtggaactcaggcgctctgac cagcggcgtgcacaccttcccagctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcaacttcggcacccagacctacacctgcaacgtagatcacaagcccagcaacaccaagg tggacaagacagttgagcgcaaatgttgtgtcgagtgcccaccgtgcccagcaccacctgtggcaggac cgtcagtcttcctcttccccccaaaacccaaggacaccctcatgatctcccggaccctgaggtcacgtgcg tggtggtggacgtgagccacgaagaccccgaggttcaagttcaactggtacgtggacggcgtggaggtg ggaggagcagttcaacagcacgttccgtgtggtcagcgtcctcacc gttgtgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccagc ccccatcgagaaaaccatctccaaaaccaaagggcagccccgagaaccacaggtgtacaccctgcccc catcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctacccagcg gccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacacctcccatgctg gactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaac gtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccg
		Human Heavy Chain Constant Region (IGHG2*01) Protein	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

		Human Heavy Chain Constant Region (IGHG2*02) Nucleotide	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACC TCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG GTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCG GCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGACC TCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAG ACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGT GCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAA GGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGT GAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCATGGAGG TGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTG TGGTCAGCGTCCTCACCGTCGTGCACCAGGACTGGCTGAACGGCAAGGAGTACA AGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAA AACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA GGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCC GCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACA AGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCT CACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT GCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGG
		Human Heavy Chain Constant Region (IGHG2*02) Protein	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVTSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGMEVHNAKT KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
		Human Heavy Chain Constant Region (IGHG2*04) Nucleotide	gcctccaccaagggcccatcggtcttccccctggcgccctgctccaggagcacctccgagagcacagcg gccctgggctgcctggtcaaggactacttccccgaaccggtgacgtgtcgtggaactcaggcgctctga ccagcggcgtgcacaccttcccagctgtcctacagtcctcaggactctactccctcagcagcgtggtgacc gtgccctccagcagcttgggcacccagacctacacctgcaacgtag gtggacaagacagttgagcgcaaatgttgtgtcgagtgcccaccgtgcccagcaccacctgtggcagga ccgtcagtcttcctcttccccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacgtgc gtggtggtggacgtgagccacgaagaccccgaggtccagttcaactggtacgtggacggcgtggaggt gcataatgccaagacaaagccacgcgggaggagcagttcaacagcacgttccgtgtggtcagcgtcctcac cgttgtgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccag ccccatcgagaaaaccatctccaaaaccaaagggcagccccgagaaccacaggtgtacaccctgccc ccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctaccccagc gccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacacctcccatgct

				ggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcagggaa cgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctcc
			Human Heavy Chain Constant Region (IGHG2*04) Protein	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
			Human Heavy Chain Constant Region (IGHG2*06) Nucleotide	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACC TCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG GTGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCG GCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC TCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAG ACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGT GCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCAAAACCCAA GGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGT GAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGG TGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTG TGGTCAGCGTCCTCACCGTCGTGCACCAGGACTGGCTGAACGGCAAGGAGTACA AGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAA AACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGA GGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCC TCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAA GACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG CATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT
			Human Heavy Chain Constant Region (IGHG2*06) Protein	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTPPMLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
			Cλ Light Chain Constant Region	GGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCACCCTCCTCTGAGGAG CTTCAAGCCAACAAGGCCACACTGGTGTGTCTCGTAAGTGACTTCAACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATGGCAGCCCCGTCAAGGTGGGAGTGGA

				GACCACCAAACCCTCCAAACAAAGCAACAACAAGTATGCGGCCAGCAGCTACCT GAGCCTGACGCCCGAGCAGTGGAAGTCCCACAGAAGCTACA GCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTGCAGAATGCTCT
			Cλ Light Chain Constant Region	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFNPGAVTVAWKADGSPVKVGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECS
			WT human IgG1 nucleotide	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg ccctggctgcctggtcaaggactacttccccgaaccggtgacgtgtcgtggaactcaggcgccctgac cagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccg tgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaagg tggacaagaaagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaact cctgggggggaccgtcagtcttcctcttccccccaaaacccaaggacaccctcatgatctcccggaccccctg aggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacg gacaaagccgcgcgggaggagcagtacaacagcacgtaccgggtggt cagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaa agccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgt acaccctgcccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggctt cccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacg cctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggca gcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctc
			Cλ Light Chain Constant Region Encoded by nucleotide sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSK QSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
			Expressed protein corresponds as per full length sequence Protein domains annotated Campath leader (double line),	**MMTGTIETTGNISAEKGGSIILQCHLSSTTAQV** **TQVNWEQQDQLLAICNADLGWHISPSFKDRVAPGPGLGLTLQSLTVND** **TGEYFCIYHTYPDGTYTGRIFLEVLESSVAEHGARFQIP**

Claims

1. An antibody or a fragment thereof, which specifically binds to hPD-L1 as defined by Seq ID No:1, and competes for binding to said hPD-L1 with the antibody 1D05, wherein the antibody or fragment comprises a V_H domain which comprises a CDRH3 comprising the motif $X_1GSGX_2YGX_3X_4FD$, wherein X_1, X_2 and X_3 are independently any amino acid, and X_4 is either present or absent, and if present, may be any amino acid.

2. The antibody or fragment according to claim 1, wherein X_1 is a hydroxyl-containing amino acid, optionally T.

3. The antibody or fragment according to claim 1 or claim 2, wherein X_2 is a basic amino acid, optionally K.

4. The antibody or fragment according to any one of claims 1 to 3, wherein X_2 is a hydroxyl-containing amino acid, optionally S or T.

5. The antibody or fragment according to any one of claims 1 to 4, wherein X_3 is an aromatic amino acid, optionally W.

6. The antibody or fragment according to any one of claims 1 to 5, wherein X_4 is absent.

7. The antibody or fragment according to any one of claims 1 to 5, wherein X_4 is present.

8. The antibody or fragment according to claim 7, wherein X_4 is an aliphatic amino acid, optionally G.

9. An antibody or a fragment thereof, optionally according to any one of claims 1 to 8, which specifically binds to hPD-L1, and competes for binding to said hPD-L1 with the antibody 1D05, wherein the antibody or fragment comprises a V_H domain which comprises the CDRH3 sequence of SEQ ID NO:29 or 32, or the CDRH3 sequence of SEQ ID NO:29 or 32 comprising 6 or fewer amino acid substitutions.

10. An antibody or fragment which specifically binds to hPD-L1 and comprises a V_H domain comprising a CDRH3 of from 12 to 20 amino acids and which is derived from the recombination of a human V_H gene segment, a human D gene segment and a human J_H gene segment, wherein the human J_H gene segment is IGHJ5 (e.g. IGHJ5*02).

11. The antibody or fragment according to claim 10, wherein the human V_H gene segment is IGHV3 (e.g. IGHV3-9, such as IGHV3-9*01).

12. The antibody or fragment according to claim 10 or claim 11, wherein the antibody or fragment comprises a V_L domain which is derived from the recombination of a human V_K gene segment,

and a human Jκ gene segment, wherein the human Vκ gene segment is IGκV1D (e.g. IGκV1D-39, suc -39*01).

13. An antibody or fragment thereof which specifically binds to an epitope that is identical to an epitope to which the antibody 1D05 specifically binds.

14. The antibody or fragment according to claim 13, wherein the epitope is identified by unrelated amino acid scanning, or by X-ray crystallography.

15. The antibody or fragment according to claim 14, wherein the contact residues of the epitope are defined by a reduction in affinity of at least 10-fold in an unrelated amino acid scan, e.g. an alanine scan as determined by SPR.

16. An antibody or fragment thereof which competes for binding to hPD-L1 with the antibody 1D05.

17. The antibody or fragment according to any one of claims 10 to 16, wherein the V_H domain comprises the CDRH3 sequence of SEQ ID NO:29 or 32, or the CDRH3 sequence of SEQ ID NO:29 or 32 comprising 6 or fewer amino acid substitutions.

18. The antibody or fragment according to any preceding claim, wherein the V_H domain comprises the CDRH1 sequence of SEQ ID NO:27 or 30 or the CDRH1 sequence of SEQ ID NO:27 or 30 comprising 3, 2 or 1 amino acid substitution(s).

19. The antibody or fragment according to any preceding claim, wherein the V_H domain comprises the CDRH2 sequence of SEQ ID NO:28 or 31, or the CDRH2 sequence of SEQ ID NO:28 or 31 comprising 4 or fewer amino acid substitutions.

20. The antibody or fragment according to any preceding claim, wherein the V_H domain comprises an amino acid sequence of SEQ ID NO:33, or a heavy chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:33.

21. The antibody or fragment according to any preceding claim comprising first and second copies of said V_H domain.

22. The antibody or fragment according to any preceding claim, comprising a V_L domain which comprises the CDRL1 sequence of SEQ ID NO:37 or 40, or the CRDL1 sequence of SEQ ID NO:37 or 40 comprising 3 or fewer amino acid substitutions.

23. The antibody or fragment according to any preceding claim, comprising a or said V_L domain, which V_L domain comprises the CDRL2 sequence of SEQ ID NO:38 or 41, or the CRDL2 sequence of SEQ ID NO:38 or 41 comprising 2 or 1 amino acid substitution(s), for example a CDRL2 sequence of Seq ID No:50.

24. The antibody or fragment according to any preceding claim, comprising a or said V_L domain, which V_L domain comprises the CDRL3 sequence of SEQ ID NO:39 or 42, or the CRDL3 sequence of SEQ ID NO:39 or 42 comprising 4 or fewer amino acid substitutions.

25. The antibody or fragment according to any preceding claim, comprising a or said V_L domain, which V_L domain comprises an amino acid sequence of SEQ ID NO:43, or a light chain variable domain amino acid sequence that is at least 80% (e.g. at least 85%, or at least 90%) identical to SEQ ID NO:43 (for example the VL domain sequence in the light chain sequence of Seq ID No:50, 51 or 298).

26. The antibody or fragment according to any one of claims 12 to 21, comprising first and second copies of a or said V_L domain.

27. The antibody or fragment according to any preceding claim which specifically binds to cynomolgus PD-L1 as defined by Seq ID No:2.

28. The antibody or fragment according to any preceding claim, wherein the antibody or fragment comprises a kappa light chain.

29. The antibody or fragment according to any one of claims 9 to 28, wherein the amino acid substitutions are conservative amino acid substitutions, optionally wherein the conservative substitutions are from one of six groups (each group containing amino acids that are conservative substitutions for one another) selected from:

    1) Alanine (A), Serine (S), Threonine (T);

    2) Aspartic acid (D), Glutamic acid (E);

    3) Asparagine (N), Glutamine (Q);

    4) Arginine (R), Lysine (K);

    5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and

    6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

30. The antibody or fragment according to any preceding claim, wherein the antibody or fragment comprises a constant region, such as a human constant region, for example an effector-null human constant region, e.g. an IgG4 constant region or an IgG1 constant region, optionally wherein the constant region is IgG4-PE (Seq ID No:199), or a disabled IgG1 as defined in Seq ID No:205.

31. The antibody or fragment according to claim 30, wherein the constant region is a murine constant region.

32. The antibody or fragment according to claim 30 or claim 31, wherein the constant region has CDC and/or ADCC activity.

33. The antibody according to any preceding claim wherein the:

a) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

b) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:33, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:43;

c) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

d) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

e) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

f) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:342 and the V_L domain comprises an amino acid sequence of SEQ ID No:43;

g) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

h) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

i) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

j) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

k) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:342 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:50;

l) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

m) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

n) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

o) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

p) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:342 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:51;

q) V_H domain comprises an amino acid sequence of SEQ ID No:33 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

r) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:47 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

s) V_H domain comprises an amino acid sequence of the V_H domain of SEQ ID No:48 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

t) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:49 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

u) V_H domain comprise an amino acid sequence of the V_H domain of SEQ ID No:342 and the V_L domain comprises an amino acid sequence of the V_L domain of SEQ ID No:298;

v) V_H domain comprises an amino acid sequence of SEQ ID No:58 and the V_L domain comprises an amino acid sequence of SEQ ID No:68;

w) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:58, and the V_L domain comprise an amino acid sequence that is at least 85% identical to SEQ ID No:68;

x) V_H domain comprises an amino acid sequence of SEQ ID No:78 and the V_L domain comprises an amino acid sequence of SEQ ID No:88;

y) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:78, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:88;

z) V_H domain comprises an amino acid sequence of SEQ ID No:98 and the V_L domain comprises an amino acid sequence of SEQ ID No:108;

aa) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:98, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:108;

bb) V_H domain comprises an amino acid sequence of SEQ ID No:118 and the V_L domain comprises an amino acid sequence of SEQ ID No:128;

cc) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:118, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:128;

dd) V_H domain comprises an amino acid sequence of SEQ ID No:158 and the V_L domain comprises an amino acid sequence of SEQ ID No:168;

ee) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:158, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:168;

ff) V_H domain comprises an amino acid sequence of SEQ ID No:178 and the V_L domain comprises an amino acid sequence of SEQ ID No:188;

gg) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:178, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:188

hh) V_H domain comprises an amino acid sequence of SEQ ID No:138 and the V_L domain comprises an amino acid sequence of SEQ ID No:148;

ii) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:138 and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:148;

jj) V_H domain comprises an amino acid sequence of SEQ ID No:244 and the V_L domain comprises an amino acid sequence of SEQ ID No:254;

kk) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:244, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:254;

ll) V_H domain comprises an amino acid sequence of SEQ ID No:264 and the V_L domain comprises an amino acid sequence of SEQ ID No:274;

mm) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:264, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:274;

nn) V_H domain comprises an amino acid sequence of SEQ ID No:284 and the V_L domain comprises an amino acid sequence of SEQ ID No:294; and

oo) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:284, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:294;

pp) V_H domain comprises an amino acid sequence of SEQ ID No:349 and the V_L domain comprises an amino acid sequence of SEQ ID No:359; and

qq) V_H domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:349, and the V_L domain comprises an amino acid sequence that is at least 85% identical to SEQ ID No:359.

34. The antibody according to any preceding claim wherein the antibody comprises a heavy chain and a light chain, and

rr) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

ss) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:45;

tt) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:47 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

uu) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:48 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

vv) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:49 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

ww) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:342 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:45;

xx) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

yy) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:47 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

zz) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:48 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

aaa) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:49 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

bbb) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:342 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:50;

ccc) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

ddd) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:47 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

eee) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:48 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

fff) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:49 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

ggg) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:342 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:51;

hhh) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:35 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

iii) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:47 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

jjj) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:48 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

kkk) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:49 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

lll) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:342 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:298;

mmm) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:60 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:70;

nnn) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:60, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:70;

ooo) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:80 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:90;

ppp) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:80, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:90;

qqq) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:100 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:110;

rrr) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:100, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:110;

sss) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:120 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:130;

ttt) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:120, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:130;

uuu) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:160 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:170;

vvv) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:160, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:170;

www) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:180 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:190;

xxx) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:180, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:190;

yyy) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:140 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:150;

zzz) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:140, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:150;

aaaa)the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:246 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:256;

bbbb) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:246, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:256;

cccc) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:266 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:276;

dddd) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:266, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:276;

eeee)the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:286 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:296; and

ffff)the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:286, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:296.

gggg) the heavy chain amino acid sequence comprises an amino acid sequence of SEQ ID No:351 and the light chain amino acid sequence comprises an amino acid sequence of SEQ ID No:361; and

hhhh) the heavy chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:351, and the light chain amino acid sequence comprises an amino acid sequence that is at least 85% identical to SEQ ID No:361.

35. The antibody or fragment according to any preceding claim which competes for binding to hPD-L1 with the antibody 1D05, optionally wherein the competition for binding to hPDL-1 is conducted using SPR.

36. The antibody or fragment according to any preceding claim wherein the antibody or fragment is capable of inhibiting PD-L1-mediated suppression of T-cells, optionally wherein the suppression of T-cells is measured by an increase in one or more of IFN , IL-2, CD25 or proliferation of T-cells in an assay that provides co-stimulation by either direct CD3/CD28 stimulation, superantigen

stimulation or provides co-stimulation by co-incubation with cells capable of inducing a T-cell response.

37. A bispecific antibody or fusion protein comprising an antibody or fragment thereof as defined in any preceding claim.

38. The bispecific antibody according to claim 37, wherein the bispecific format is selected from DVD-Ig, mAb^2, FIT-Ig, mAb-dAb, dock and lock, SEEDbody, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, Fab-scFv-Fc, Fab-scFv, intrabody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH_3, Diabody-CH_3, minibody, knobs-in-holes, knobs-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs, charge pairs, charge pairs with common light chain, in particular mAb^2, knob-in-holes, knob-in-holes with common light chain, knobs-in-holes with common light chain and charge pairs and FIT-Ig, e.g. mAb^2 and FIT-Ig.

39. The bispecific antibody according to claim 37 or claim 38, wherein the bispecific antibody specifically binds to hPD-L1 and another target antigen selected from immune checkpoint inhibitors (such as PD-1, CTLA-4, TIGIT, TIM-3, LAG-3 and VISTA, e.g. TIGIT, TIM-3 and LAG-3), immune modulators (such as BTLA, hHVEM, CSF1R, CCR4, CD39, CD40, CD73, CD96, CXCR2, CXCR4, CD200, GARP, SIRPα, CXCL9, CXCL10, CD155 and CD137, e.g. GARP, SIRPα, CXCR4, BTLA, hVEM and CSF1R), immune activators (such as CD137, GITR, OX40, CD40, CXCR3 (e.g. agonistic anti-CXCR3 antibodies), CD3, CD27 and ICOS (e.g. agonistic anti-ICOS antibodies), for example ICOS, CD137, GITR and OX40).

40. The bispecific antibody according to claim 39, wherein the another target antigen is TIGIT or LAG3.

41. An antibody or fragment as defined in any preceding claim for use in treating or preventing a hPD-L1-mediated disease or condition, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

42. Use of an antibody or fragment as defined in any one of claims 1 to 40 in the manufacture of a medicament for administration to a human for treating or preventing a hPD-L1 mediated disease or condition in the human, e.g. selected from neoplastic or non-neoplastic disease, chronic viral

infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas).

43. A method of treating or preventing a hPD-L1 mediated disease or condition, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease and diffuse large B-cell lymphoma (for example melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or for example virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas) in a human, comprising administering to said human a therapeutically effective amount of an antibody or fragment as defined in any one of claims 1 to 40, wherein the hPD-L1 mediated disease or condition is thereby treated or prevented.

44. The antibody or fragment according to claim 41, the use according to claim 42 or the method according to claim 43, wherein the hPD-L1-mediated disease or condition is cancer.

45. The antibody or fragment, the use or the method according to claim 44, wherein the cancer is selected from melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma and mesothelioma or is selected from virally induced cancers (such as cervical cancer and nasopharyngeal cancer) and soft tissue sarcomas.

46. The antibody or fragment according to claim 41, the use according to claim 42 or the method according to claim 43, wherein the hPD-L1-mediated disease or condition is a neurodegenerative disease, disorder or condition, e.g. selected from Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, corticobasal degeneration, Rett syndrome, a retinal degeneration disorder selected from age-related macular degeneration and retinitis pigmentosa; anterior ischemic optic neuropathy, glaucoma, uveitis, depression, trauma-associated stress or post-traumatic stress disorder, frontotemporal dementia, Lewy body dementias, mild cognitive

impairments, posterior cortical atrophy, primary progressive aphasia and progressive supranuclear palsy or aged-related dementia, in particular, the neurodegenerative disease, disorder or condition is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease, for example, Alzheimer's disease.

47. The antibody or fragment, use or the method according to any one of claims 41 to 46, further comprising administering to the human a further therapy, for example a further therapeutic agent, optionally wherein the further therapeutic agent is independently selected from the group consisting of:

a) other immune checkpoint inhibitors (such as anti-TIM-3 antibodies, anti-CTLA-4 antibodies, anti-TIGIT antibodies and anti-LAG-3 antibodies);

b) immune stimulators (such as anti-OX40 antibodies, anti-GITR antibodies, anti-CD137 antibodies, anti-ICOS antibodies and anti-CD40 antibodies);

c) chemokine receptor antagonists (such as CXCR4, CCR4 and CXCR2);

d) targeted kinase inhibitors (such as CSF-1R or VEGFR inhibitors);

e) angiogenesis inhibitors (such as anti-VEGF-A or Delta-like Ligand-4);

f) immune stimulating peptides or chemokines (such as CXCL9 or CXCL10);

g) cytokines (such as IL-15 and IL-21);

h) bispecific T-cell engagers (BiTEs) having at least one specificity against CD3 (e.g. CD3/CD19 BiTE);

i) other bi-specific molecules (for example IL-15-containing molecules targeted towards tumour associated antigens, for example Epidermal growth factor receptors such as EGFR, Her-2, New York Esophageal Cancer-1 (NY-ESO-1), GD2, EpCAM or Melanoma Associated Antigen-3 (MAGE-A3));

j) oncolytic viruses (such as HSV virus (optionally which secretes GMCSF), Newcastle disease virus and Vaccinia virus);

k) vaccination with tumour associated antigens (such as New York Esophageal Cancer-1 [NY-ESO-1], Melanoma Associated Antigen-3 [MAGE-3]);

l) cell-based therapies (such as chimeric Antigen Receptor-T-cells (CAR-T) for example expressing anti-CD19, anti-EpCam or anti-mesothelin);

m) bi-specific NK cell engagers having a specificity against an activating MK receptor such as NKG2D or CD16a; and

n) adoptive transfer of tumour specific T-cells or LAK cells,

or optionally wherein the further therapy is chemotherapy, radiotherapy and surgical removal of tumours.

48. A pharmaceutical composition comprising an antibody of fragment as defined in any one of claims 1 to 40 and a pharmaceutically acceptable excipient, diluent or carrier and optionally further comprising a further therapeutic agent independently selected from the group consisting of:

A) other immune checkpoint inhibitors (such as anti-TIM-3 antibodies, anti-CTLA-4 antibodies, anti-TIGIT antibodies and anti-LAG-3 antibodies);

B) immune stimulators (such as anti-OX40 antibodies, anti-GITR antibodies, anti-CD137 antibodies, anti-ICOS antibodies and anti-CD40 antibodies);

C) chemokine receptor antagonists (such as CXCR4, CCR4 and CXCR2);

D) targeted kinase inhibitors (such as CSF-1R or VEGFR inhibitors);

E) angiogenesis inhibitors (such as anti-VEGF-A or Delta-like Ligand-4);

F) immune stimulating peptides or chemokines (such as CXCL9 or CXCL10);

G) cytokines (such as IL-15 and IL-21);

H) bispecific T-cell engagers (BiTEs) having at least one specificity against CD3 (e.g. CD3/CD19 BiTE);

I) other bi-specific molecules (for example IL-15-containing molecules targeted towards tumour associated antigens, for example Epidermal growth factor receptors such as EGFR, Her-2, New York Esophageal Cancer-1 (NY-ESO-1), GD2, EpCAM or Melanoma Associated Antigen-3 (MAGE-A3));

J) oncolytic viruses (such as HSV virus (optionally which secretes GMCSF), Newcastle disease virus and Vaccinia virus);

K) vaccination with tumour associated antigens (such as New York Esophageal Cancer-1 [NY-ESO-1], Melanoma Associated Antigen-3 [MAGE-3]);

L) cell-based therapies (such as chimeric Antigen Receptor-T-cells (CAR-T) for example expressing anti-CD19, anti-EpCam or anti-mesothelin);

M) bi-specific NK cell engagers having a specificity against an activating MK receptor such as NKG2D or CD16a; and

N) adoptive transfer of tumour specific T-cells or LAK cells.

49. A pharmaceutical composition according to claim 48, or a kit comprising a pharmaceutical composition as defined in claim 48, wherein the composition is for treating and/or preventing a hPD-L1-mediated condition or disease, e.g. selected from neoplastic or non-neoplastic disease, chronic viral infections, and malignant tumours, such as melanoma, Merkel cell carcinoma, non-small cell lung cancer (squamous and non-squamous), renal cell cancer, bladder cancer, head and neck squamous cell carcinoma, mesothelioma, virally induced cancers (such as cervical cancer and nasopharyngeal cancer), soft tissue sarcomas, haematological malignancies such as Hodgkin's and non-Hodgkin's disease, diffuse large B-cell lymphoma.

50. A pharmaceutical composition according to claim 48, or a kit comprising a pharmaceutical composition as defined in claim 48, wherein the composition is for treating and/or preventing a neurodegenerative disease, disorder or condition, e.g. selected from Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, corticobasal degeneration, Rett syndrome, a retinal degeneration disorder selected from age-related macular degeneration and retinitis pigmentosa; anterior ischemic optic neuropathy, glaucoma, uveitis, depression, trauma-associated stress or post-traumatic stress disorder, frontotemporal dementia, Lewy body dementias, mild cognitive impairments, posterior cortical atrophy, primary progressive aphasia and progressive supranuclear palsy or aged-related dementia, in particular, the neurodegenerative disease, disorder or condition is selected from Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease, for example, Alzheimer's disease.

51. A pharmaceutical composition according to claim 48, claim 49 or claim 50 in combination with, or kit according to claim 49 or claim 50 comprising, a label or instructions for use to treat and/or prevent said disease or condition in a human; optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number); optionally wherein the kit comprises an IV or injection device that comprises the antibody or fragment.

52. A method of modulating PD-1/PD-L1 interaction in a patient, comprising administering an effective amount of an antibody or fragment as defined in any one of claims 1 to 40 to said patient.

53. A method of inhibiting PD-L1 activity in a patient, comprising administering an effective amount of an antibody or fragment as defined in any one of claims 1 to 40 to said patient.

54. A method of treating a proliferative disease in an animal (e.g. a human), comprising administering an effective amount of an antibody or fragment as defined in any one of claims 1 to 40 to said patient.

55. A nucleic acid that encodes the CDRH3 of an antibody or fragment as defined in any one of claims 1 to 40.

56. A nucleic acid that encodes a V_H domain and/or a V_L domain of an antibody or fragment as defined in any one of claims 1 to 40.

57. The nucleic acid according to claim 56 comprising a nucleotide sequence that is at least 80% identical to the sequence of SEQ ID NO:36 and/or SEQ ID NO:46.

58. A nucleic acid that encodes a heavy chain or a light chain of an antibody as defined in any one of claims 1 to 40.

59. A vector comprising the nucleic acid as defined in any one of claims 55 to 58; optionally wherein the vector is a CHO or HEK293 vector.

60. A host comprising the nucleic acid of any one of claims 55 to 58 or the vector as defined in claim 59.

61. An immunocytokine comprising an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

o) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and

p) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

q) A V_L domain comprising CDRL1, CDRL2 and CDRL3;

r) A light chain constant region, (C_L);

s) Optionally, a linker, (L); and

t) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to hPD-L1 as defined by Seq ID No:1, and competes for binding to said hPD-L1 with the antibody 1D05; and

wherein the immunocytokine comprises a V_H domain which comprises a CDRH3 comprising the motif $X_1GSGX_2YGX_3X_4FD$, wherein X_1, X_2 and X_3 are independently any amino acid, and X_4 is either present or absent, and if present, may be any amino acid.

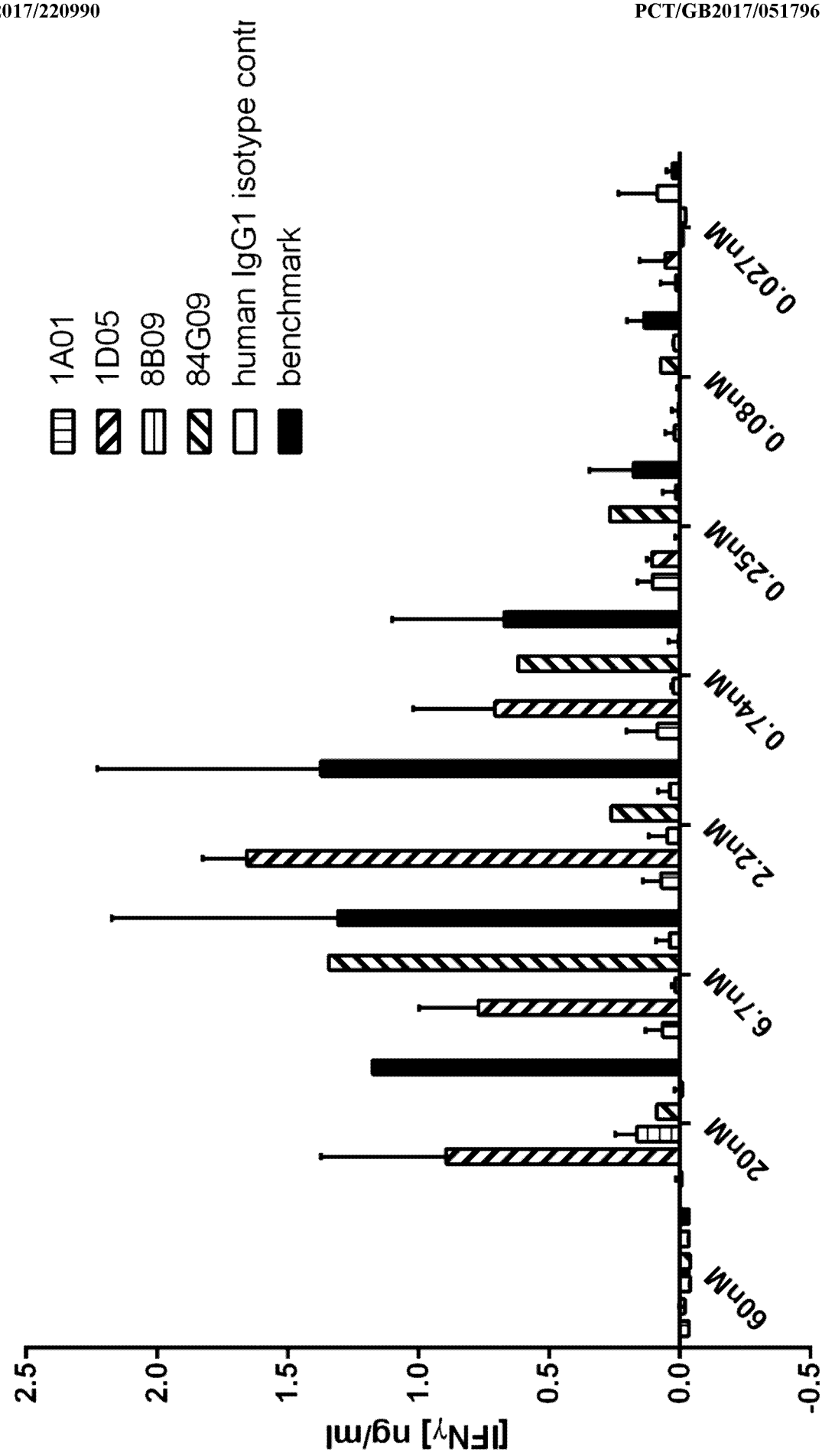

1A01
1D05
8B09
84G09
human IgG1 isotype contr
benchmark
[IFNγ] ng/ml
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
60nM
20nM
6.7nM
2.2nM
0.74nM
0.25nM
0.08nM
0.027nM

Figure 1

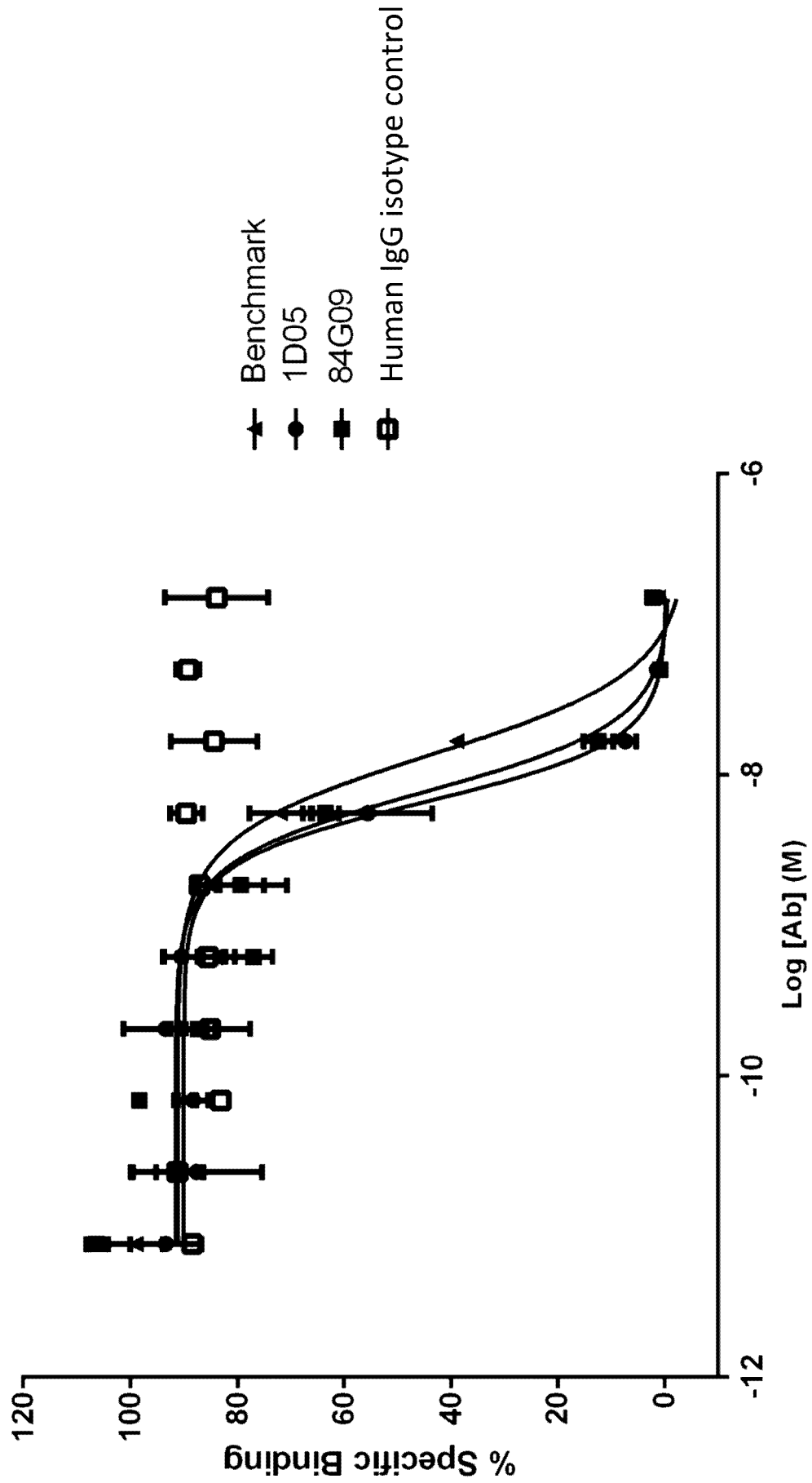

Benchmark
1D05
84G09
Human IgG isotype control
% Specific Binding
120
100
80
60
40
20
0
-12
-10
-8
-6
Log [Ab] (M)

Figure 2

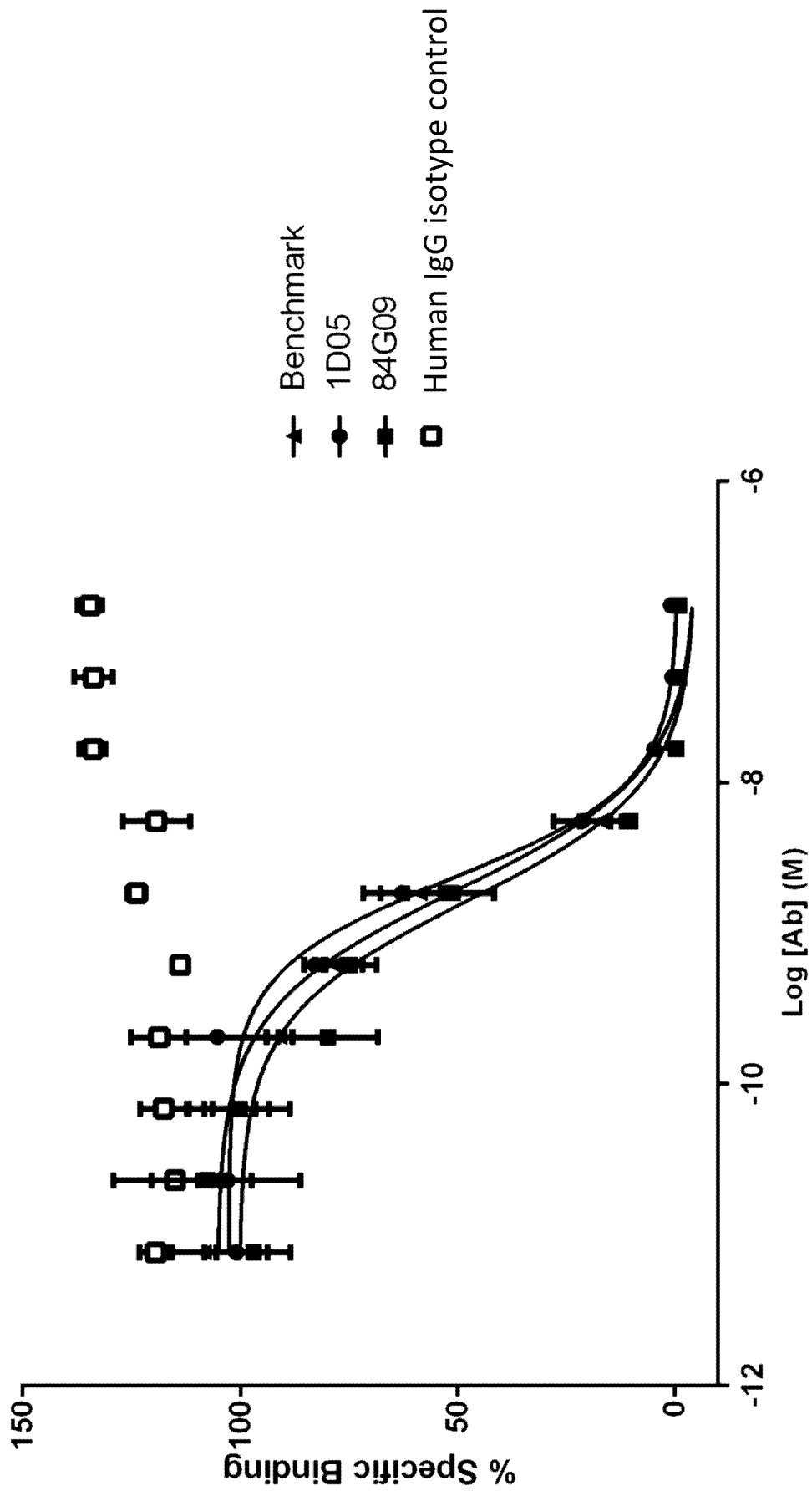

Benchmark
1D05
84G09
Human IgG isotype control
% Specific Binding
150
100
50
0
-12
-10
-8
-6
Log [Ab] (M)

Figure 3

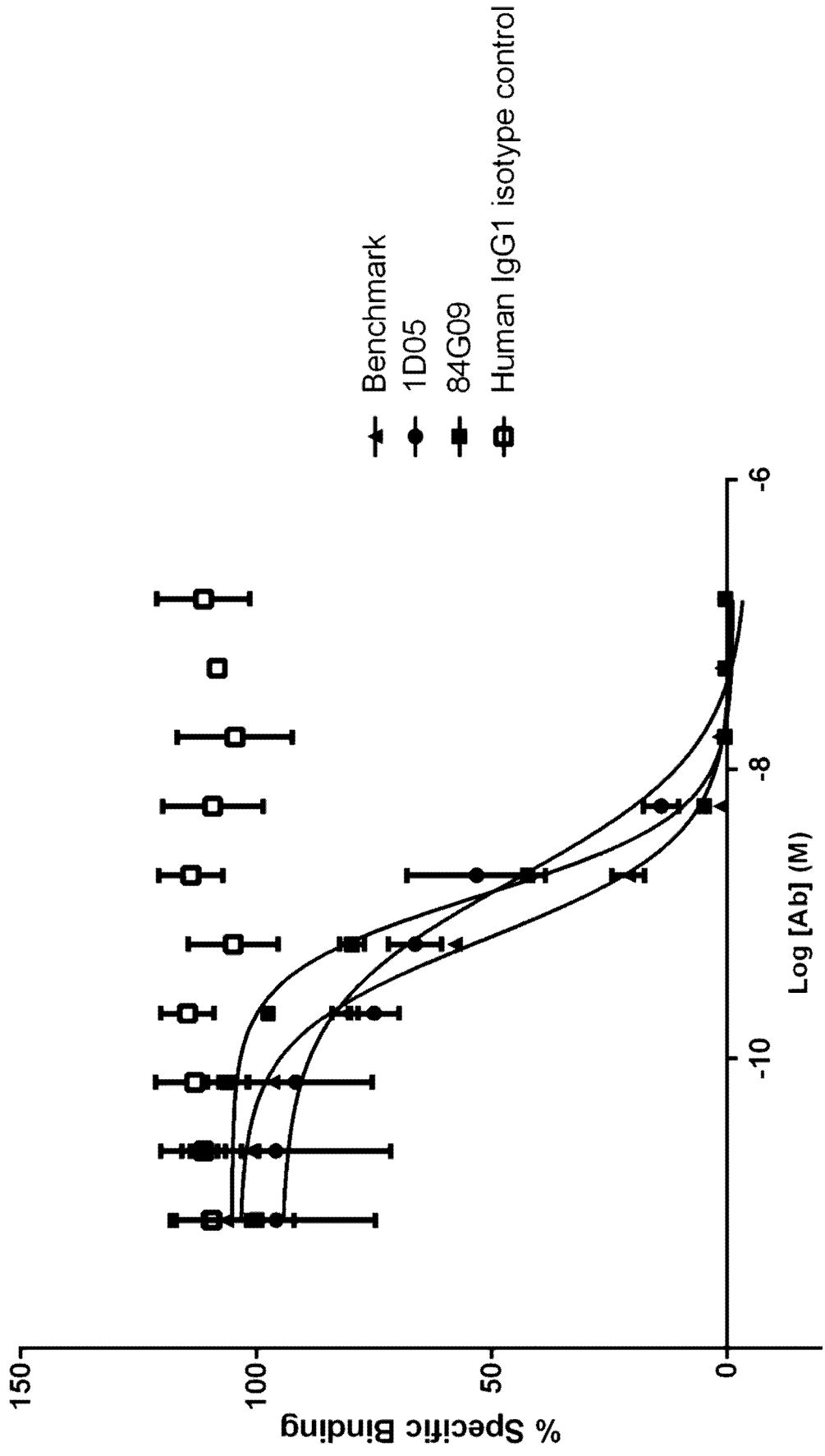

Benchmark
1D05
84G09
Human IgG1 isotype control
% Specific Binding
150
100
50
0
-6
-8
-10
Log [Ab] (M)

Figure 4

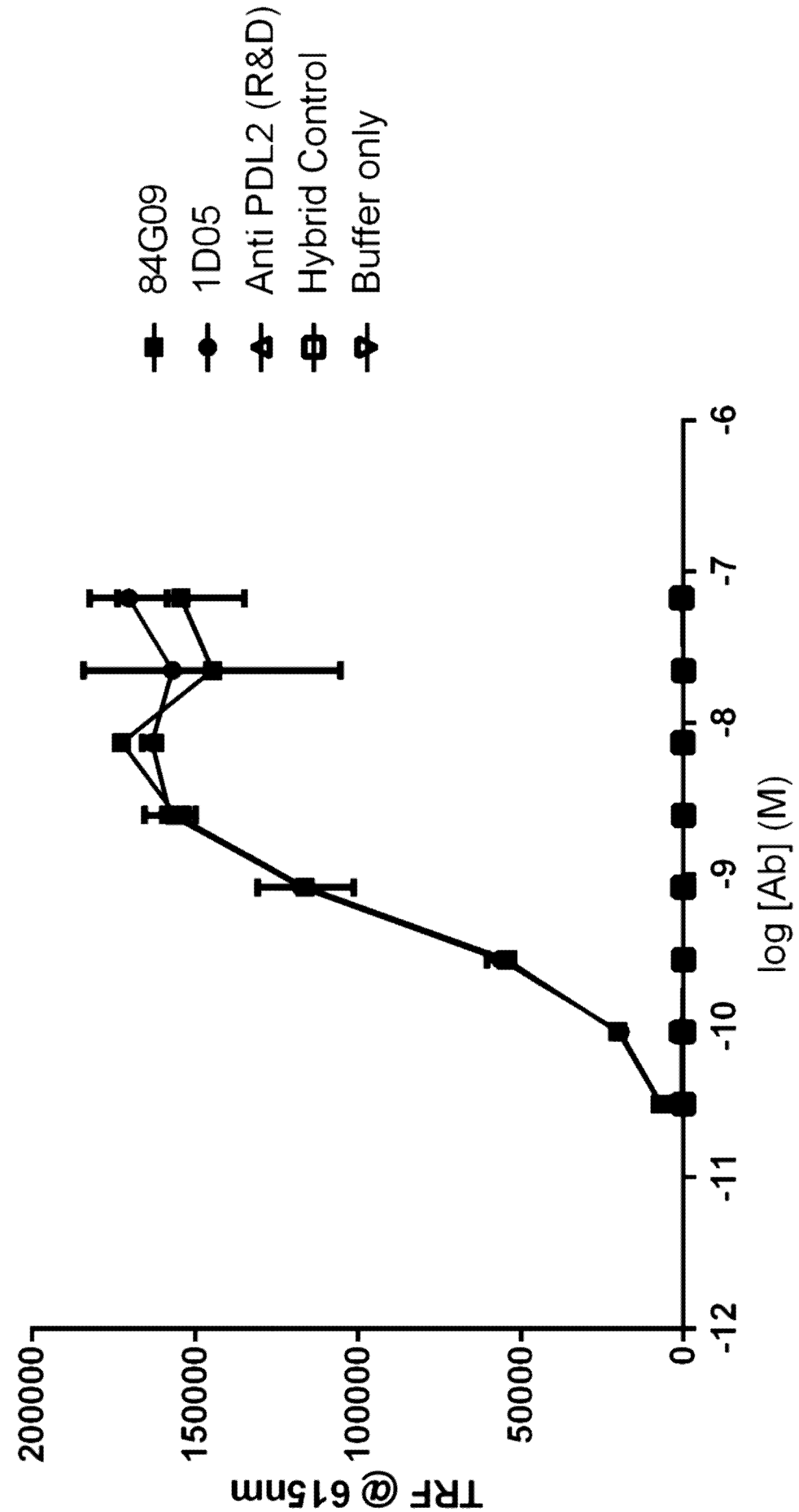

84G09
1D05
Anti PDL2 (R&D)
Hybrid Control
Buffer only
TRF @ 615nm
200000
150000
100000
50000
0
-12
-11
-10
-9
-8
-7
-6
log [Ab] (M)

Figure 5a

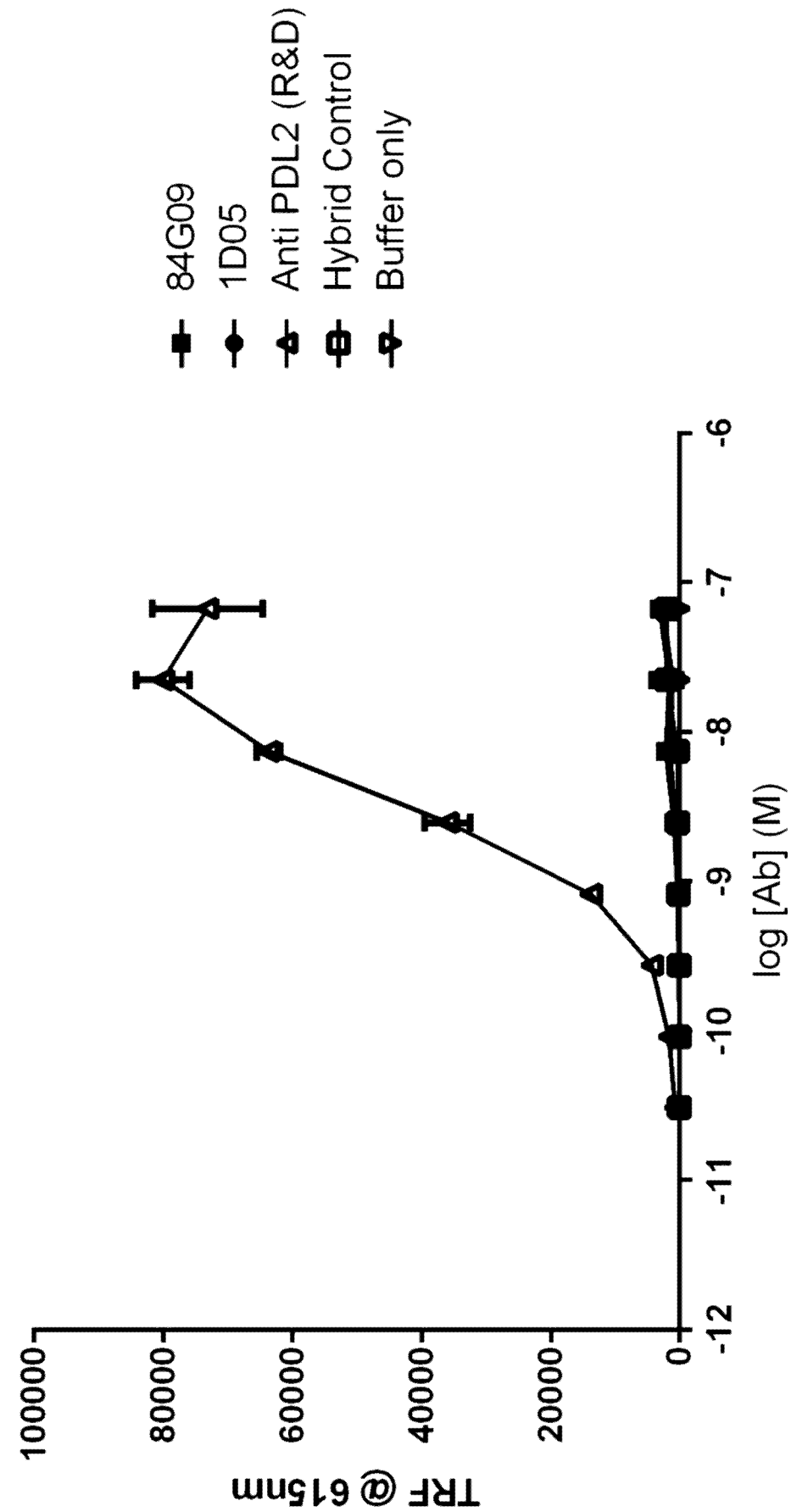

84G09
1D05
Anti PDL2 (R&D)
Hybrid Control
Buffer only
TRF @ 615nm
100000
80000
60000
40000
20000
0
-12
-11
-10
-9
-8
-7
-6
log [Ab] (M)

Figure 5b

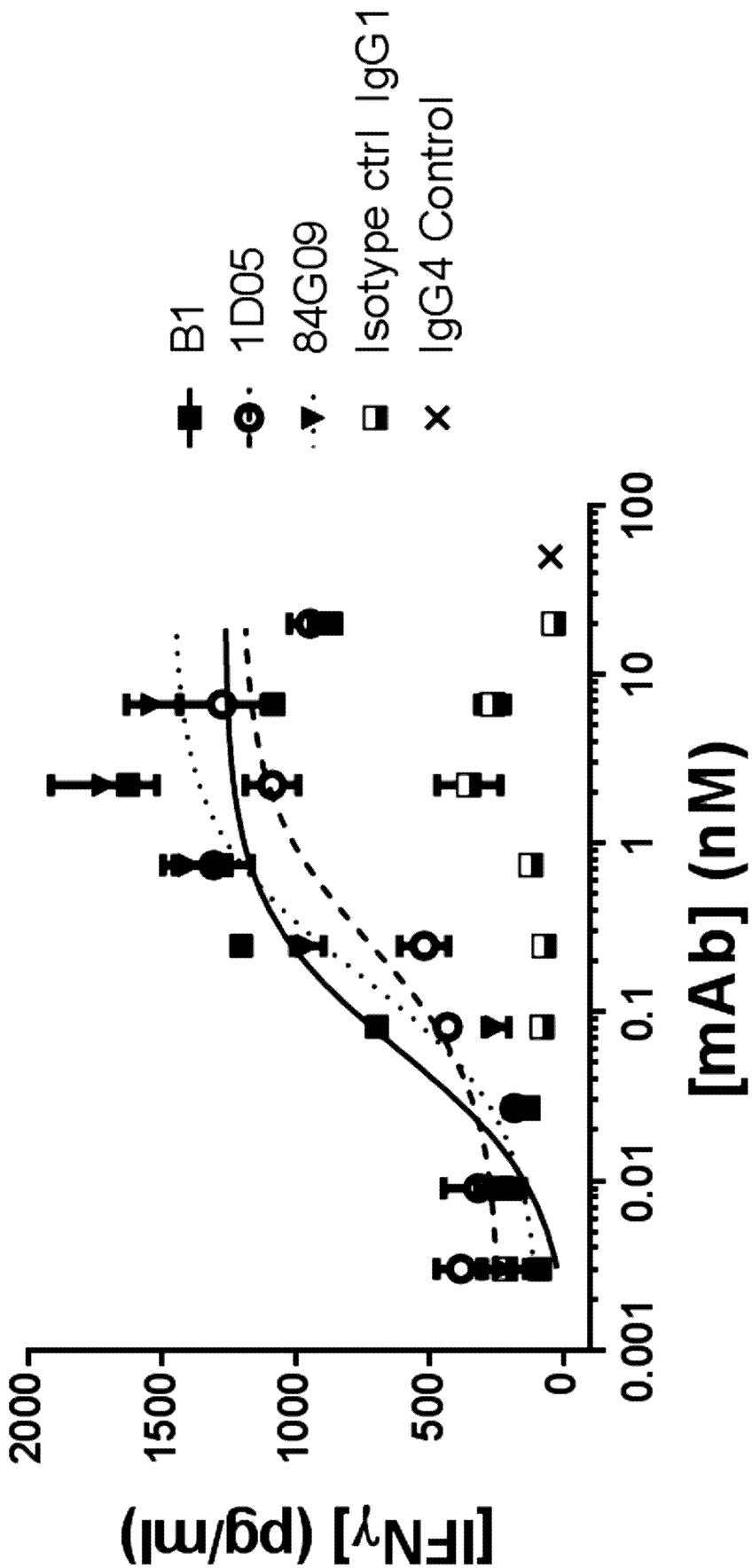

B1
1D05
84G09
Isotype ctrl IgG1
IgG4 Control
[IFNγ] (pg/ml)
2000
1500
1000
500
0
0.001
0.01
0.1
1
10
100
[mAb] (nM)

Figure 6

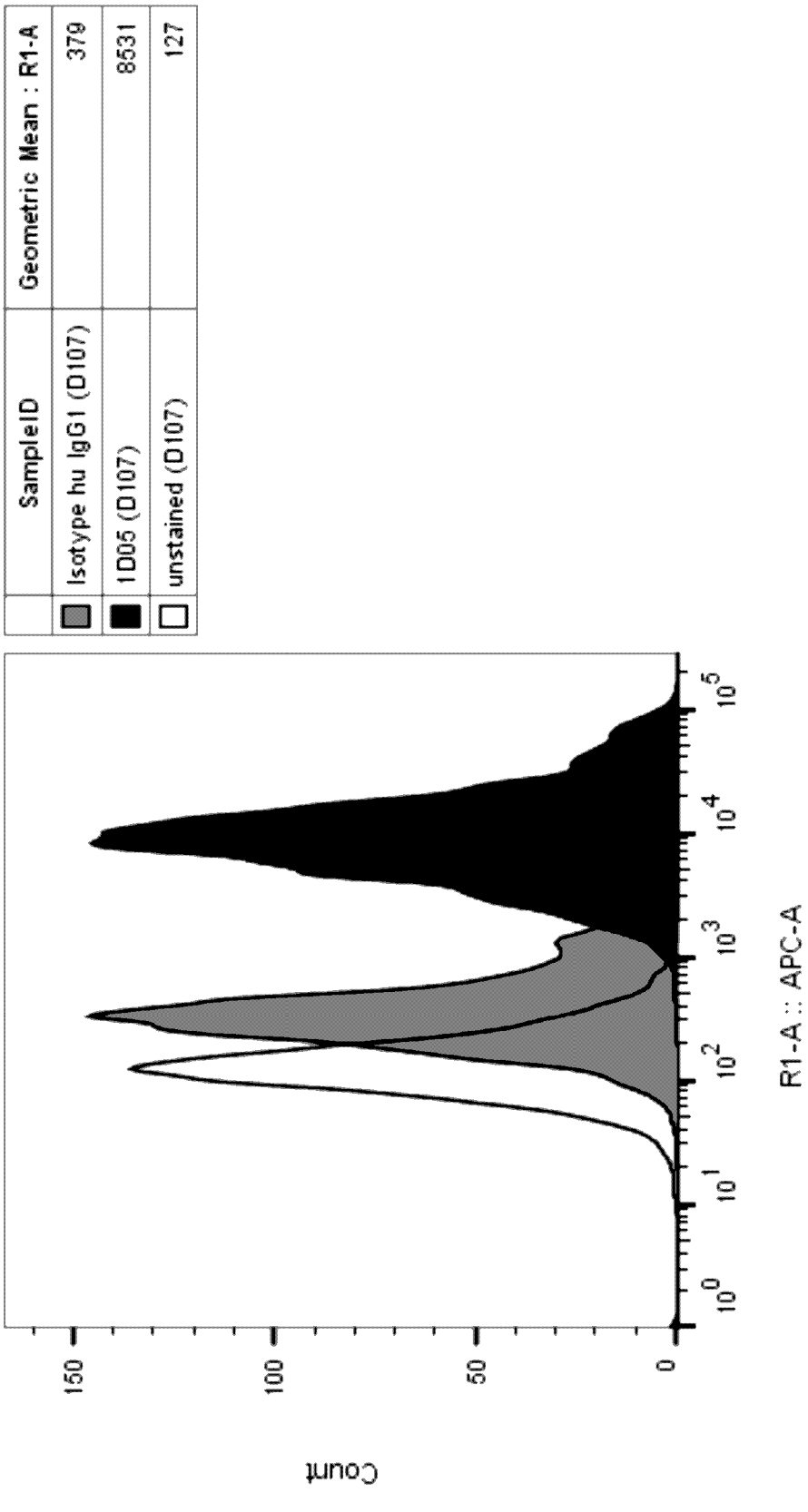

SampleID
Geometric Mean : R1-A
Isotype hu IgG1 (D107)
379
1D05 (D107)
8531
unstained (D107)
127
Count
150
100
50
0
10^0
10^1
10^2
10^3
10^4
10^5
R1-A :: APC-A

Figure 7a

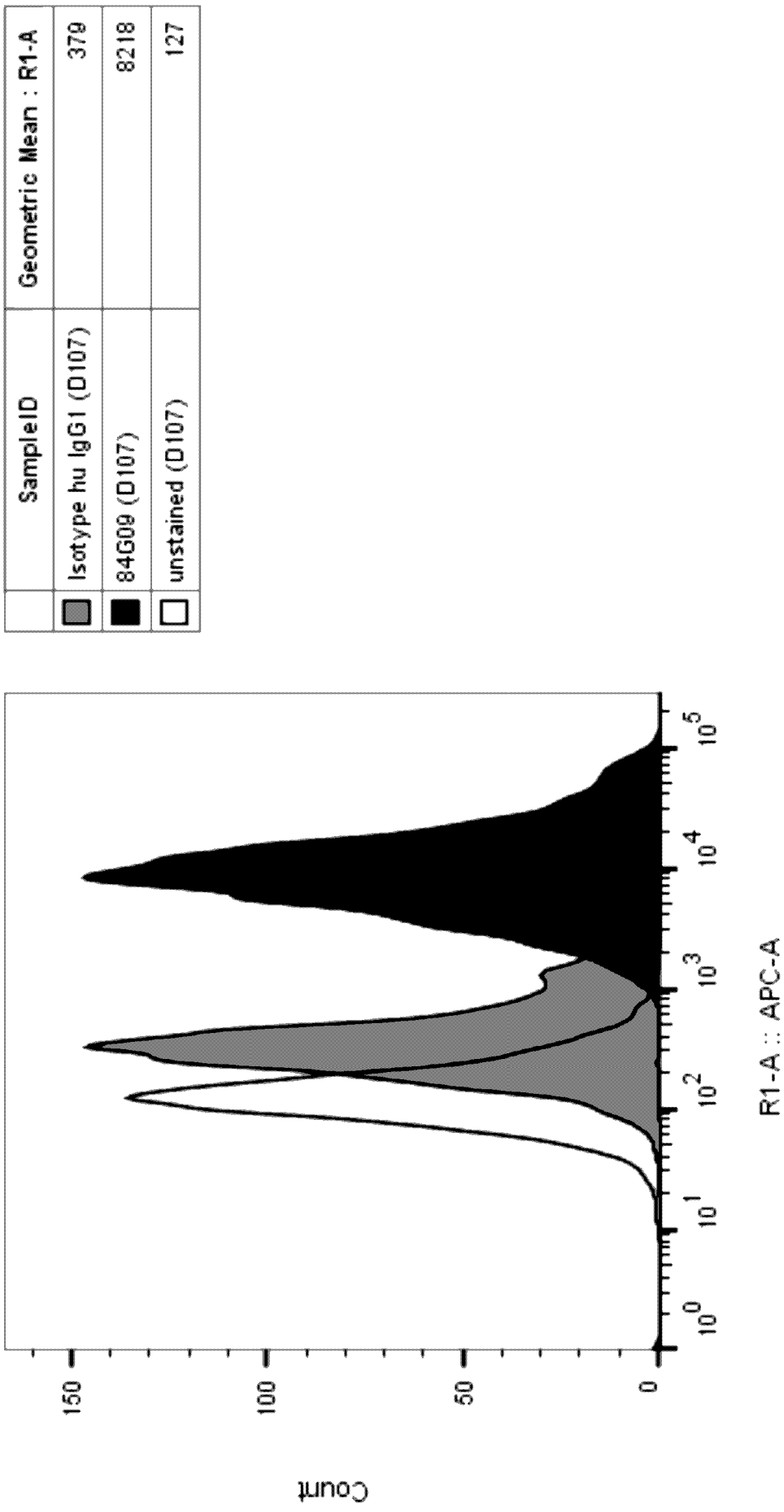

SampleID
Geometric Mean : R1-A
Isotype hu IgG1 (D107)
379
84G09 (D107)
8218
unstained (D107)
127
Count
150
100
50
0
10^0
10^1
10^2
10^3
10^4
10^5
R1-A :: APC-A

Figure 7b

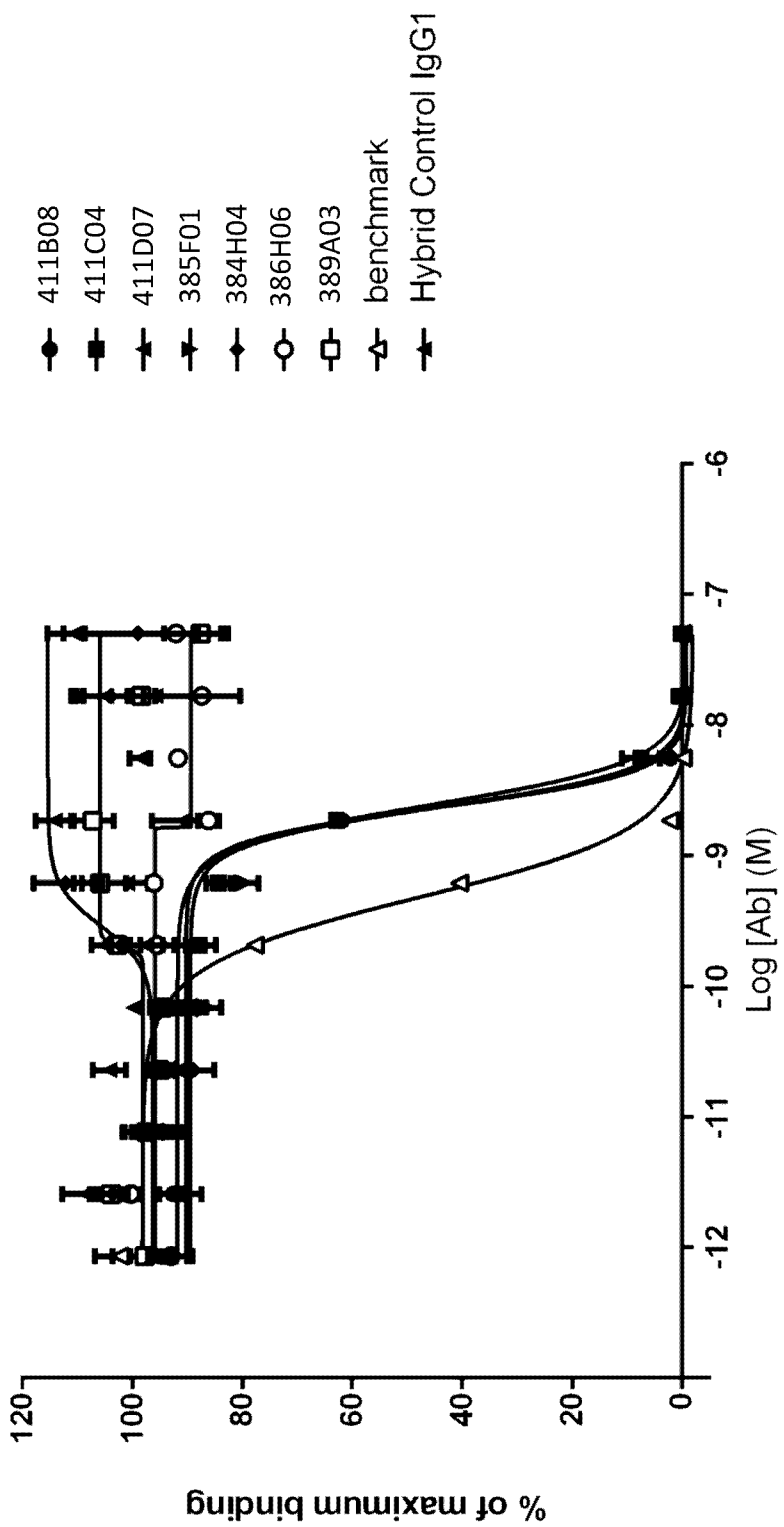

411B08
411C04
411D07
385F01
384H04
386H06
389A03
benchmark
Hybrid Control IgG1
% of maximum binding
120
100
80
60
40
20
0
-6
-7
-8
-9
-10
-11
-12
Log [Ab] (M)

Figure 8a

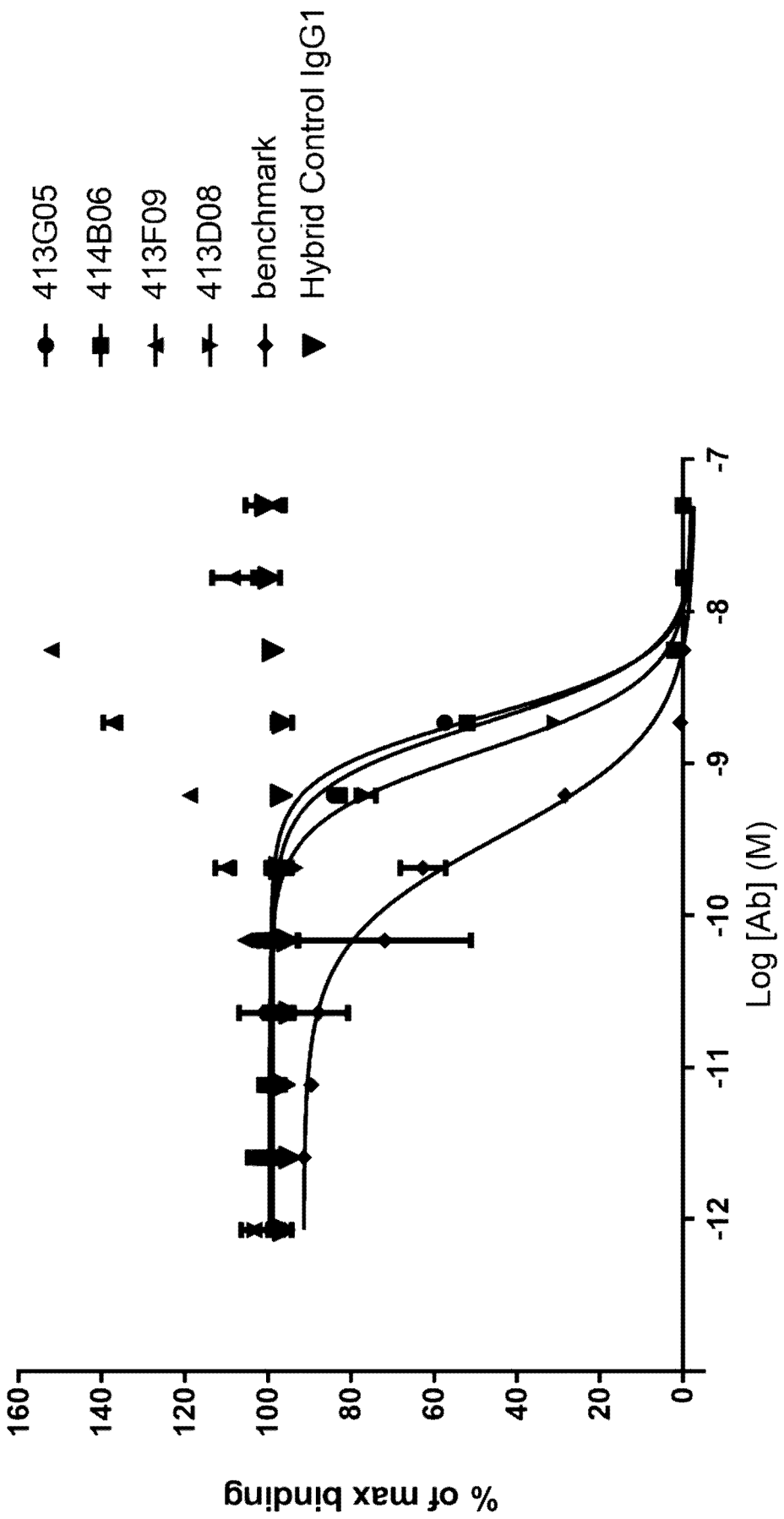

413G05
414B06
413F09
413D08
benchmark
Hybrid Control IgG1
% of max binding
160
140
120
100
80
60
40
20
0
-7
-8
-9
-10
-11
-12
Log [Ab] (M)

Figure 8b

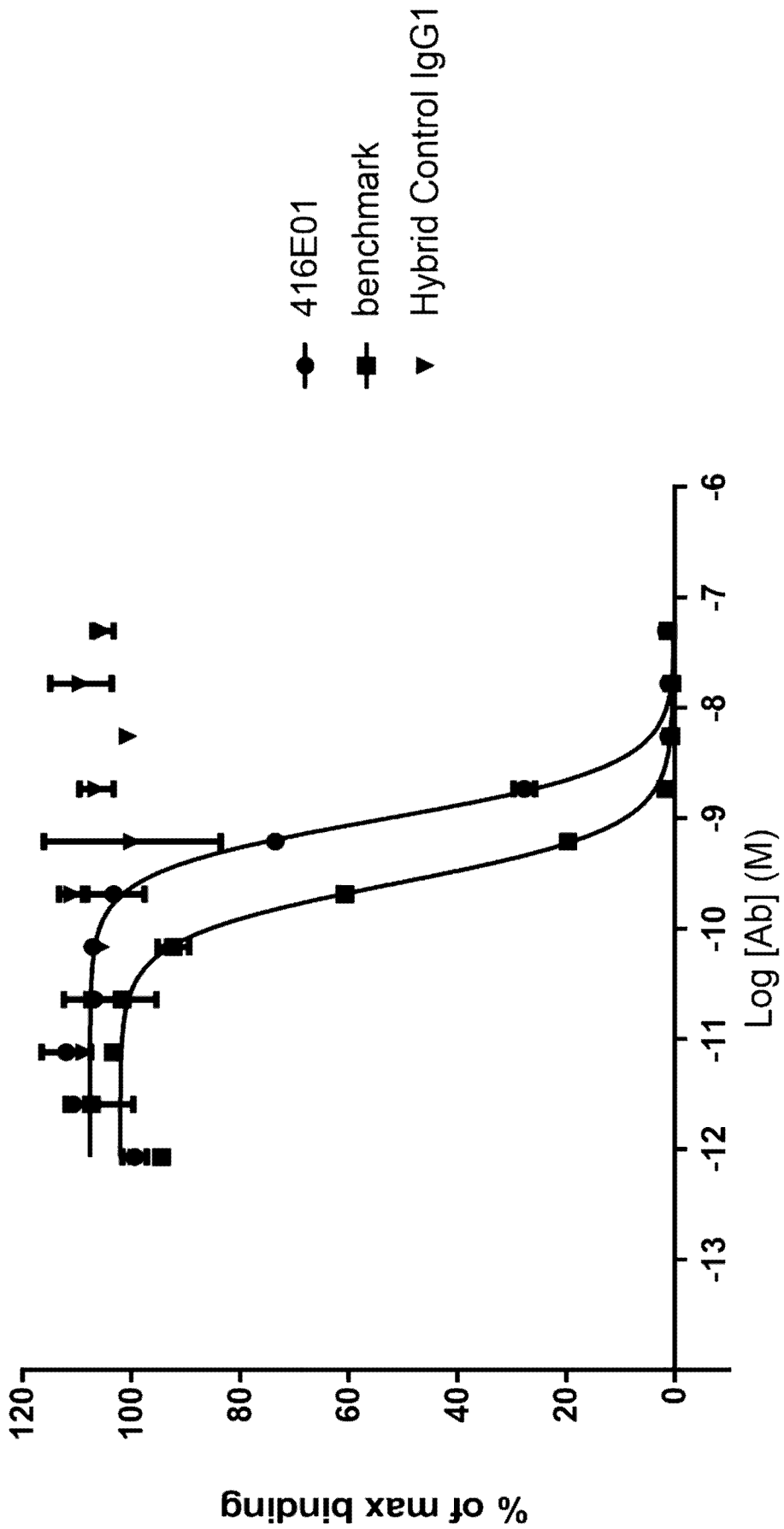

416E01
benchmark
Hybrid Control IgG1
% of max binding
120
100
80
60
40
20
0
-13
-12
-11
-10
-9
-8
-7
-6
Log [Ab] (M)

Figure 8c

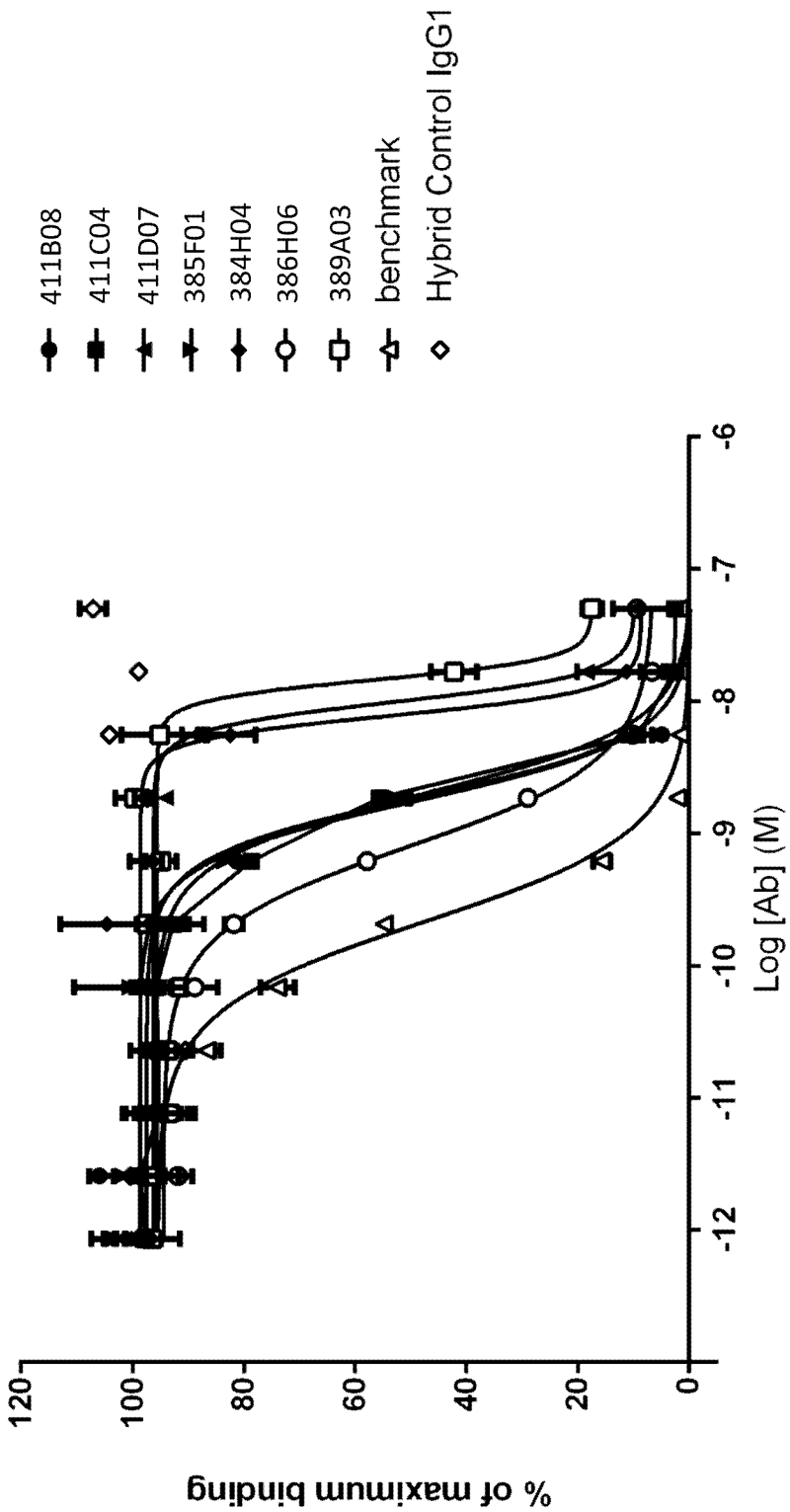

411B08
411C04
411D07
385F01
384H04
386H06
389A03
benchmark
Hybrid Control IgG1
% of maximum binding
120
100
80
60
40
20
0
-6
-7
-8
-9
-10
-11
-12
Log [Ab] (M)

Figure 9a

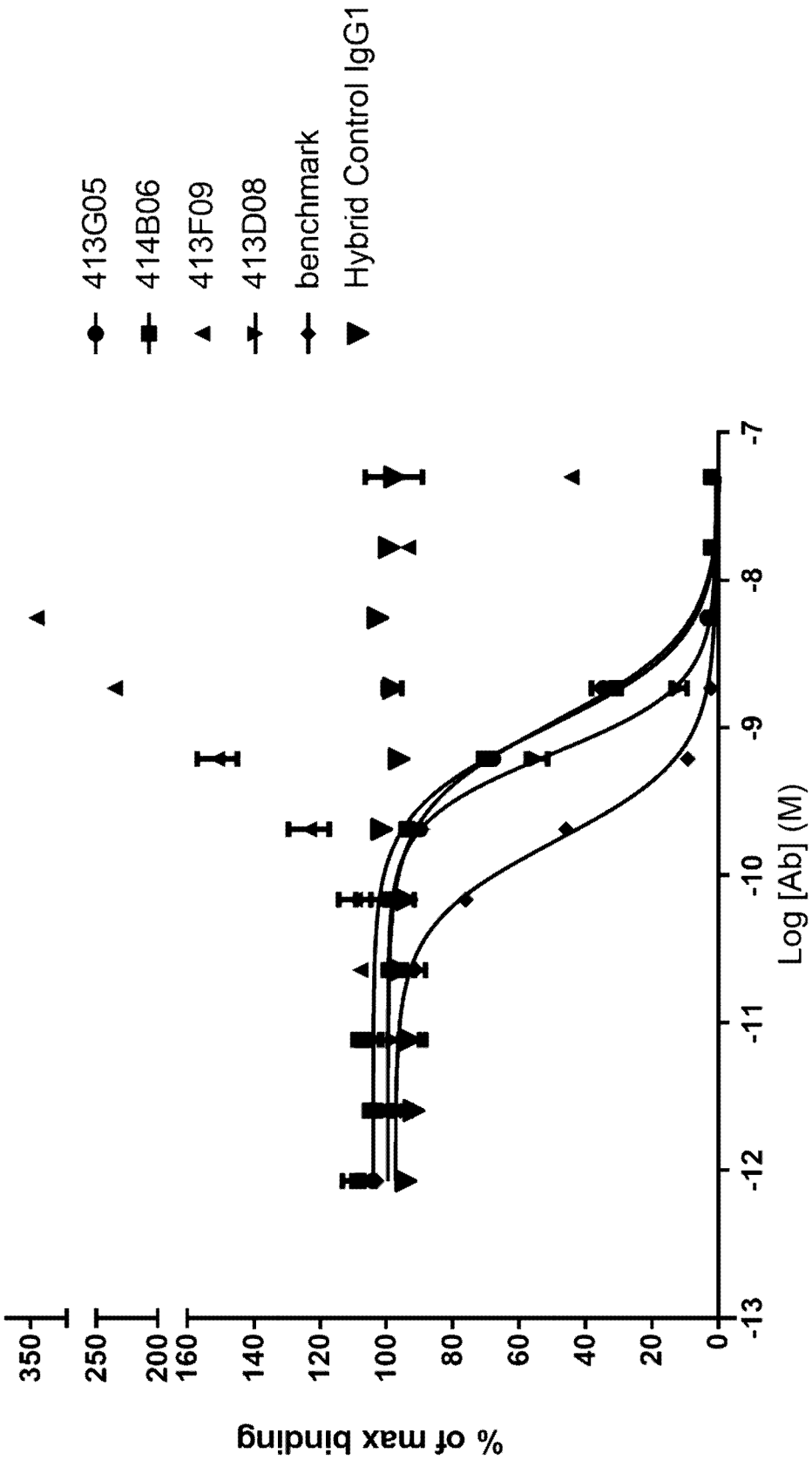

413G05
414B06
413F09
413D08
benchmark
Hybrid Control IgG1
% of max binding
350
250
200
160
140
120
100
80
60
40
20
0
-13
-12
-11
-10
-9
-8
-7
Log [Ab] (M)

Figure 9b

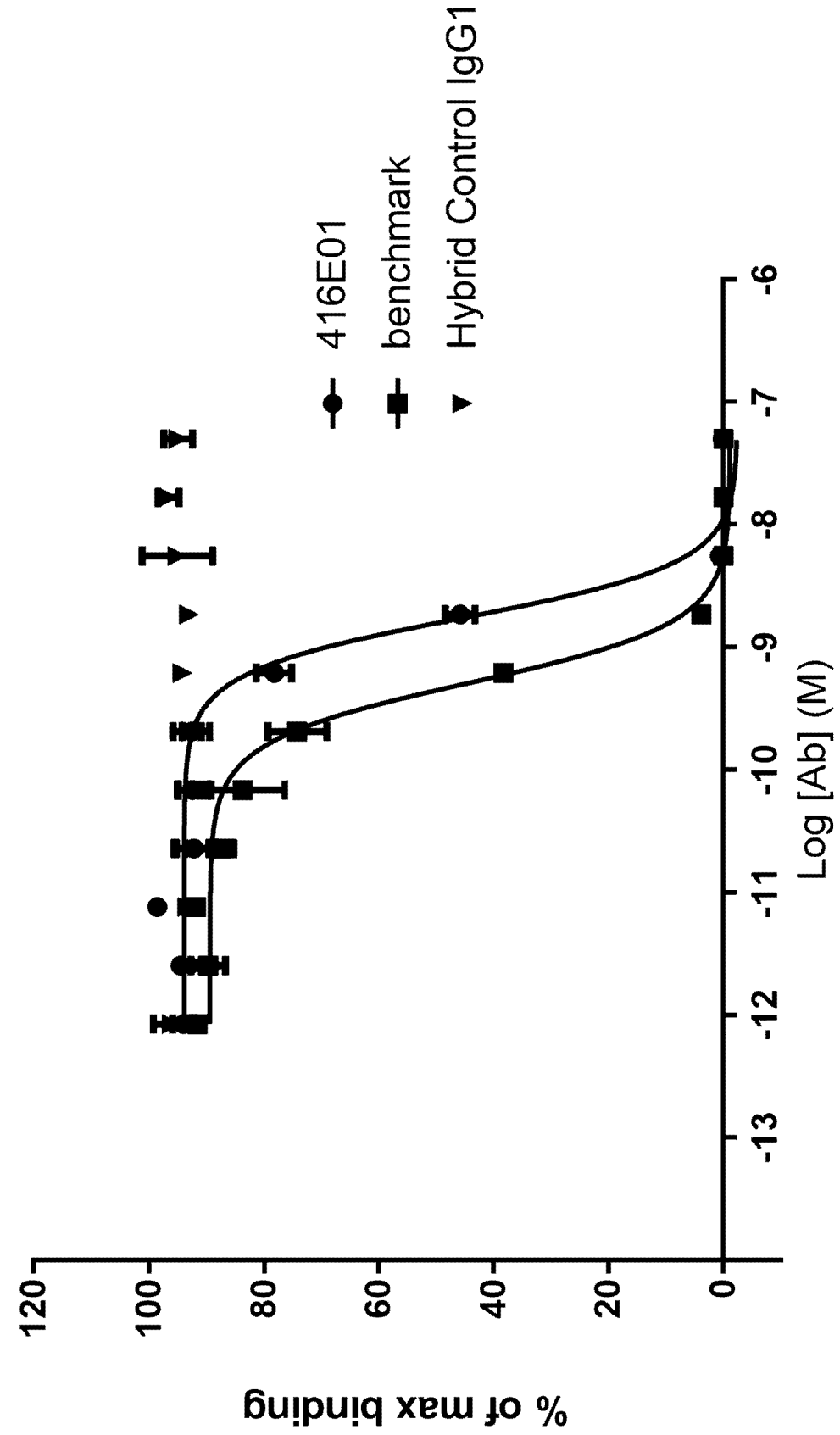

% of max binding
120
100
80
60
40
20
0
-13
-12
-11
-10
-9
-8
-7
-6
Log [Ab] (M)
416E01
benchmark
Hybrid Control IgG1

Figure 9c

Figure 10

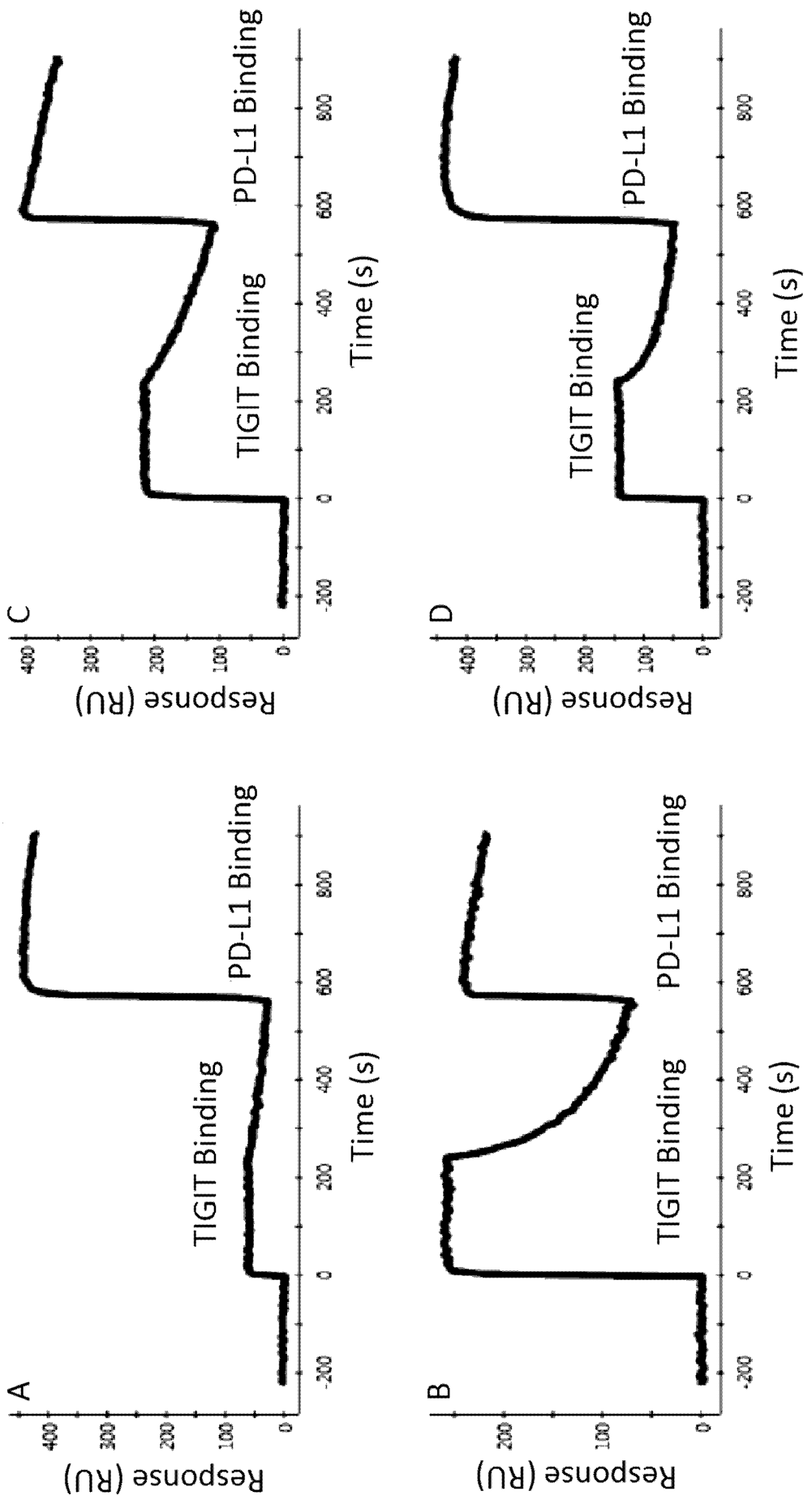

A
B
C
D
Response (RU)
Time (s)
TIGIT Binding
PD-L1 Binding
-200
0
200
400
600
800
0
100
200
300
400

Figure 11

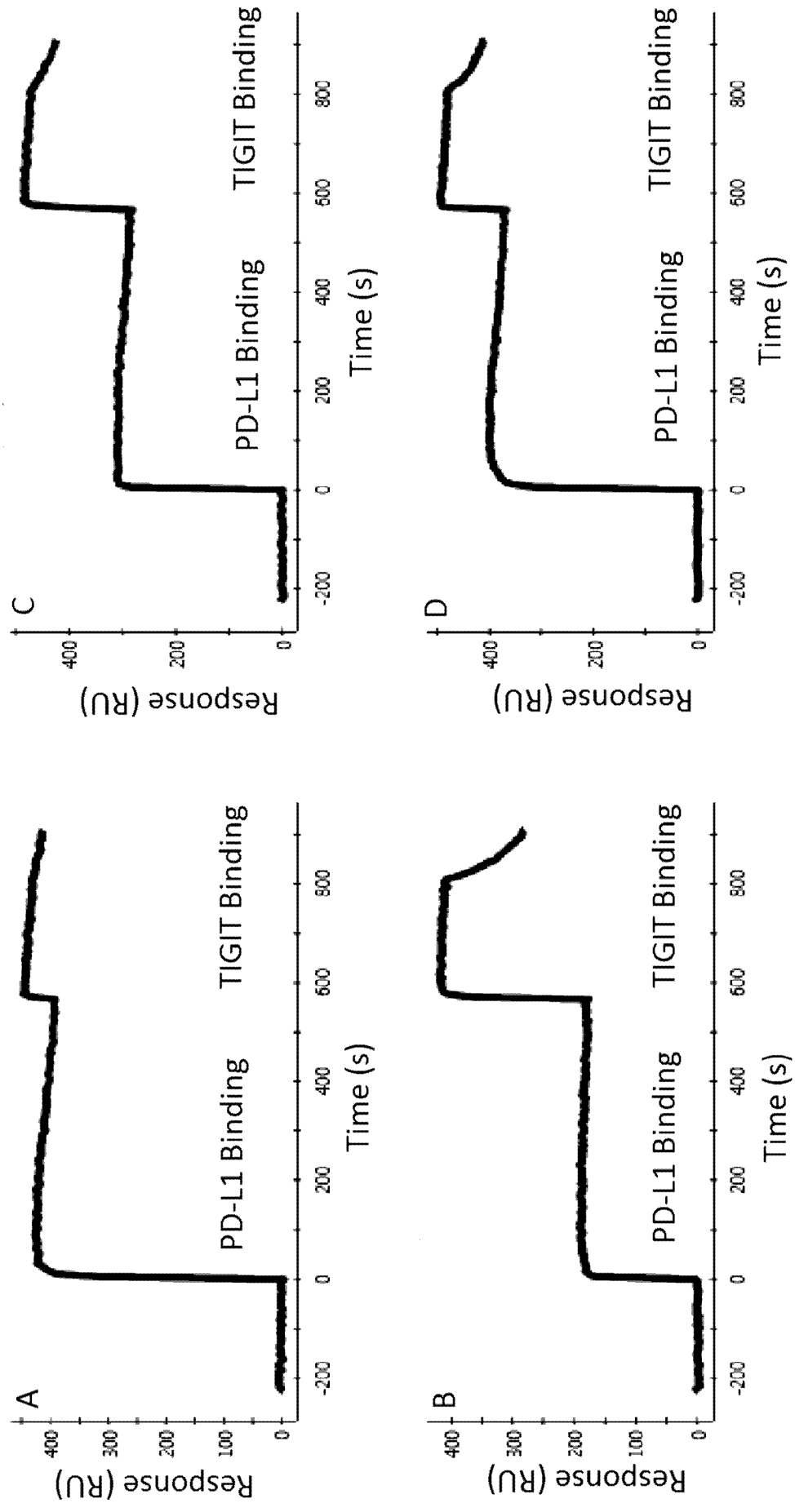
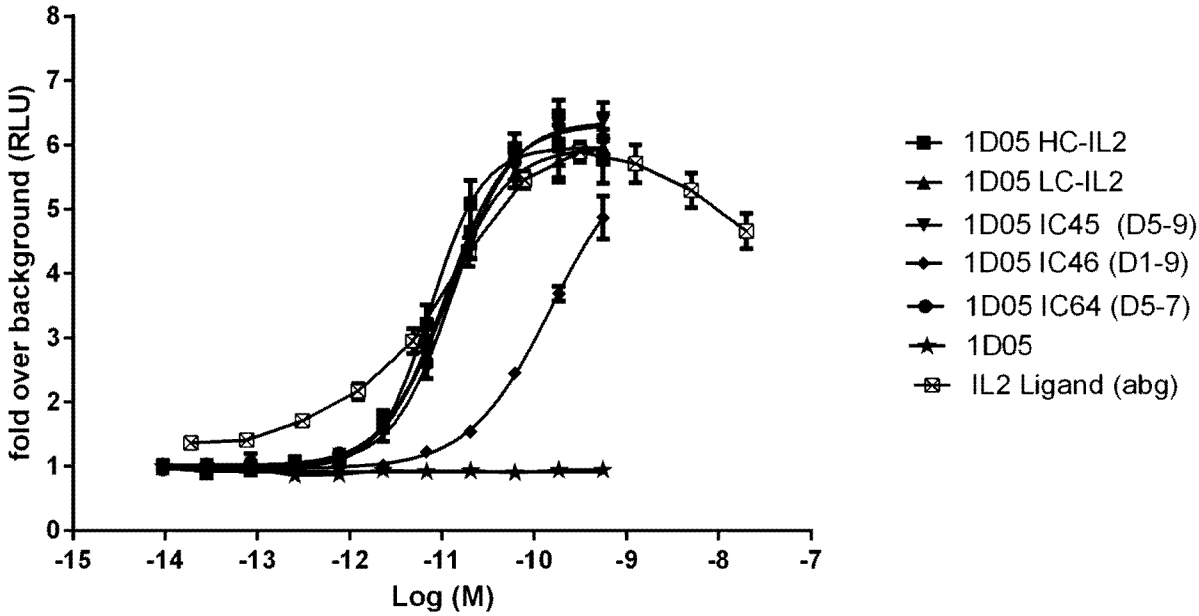

A
B
C
D
Response (RU)
Time (s)
PD-L1 Binding
TIGIT Binding
0
100
200
300
400
-200
0
200
400
600
800

Figure 12(a)


fold over background (RLU)
Log (M)
1D05 HC-IL2
1D05 LC-IL2
1D05 IC45 (D5-9)
1D05 IC46 (D1-9)
1D05 IC64 (D5-7)
1D05
IL2 Ligand (abg)

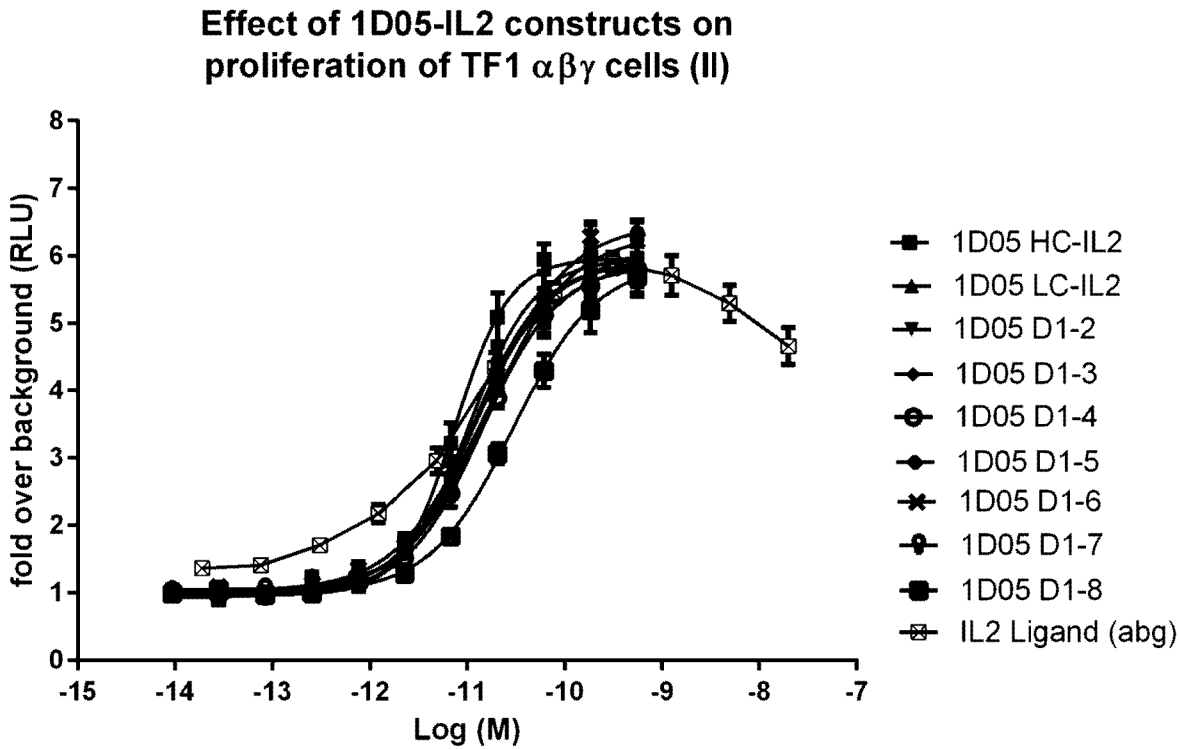

Effect of 1D05-IL2 constructs on proliferation of TF1 αβγ cells (II)
fold over background (RLU)
Log (M)
1D05 HC-IL2
1D05 LC-IL2
1D05 D1-2
1D05 D1-3
1D05 D1-4
1D05 D1-5
1D05 D1-6
1D05 D1-7
1D05 D1-8
IL2 Ligand (abg)

Figure 12(a) cont…

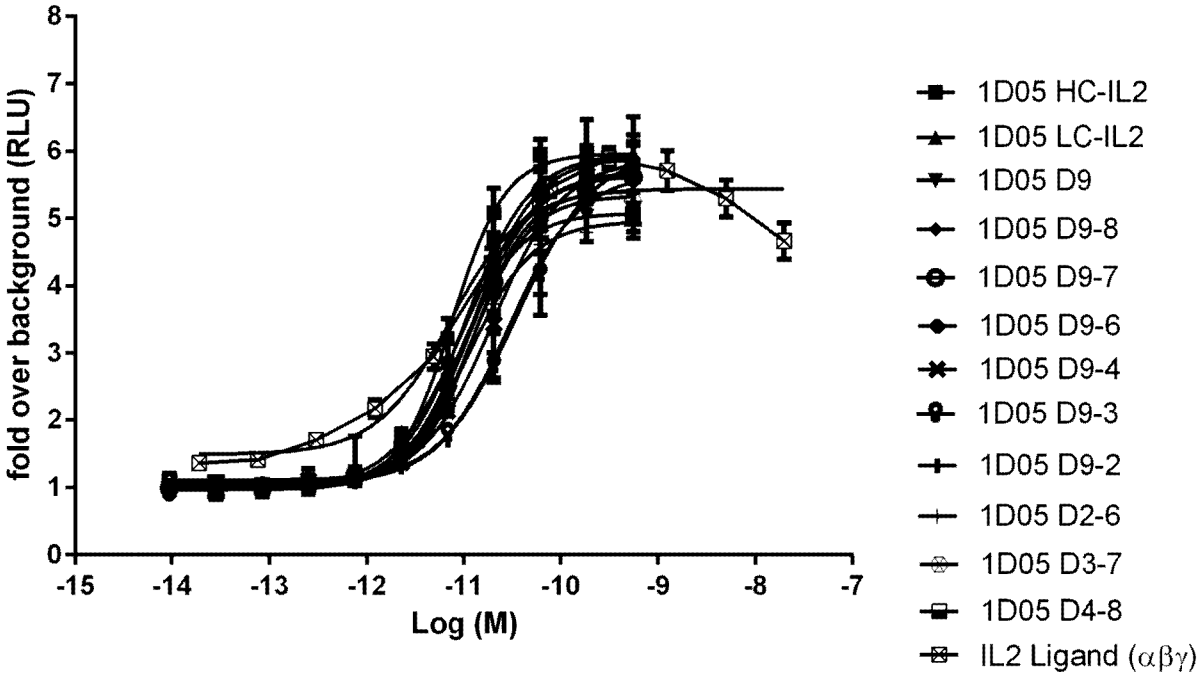
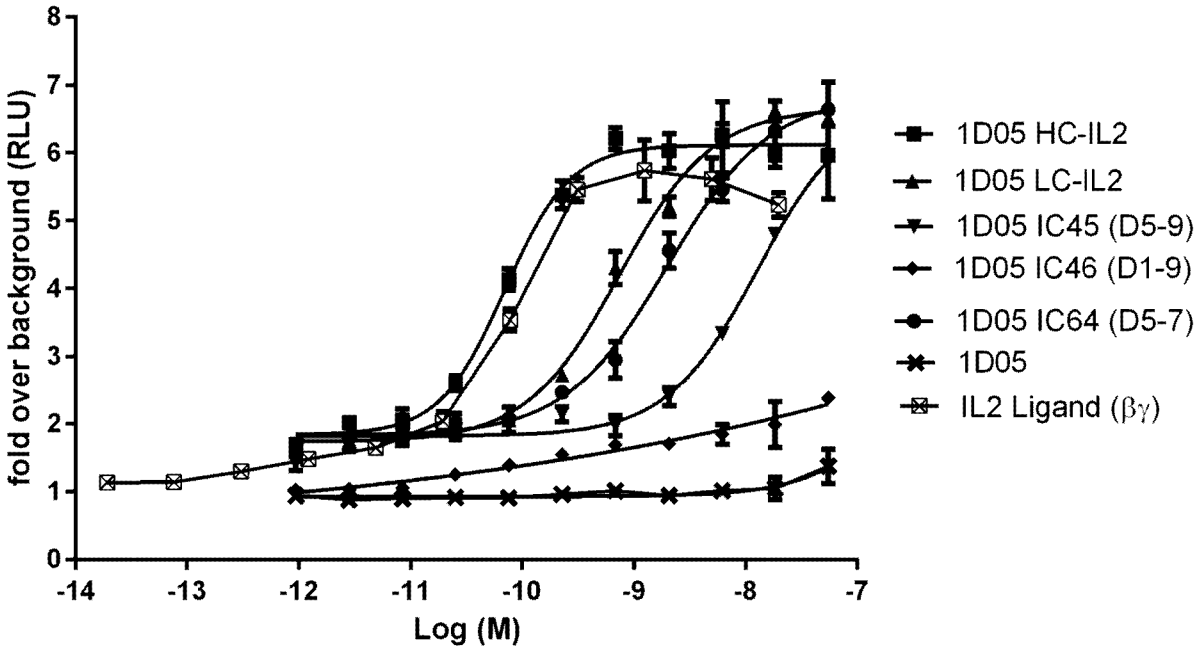


Figure 12(b)


fold over background (RLU)
Log (M)
1D05 HC-IL2
1D05 LC-IL2
1D05 IC45 (D5-9)
1D05 IC46 (D1-9)
1D05 IC64 (D5-7)
1D05
IL2 Ligand (βγ)

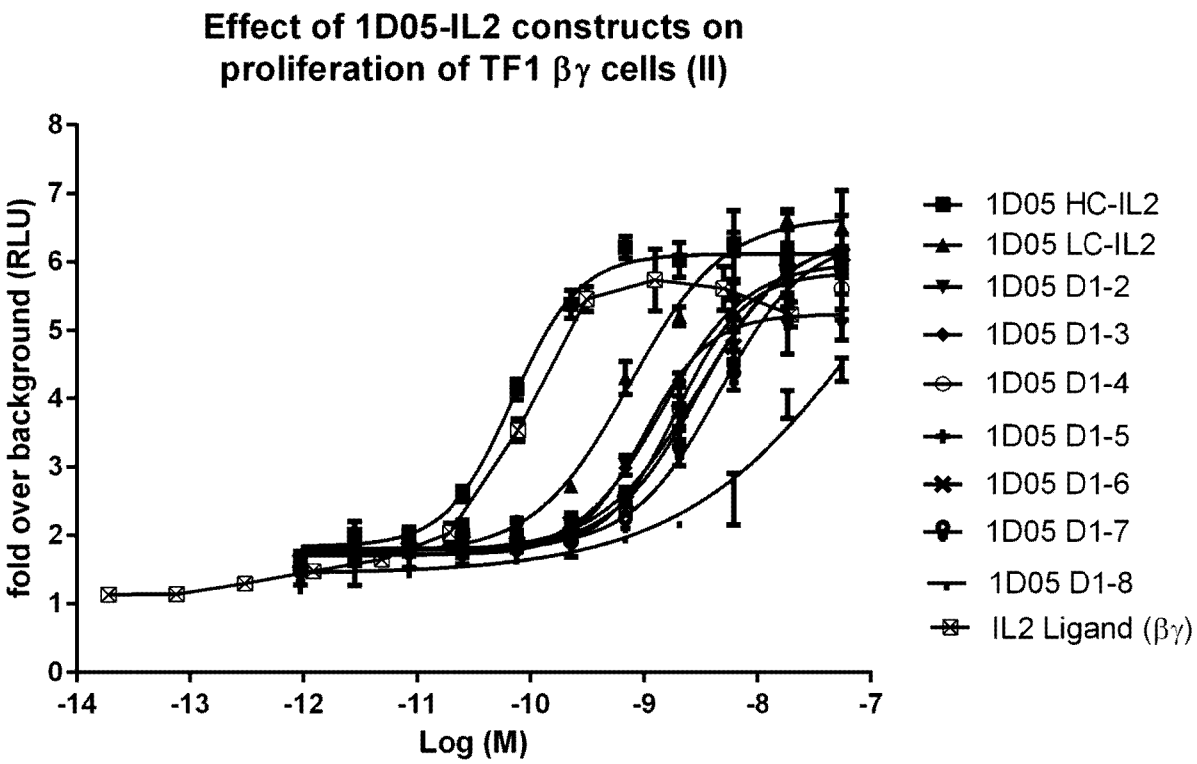
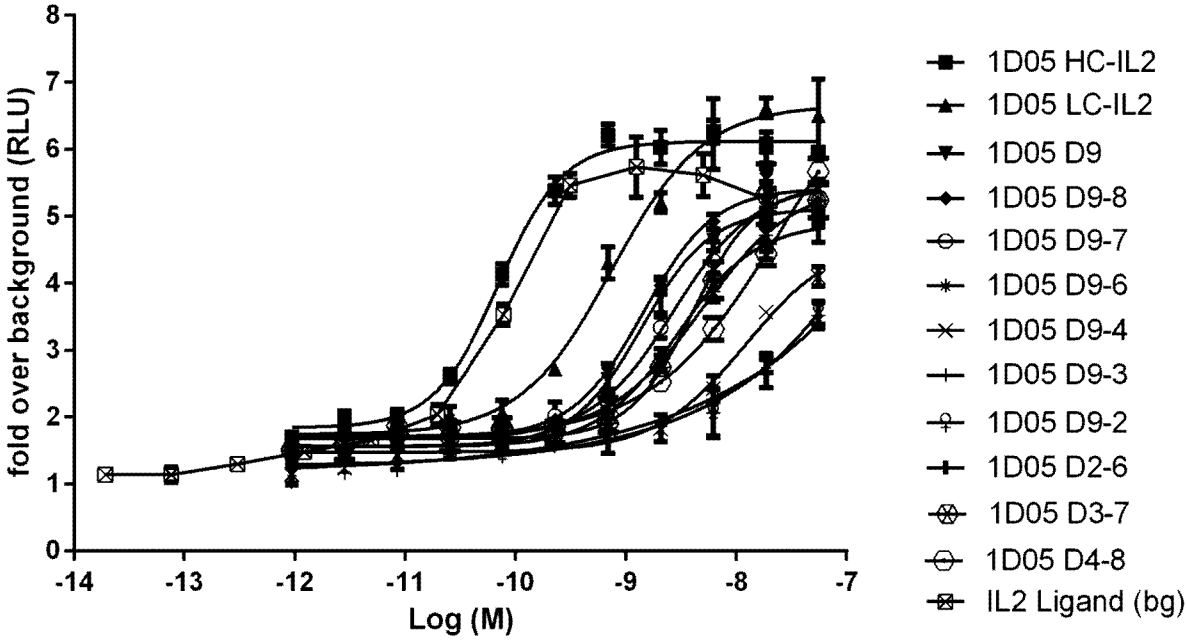

Effect of 1D05-IL2 constructs on proliferation of TF1 βγ cells (II)
fold over background (RLU)
Log (M)
1D05 HC-IL2
1D05 LC-IL2
1D05 D1-2
1D05 D1-3
1D05 D1-4
1D05 D1-5
1D05 D1-6
1D05 D1-7
1D05 D1-8
IL2 Ligand (βγ)

Figure 12(b) cont



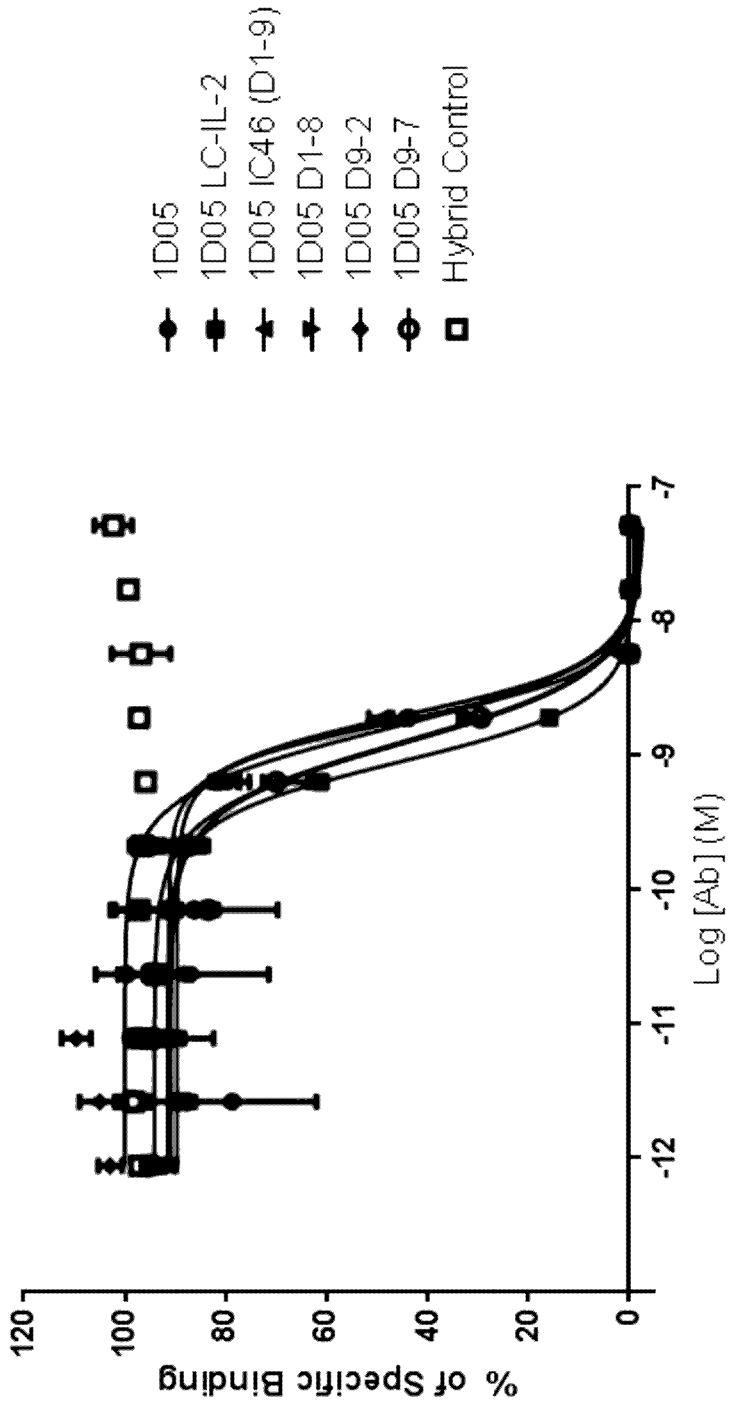

1D05
1D05 LC-IL-2
1D05 IC46 (D1-9)
1D05 D1-8
1D05 D9-2
1D05 D9-7
Hybrid Control
% of Specific Binding
120
100
80
60
40
20
0
-12
-11
-10
-9
-8
-7
Log [Ab] (M)

Figure 13(a)

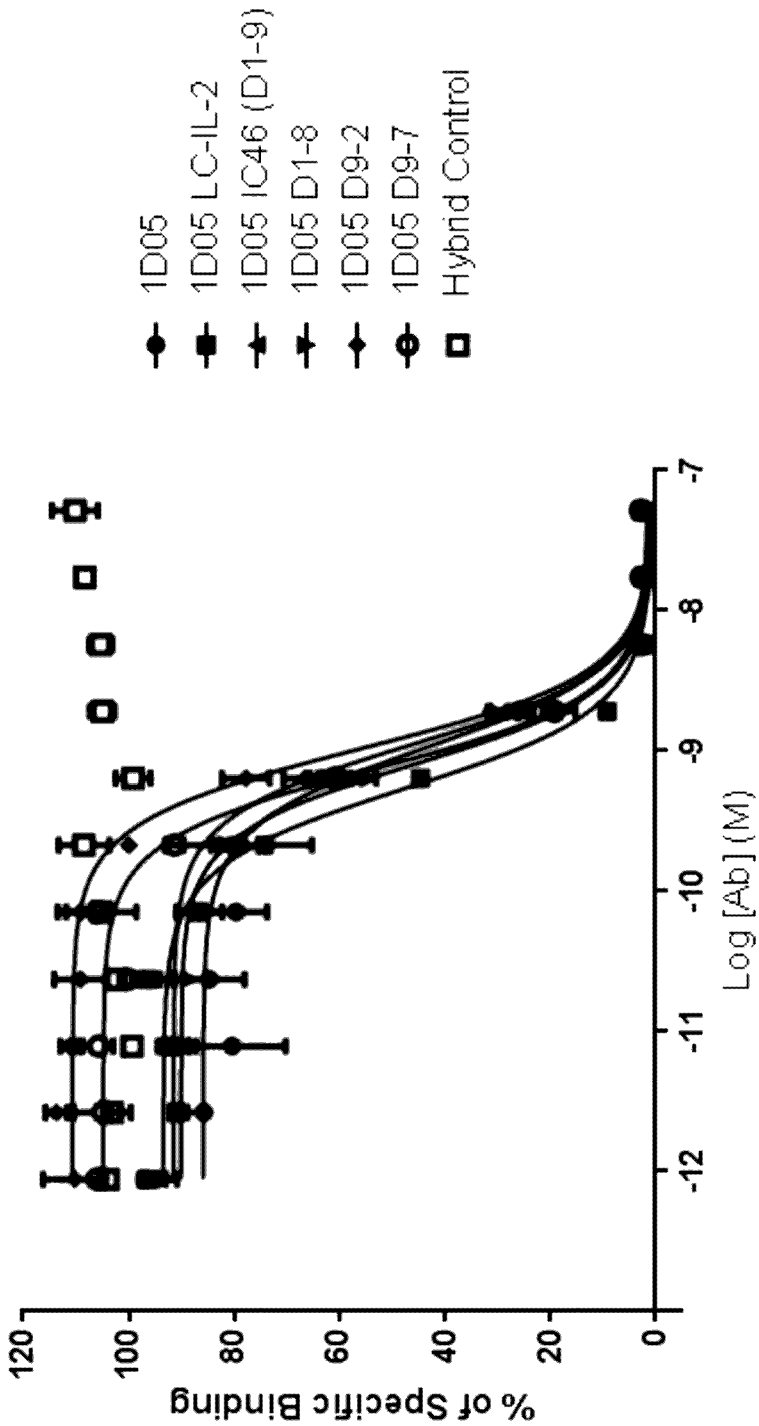

1D05
1D05 LC-IL-2
1D05 IC46 (D1-9)
1D05 D1-8
1D05 D9-2
1D05 D9-7
Hybrid Control
% of Specific Binding
120
100
80
60
40
20
0
-7
-8
-9
-10
-11
-12
Log [Ab] (M)

Figure 13(b)

Figure 14

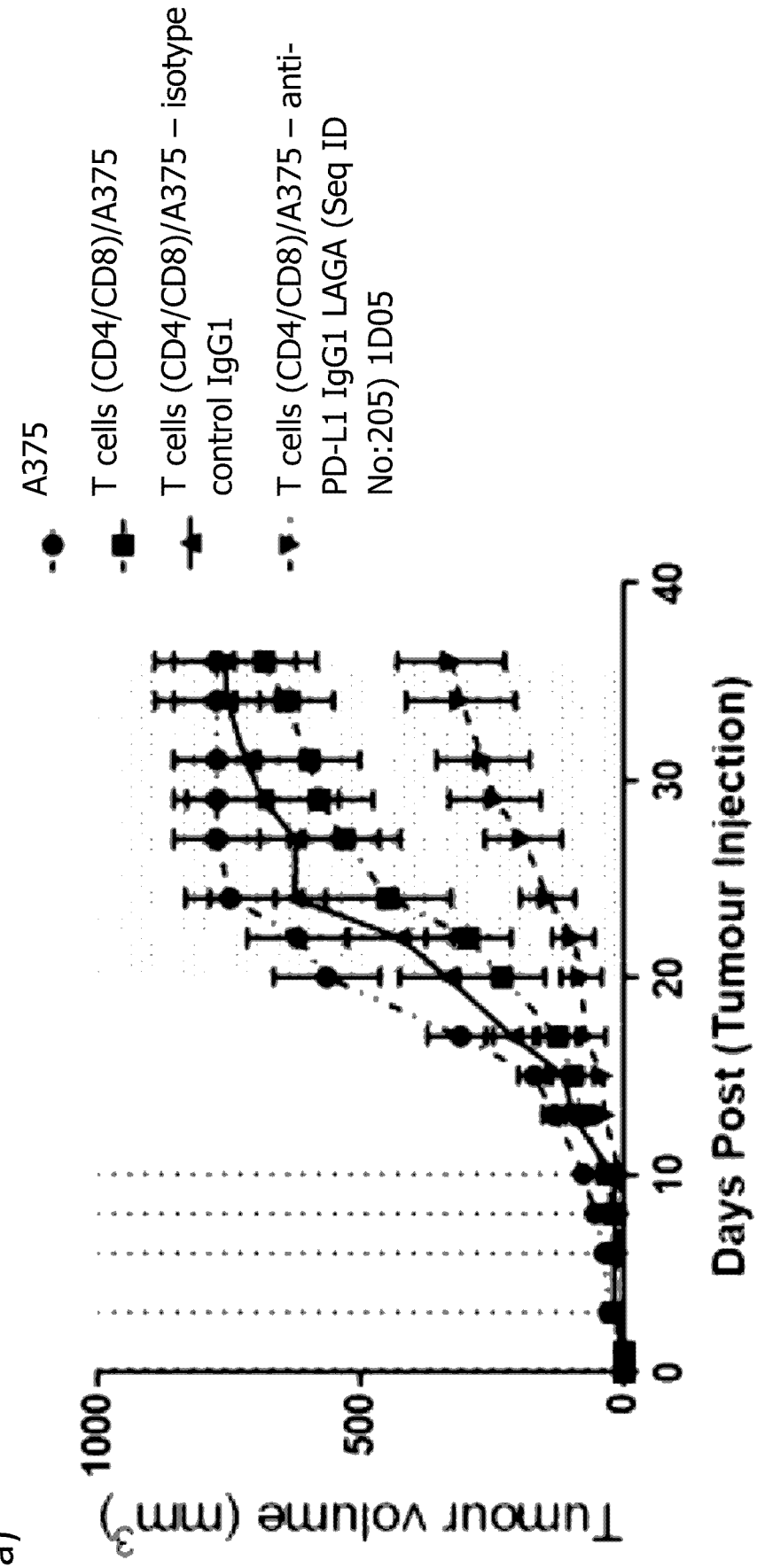

a)
Tumour volume (mm3)
1000
500
0
0
10
20
30
40
Days Post (Tumour Injection)
A375
T cells (CD4/CD8)/A375
T cells (CD4/CD8)/A375 – isotype control IgG1
T cells (CD4/CD8)/A375 – anti-PD-L1 IgG1 LAGA (Seq ID No:205) 1D05

Figure 14 continued...

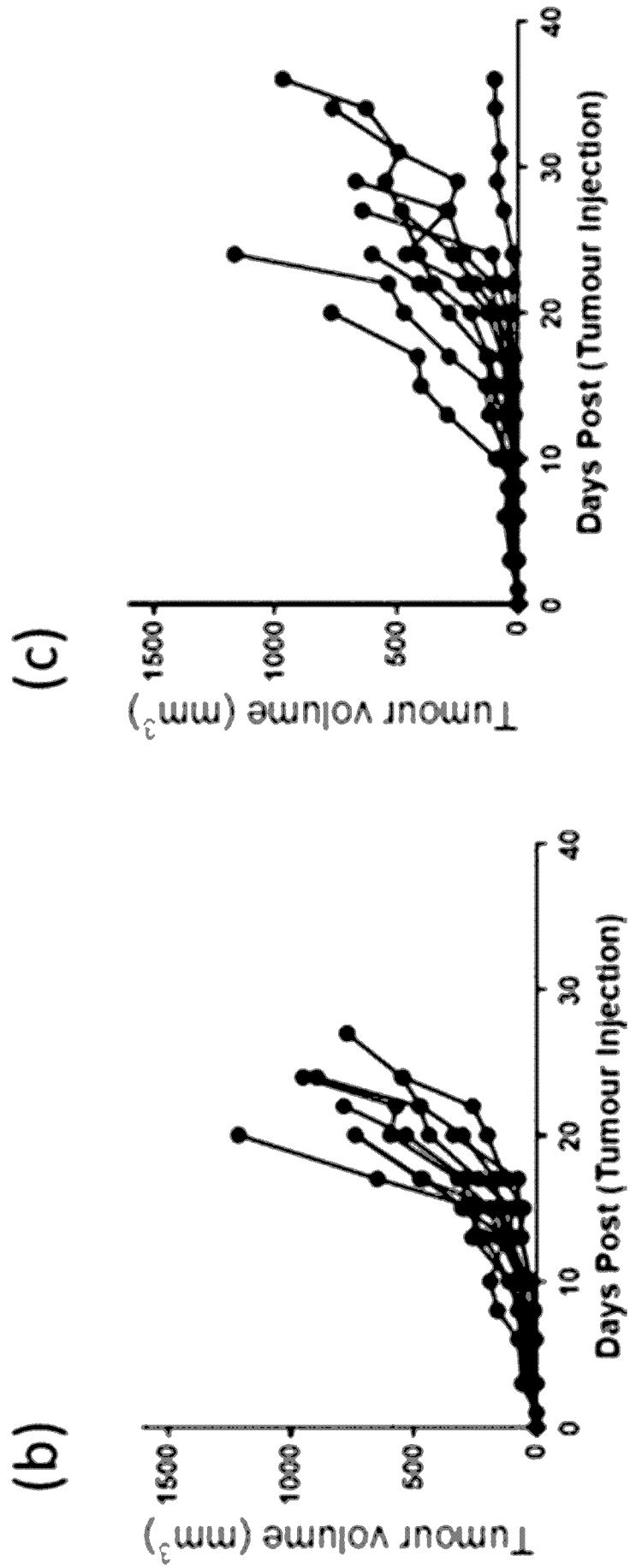
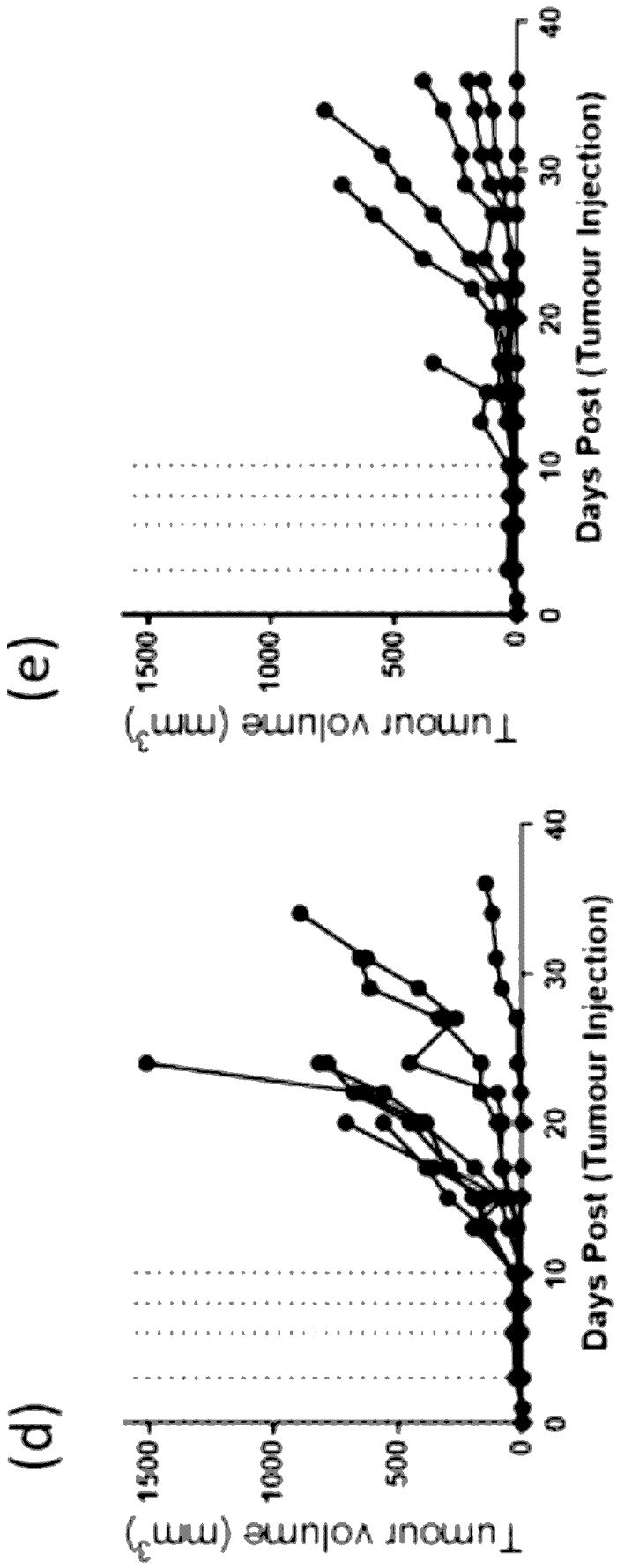


Figure 14 continued...



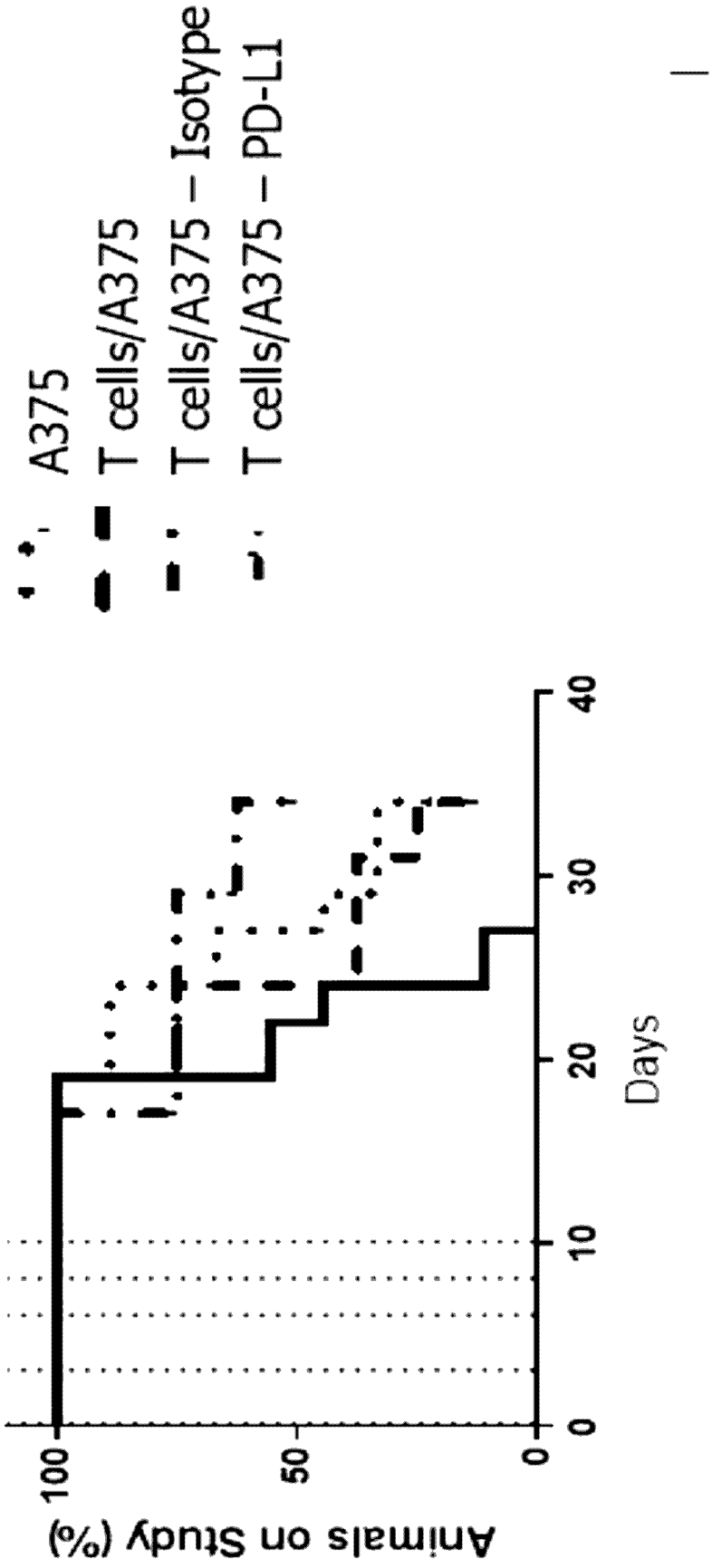

A375
T cells/A375
T cells/A375 – Isotype
T cells/A375 – PD-L1
Animals on Study (%)
100
50
0
0
10
20
30
40
Days

Figure 15

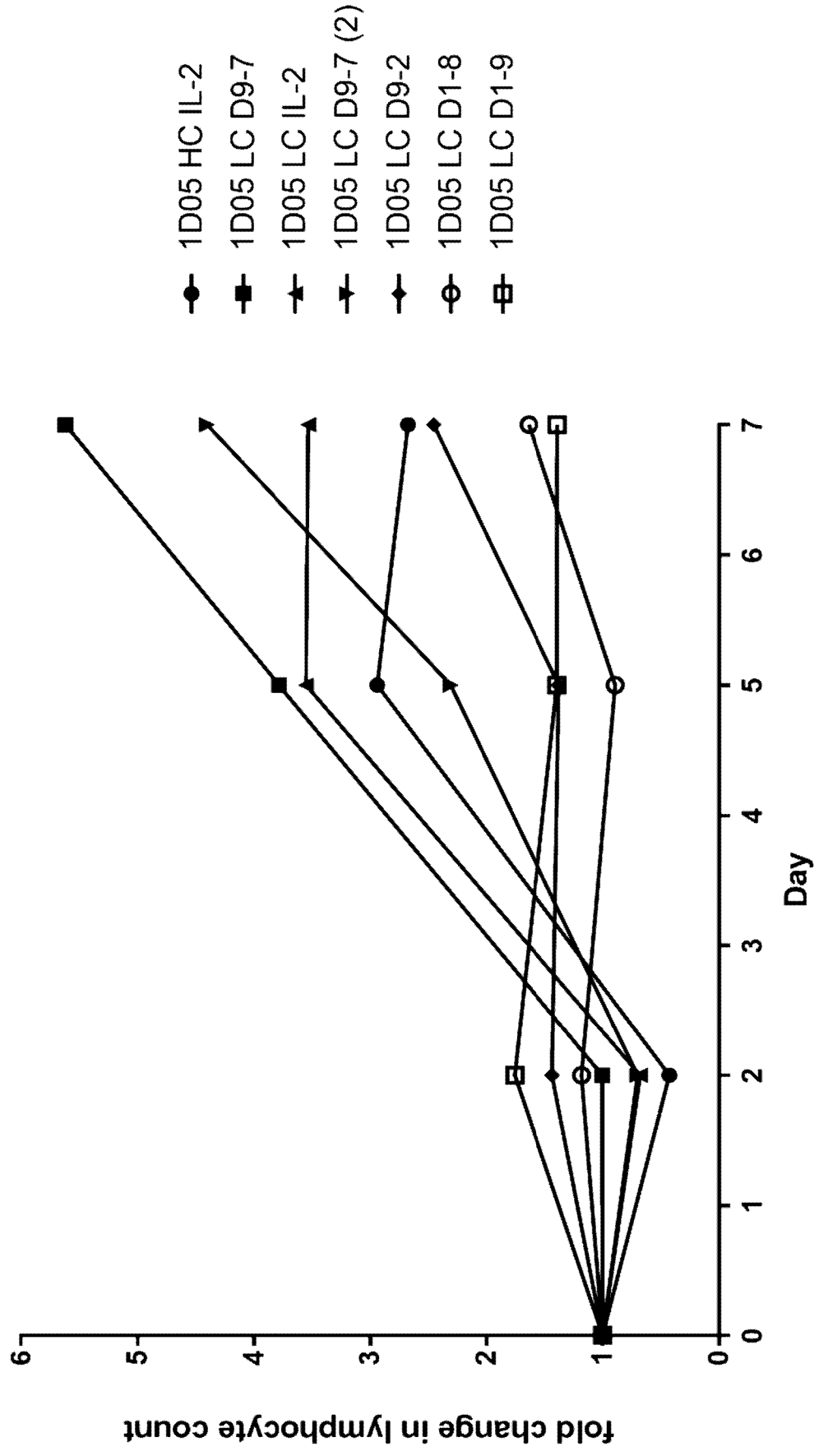

1D05 HC IL-2
1D05 LC D9-7
1D05 LC IL-2
1D05 LC D9-7 (2)
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D1-9
fold change in lymphocyte count
Day
0
1
2
3
4
5
6
7

Figure 16

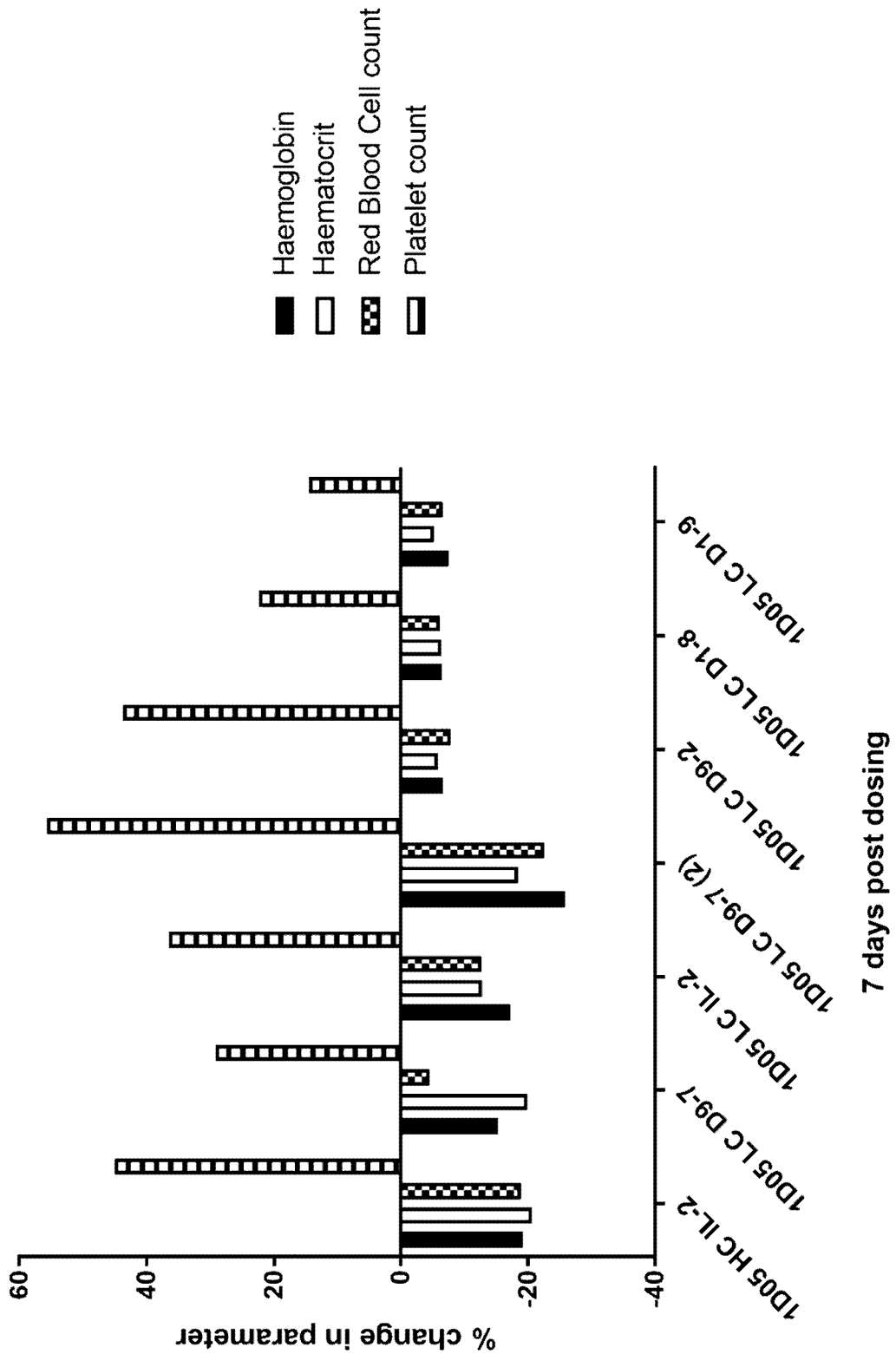

Haemoglobin
Haematocrit
Red Blood Cell count
Platelet count
% change in parameter
60
40
20
0
-20
-40
1D05 HC IL-2
1D05 LC D9-7
1D05 LC IL-2
1D05 LC D9-7 (2)
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D1-9
7 days post dosing

Figure 17

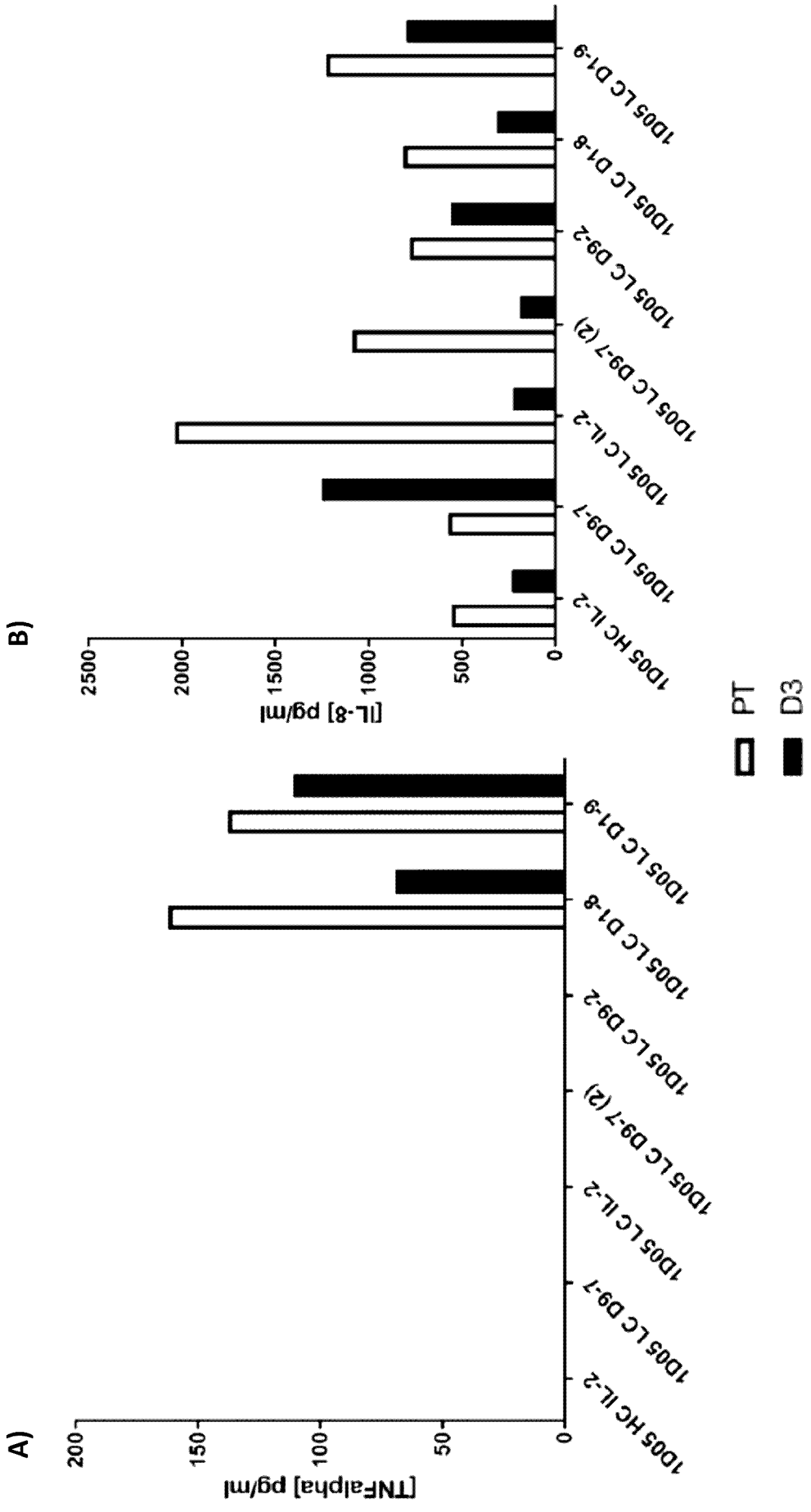

A)
[TNFalpha] pg/ml
200
150
100
50
0
1DO5 HC IL-2
1DO5 LC D9-7
1DO5 LC IL-2
1DO5 LC D9-7 (2)
1DO5 LC D9-2
1DO5 LC D1-8
1DO5 LC D1-9
B)
[IL-8] pg/ml
2500
2000
1500
1000
500
0
1DO5 HC IL-2
1DO5 LC D9-7
1DO5 LC IL-2
1DO5 LC D9-7 (2)
1DO5 LC D9-2
1DO5 LC D1-8
1DO5 LC D1-9
PT
D3

Figure 18

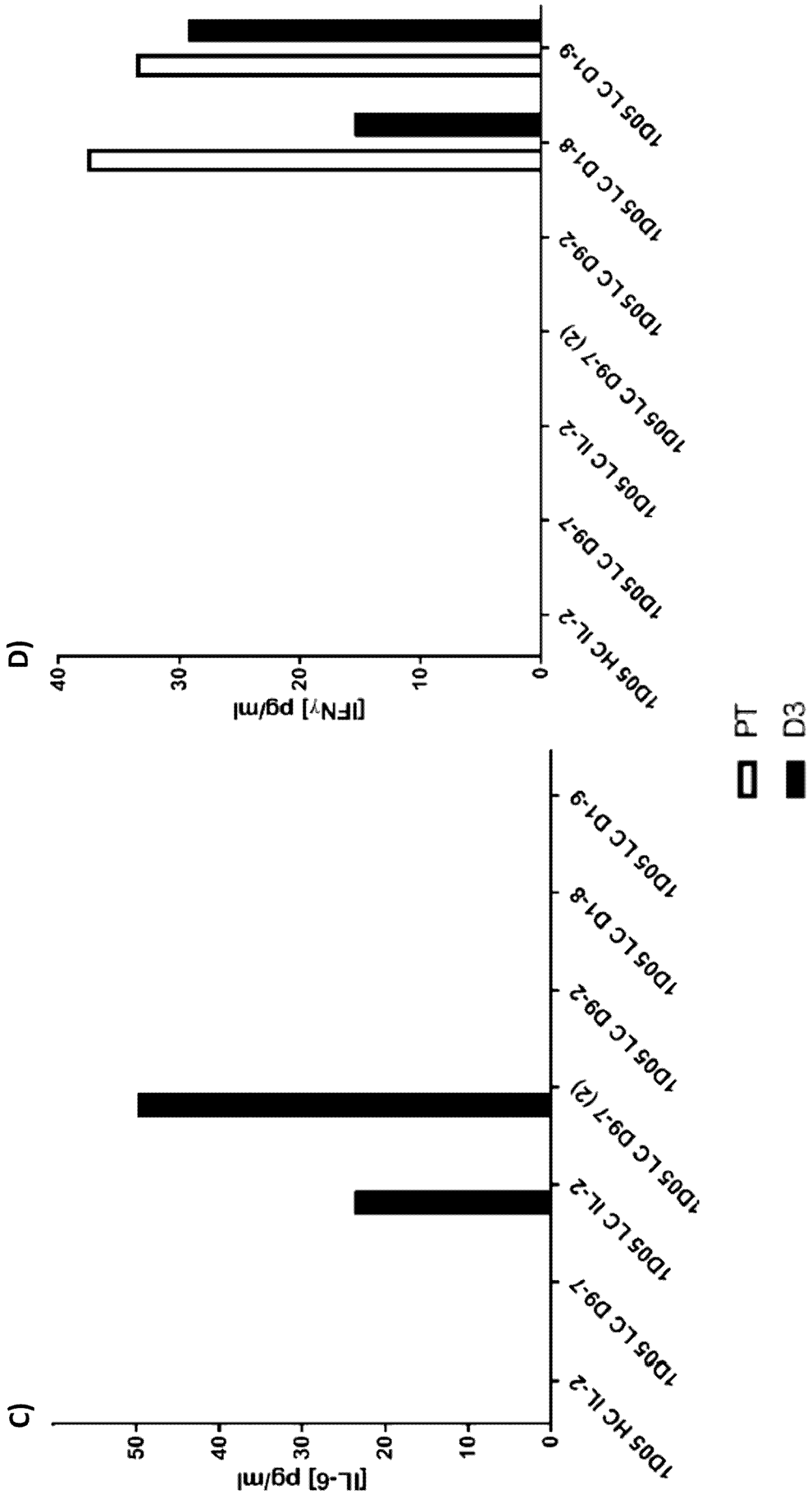


Figure 18 cont

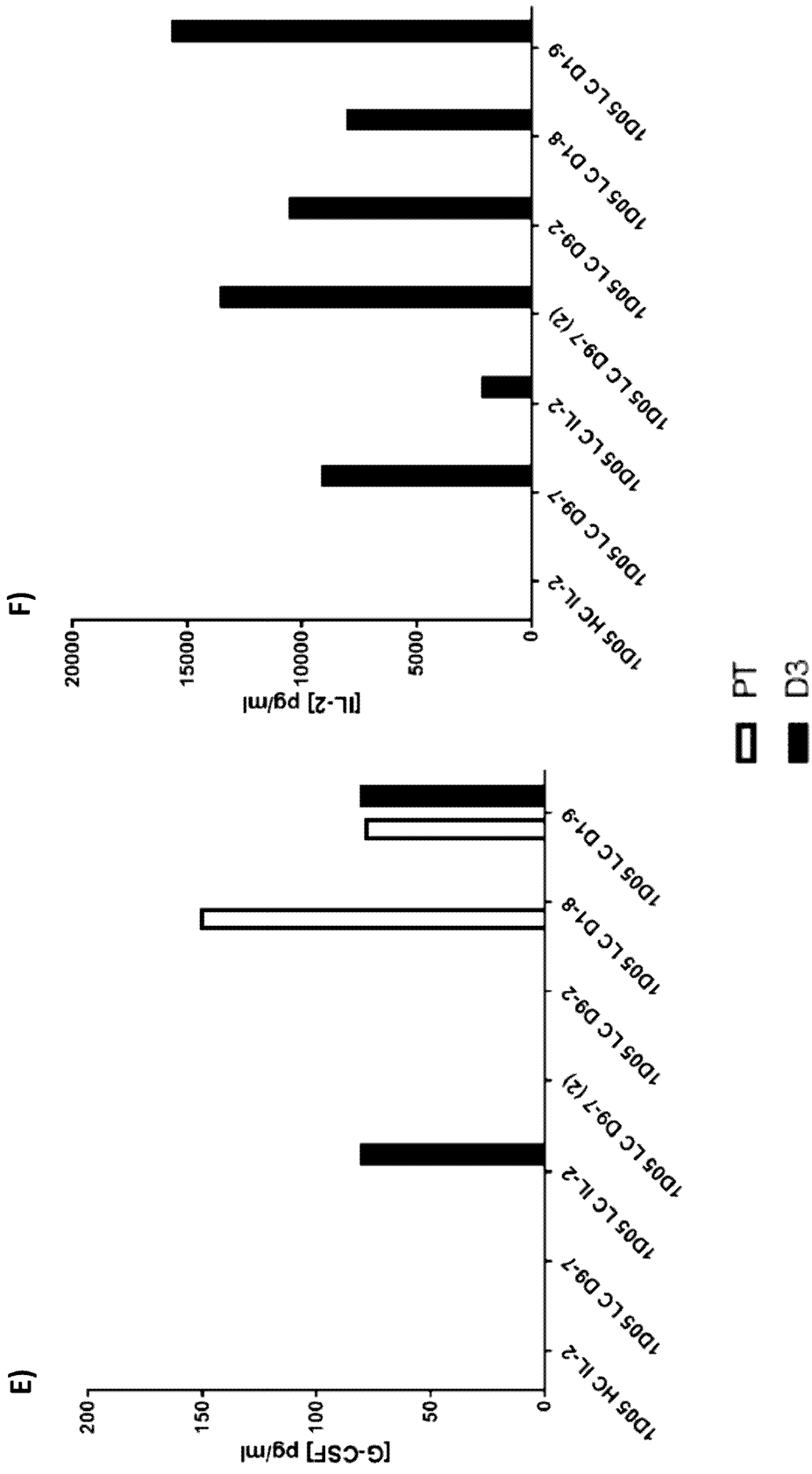


Figure 18 cont

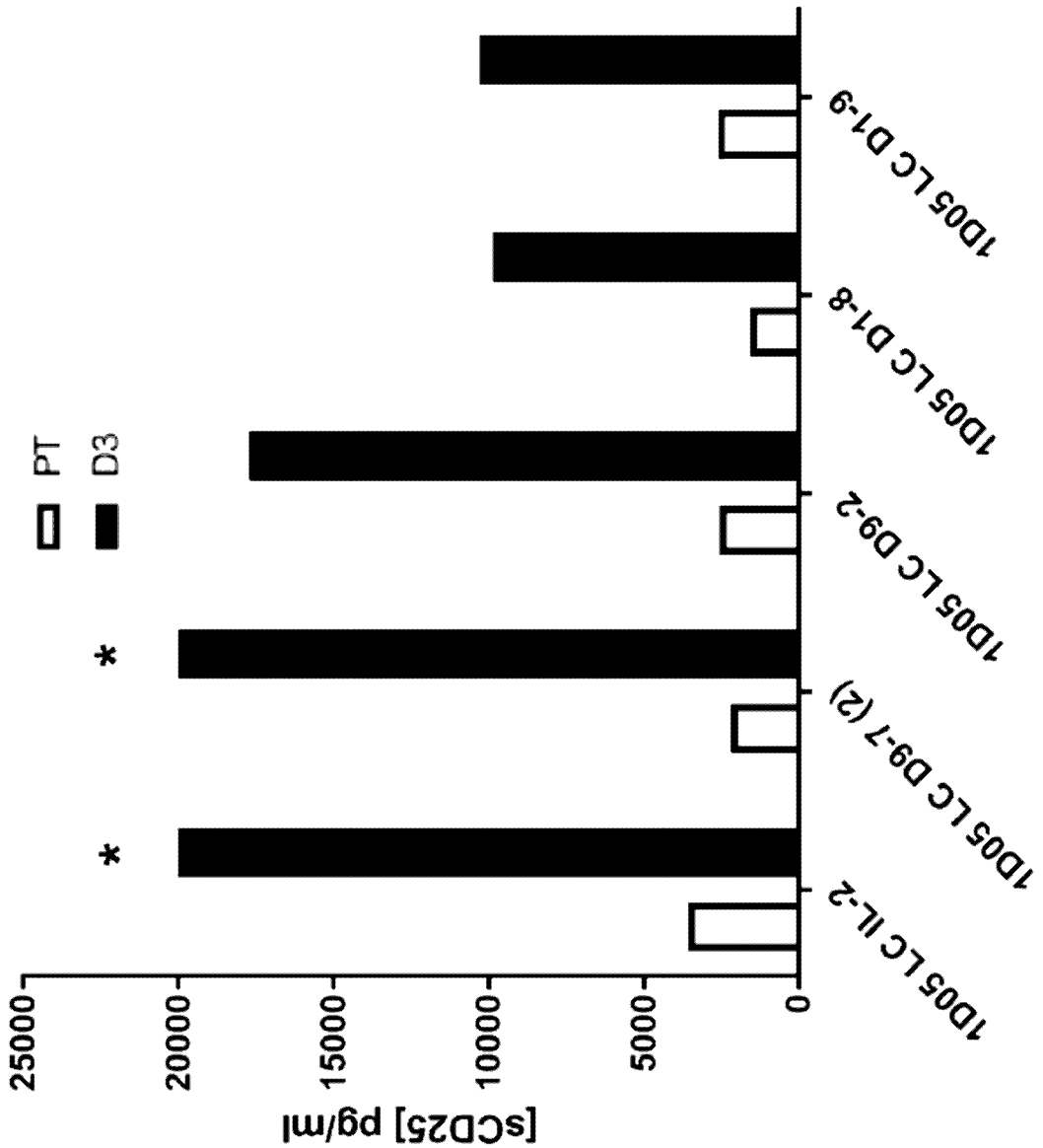

[sCD25] pg/ml
25000
20000
15000
10000
5000
0
PT
D3
*
*
1D05 LC IL-2
1D05 LC D9-7 (2)
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D1-9

Figure 19

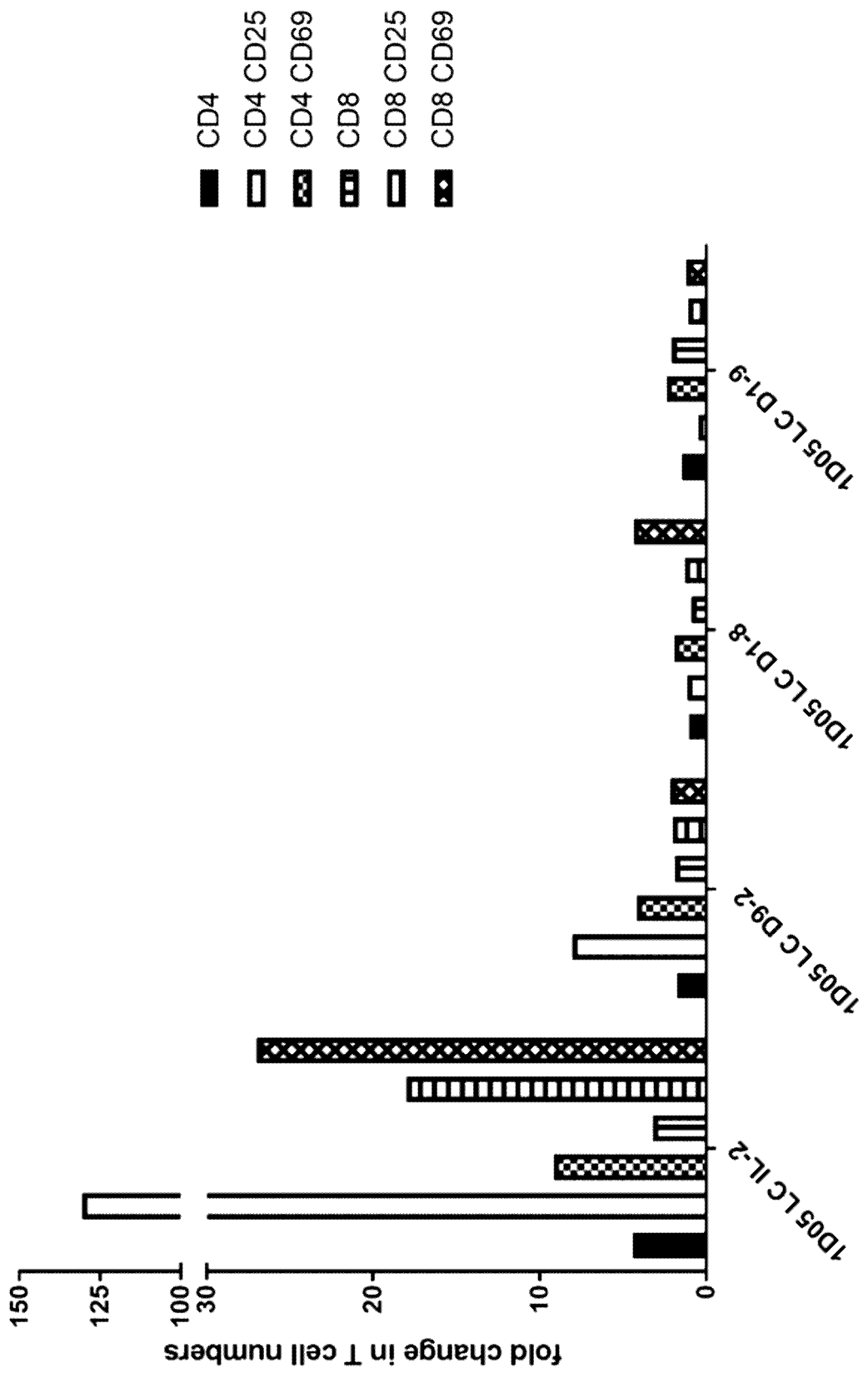

CD4
CD4 CD25
CD4 CD69
CD8
CD8 CD25
CD8 CD69
fold change in T cell numbers
150
125
100
30
20
10
0
1D05 LC IL-2
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D1-9

Figure 20a

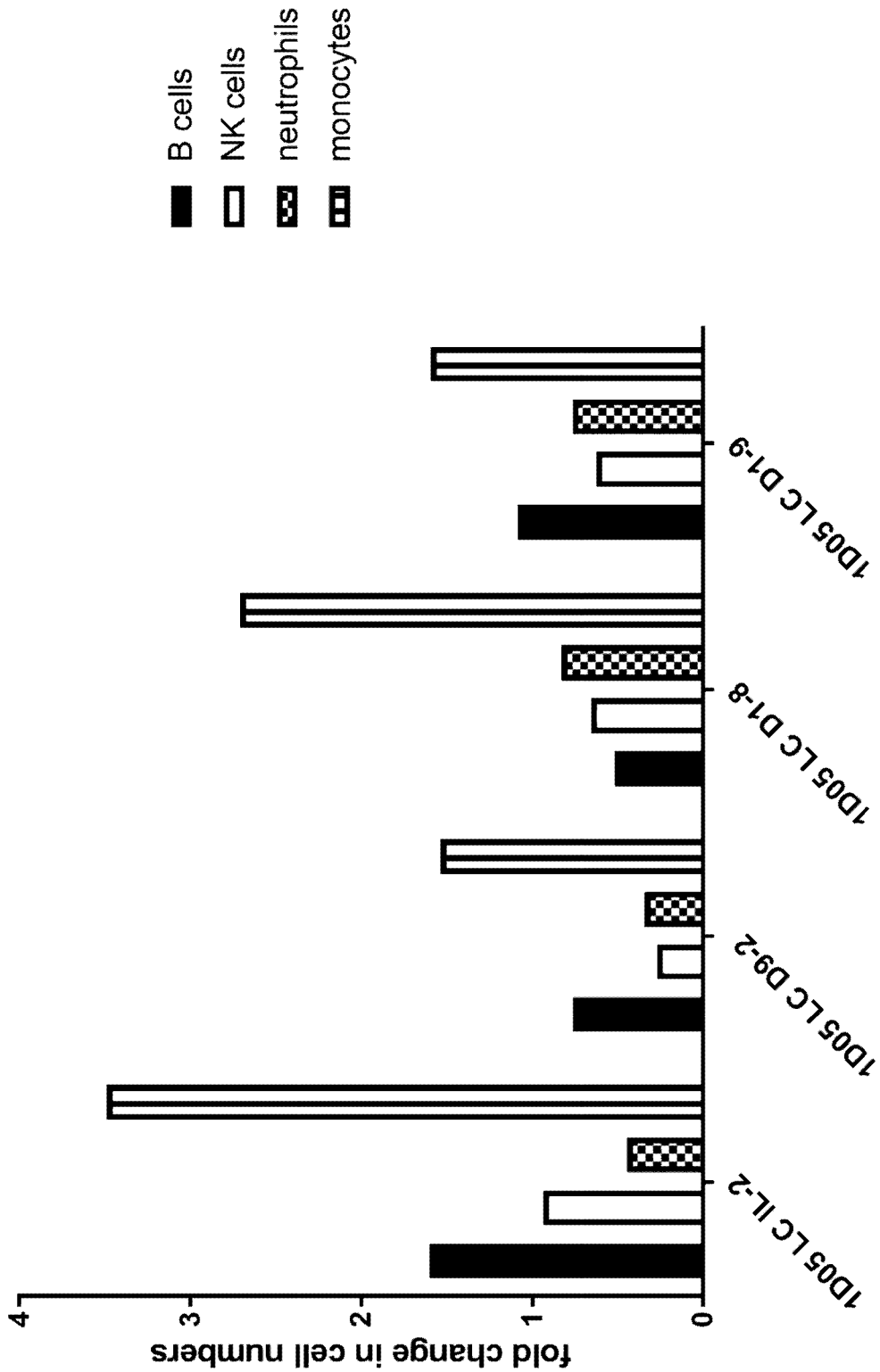

B cells
NK cells
neutrophils
monocytes
fold change in cell numbers
0
1
2
3
4
1D05 LC IL-2
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D1-9

Figure 20b

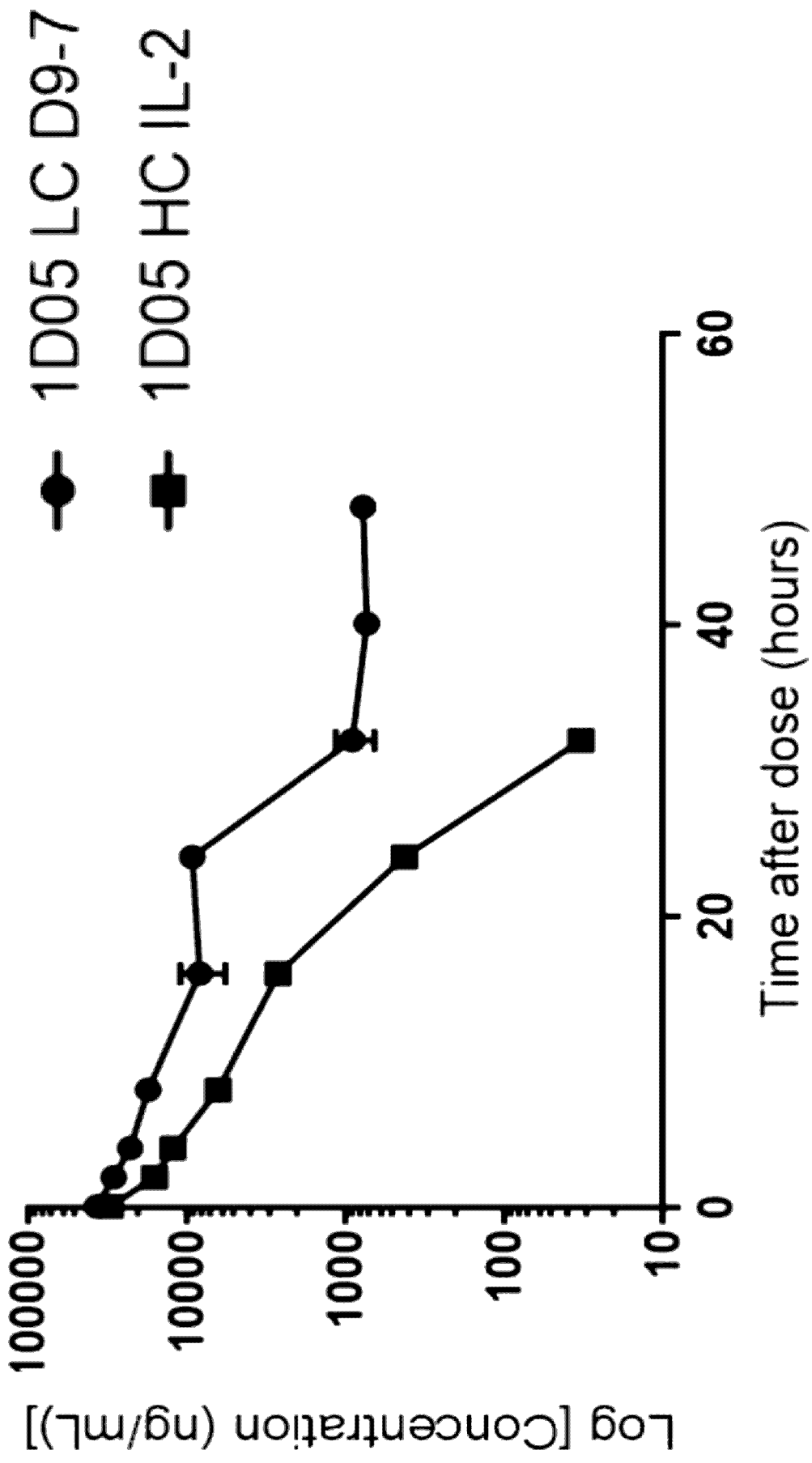

1D05 LC D9-7
1D05 HC IL-2
Log [Concentration (ng/mL)]
100000
10000
1000
100
10
0
20
40
60
Time after dose (hours)

Figure 21a

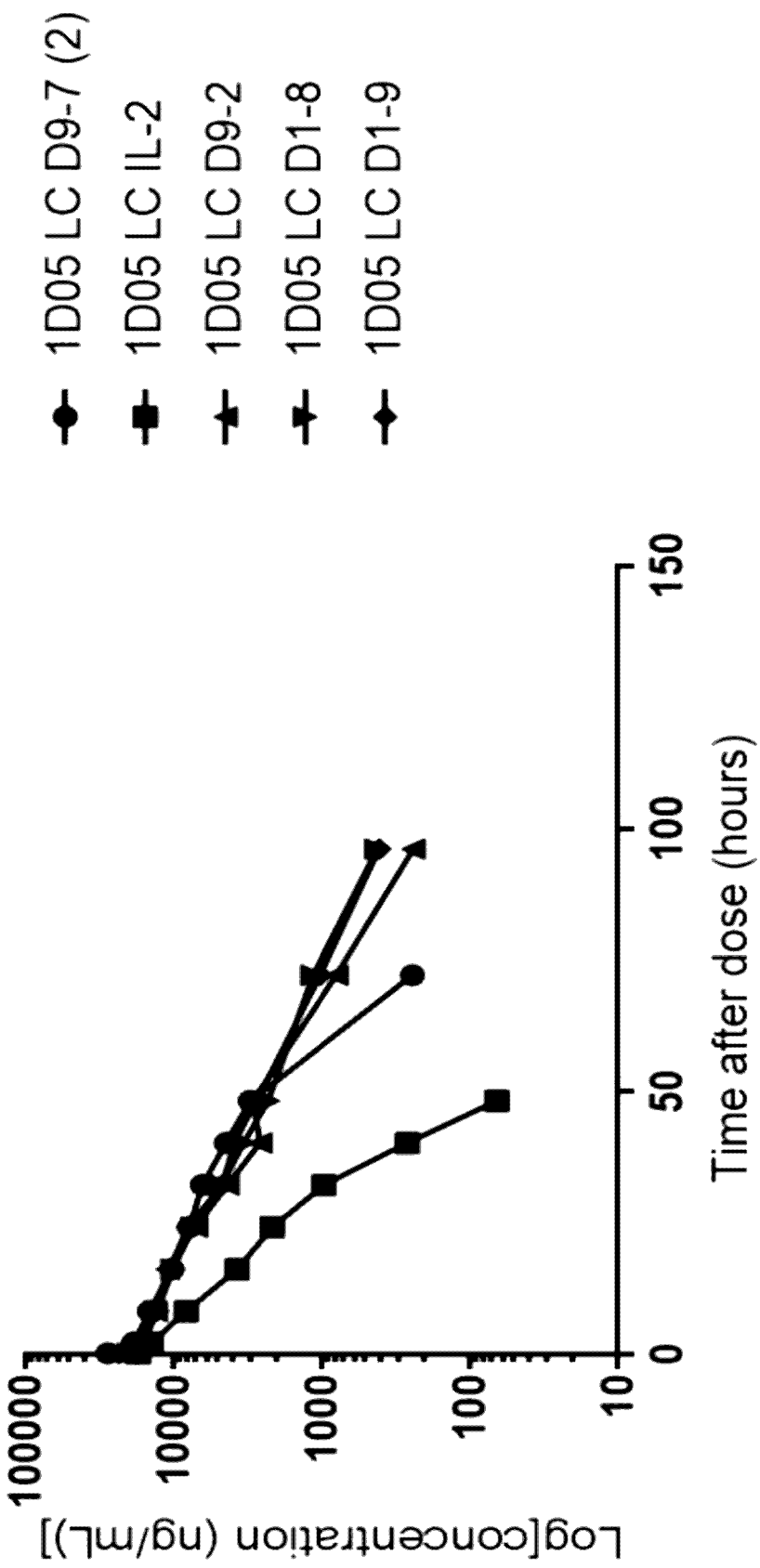

1D05 LC D9-7 (2)
1D05 LC IL-2
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D1-9
Log[concentration (ng/mL)]
100000
10000
1000
100
10
0
50
100
150
Time after dose (hours)

Figure 21b

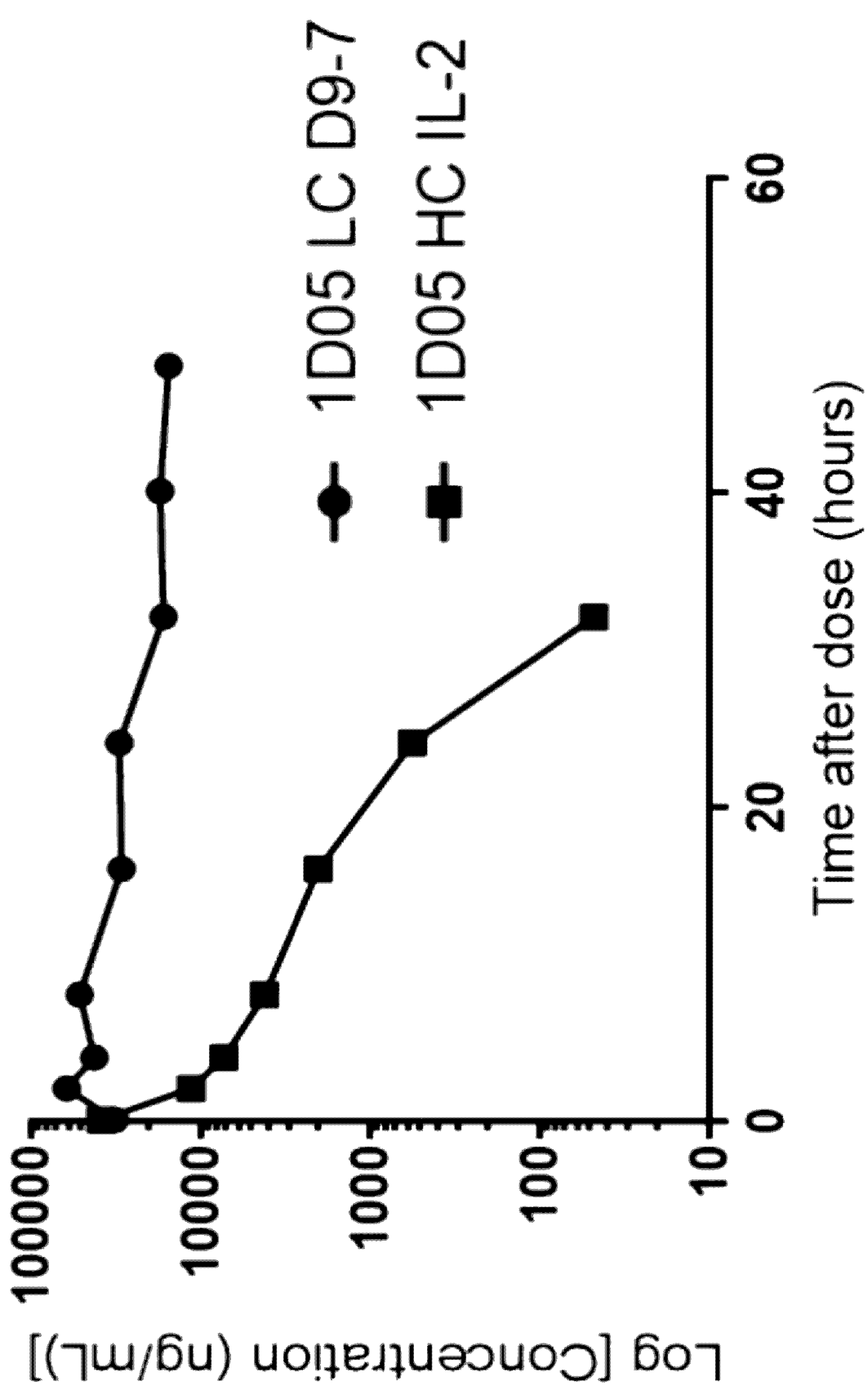

Log [Concentration (ng/mL)]
100000
10000
1000
100
10
0
20
40
60
Time after dose (hours)
1D05 LC D9-7
1D05 HC IL-2

Figure 21c

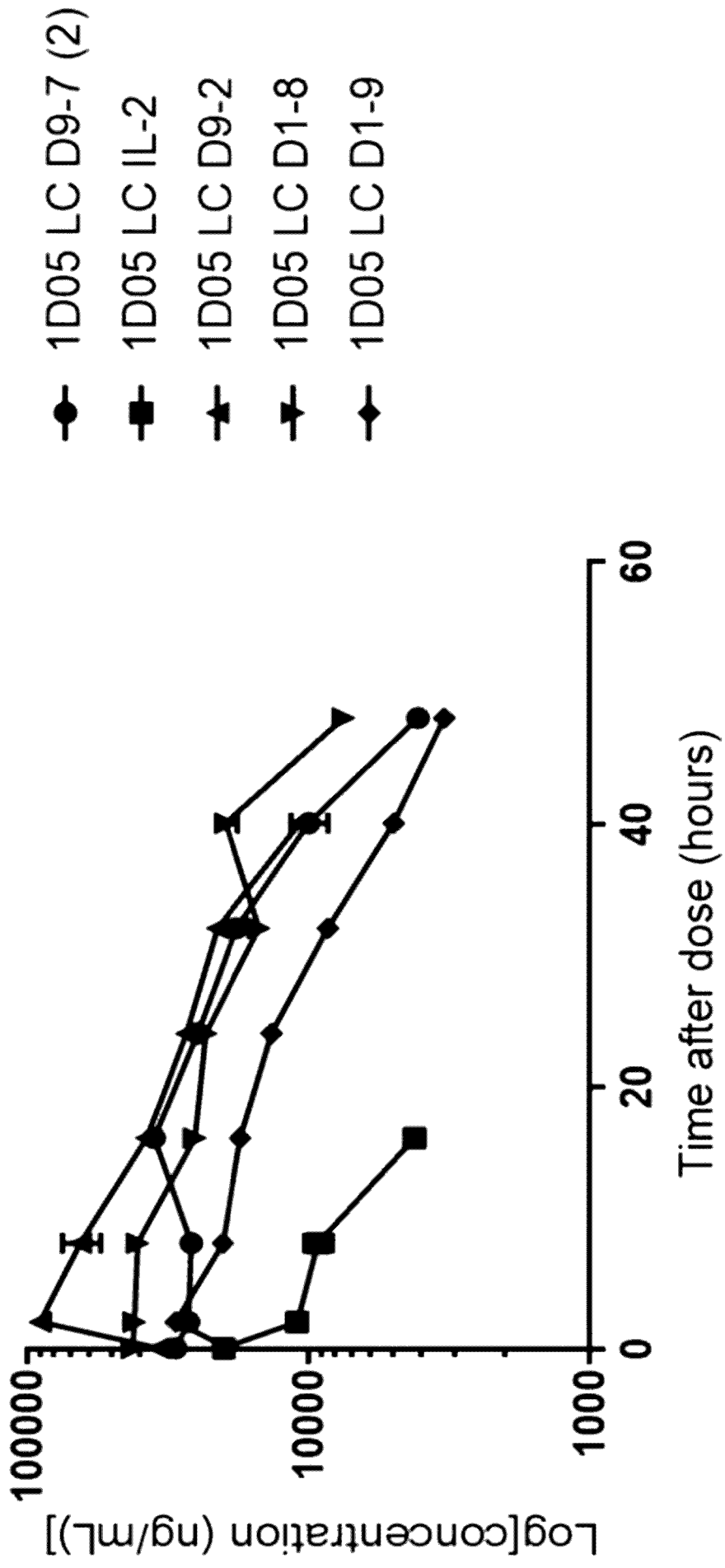

1D05 LC D9-7 (2)
1D05 LC IL-2
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D1-9
Log[concentration (ng/mL)]
100000
10000
1000
0
20
40
60
Time after dose (hours)

Figure 21d

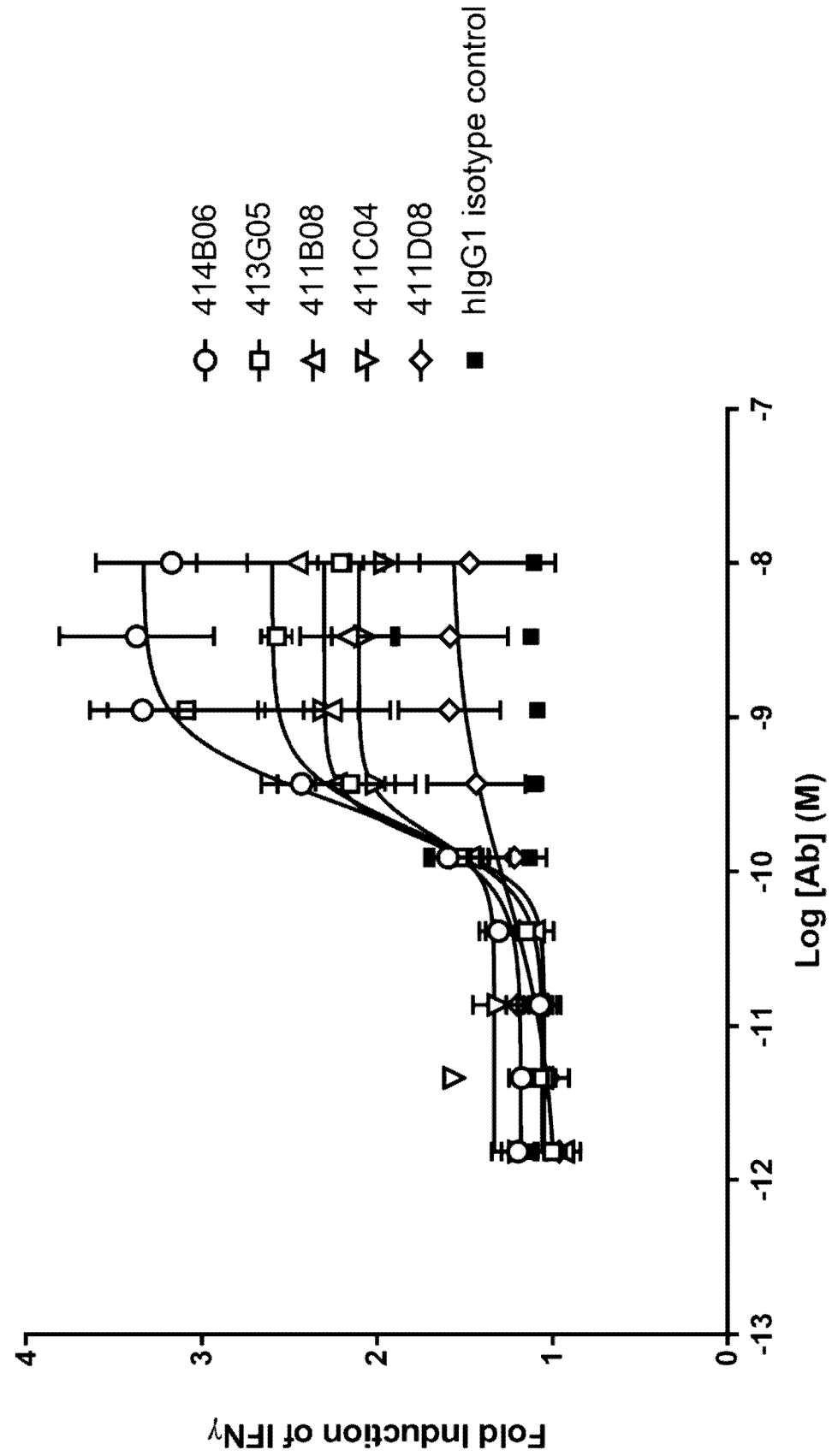

414B06
413G05
411B08
411C04
411D08
hIgG1 isotype control
Fold Induction of IFNγ
0
1
2
3
4
-13
-12
-11
-10
-9
-8
-7
Log [Ab] (M)

Figure 22a

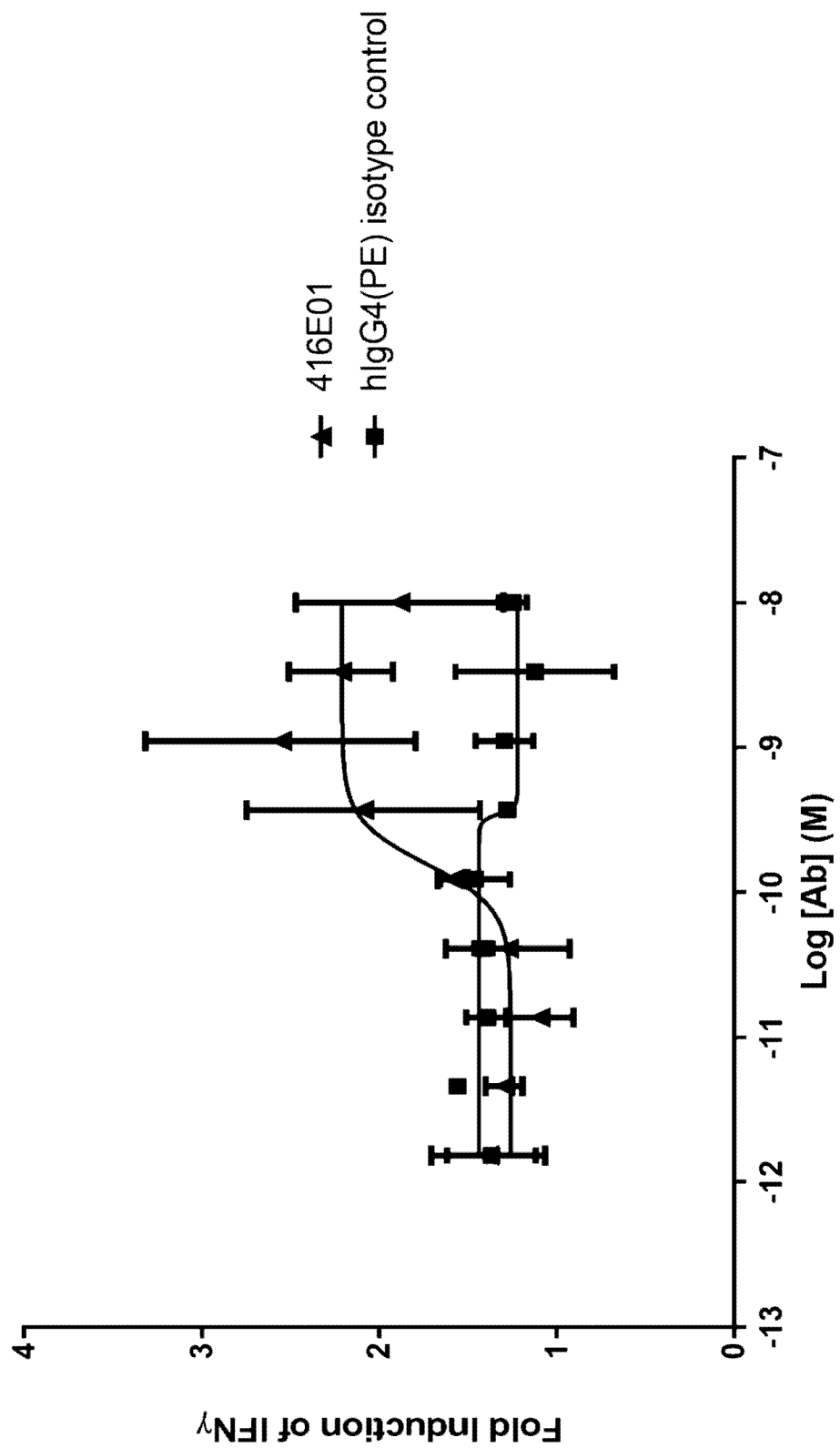

416E01
hIgG4(PE) isotype control
Fold Induction of IFNγ
Log [Ab] (M)
0
1
2
3
4
-13
-12
-11
-10
-9
-8
-7

Figure 22b

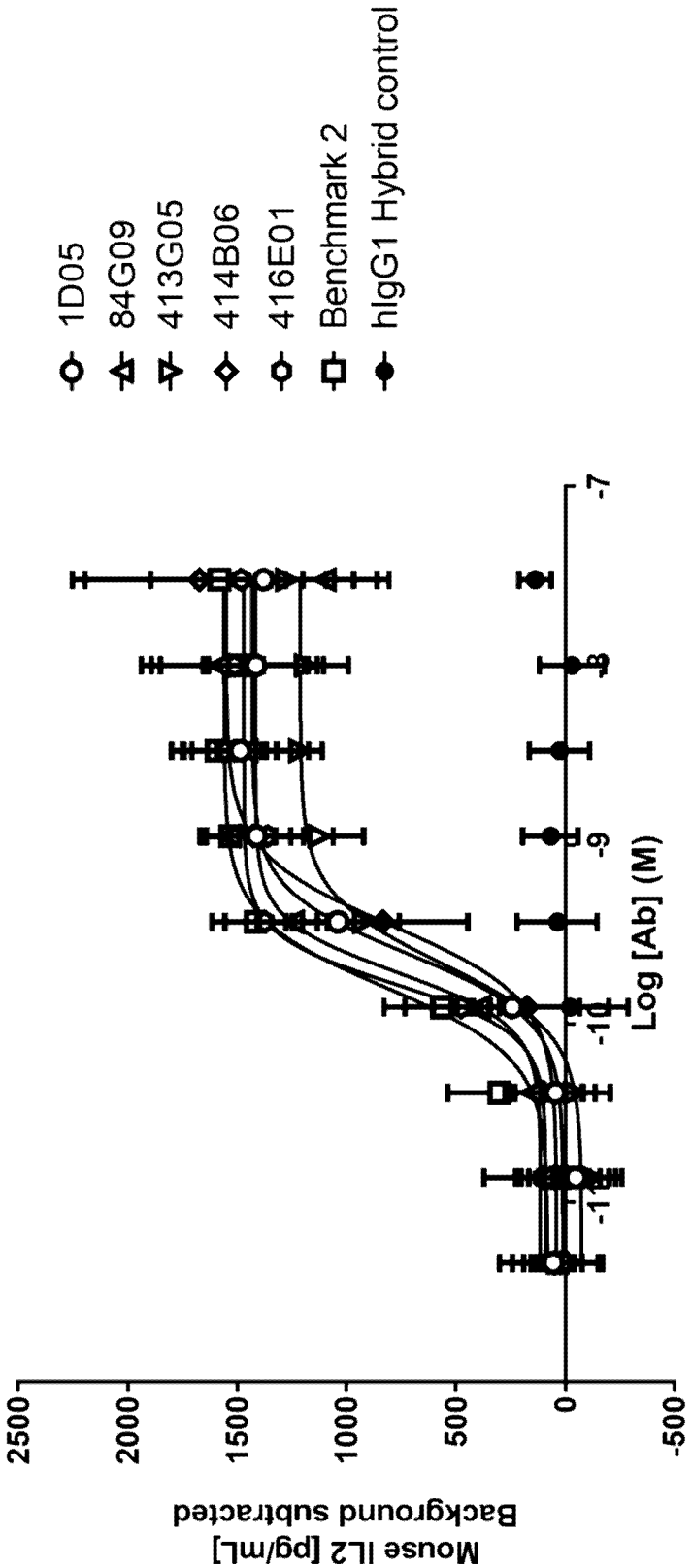

1D05
84G09
413G05
414B06
416E01
Benchmark 2
hIgG1 Hybrid control
Mouse IL2 [pg/mL]
Background subtracted
2500
2000
1500
1000
500
0
-500
-7
-8
-9
-10
-11
-12
Log [Ab] (M)

Figure 23(a)

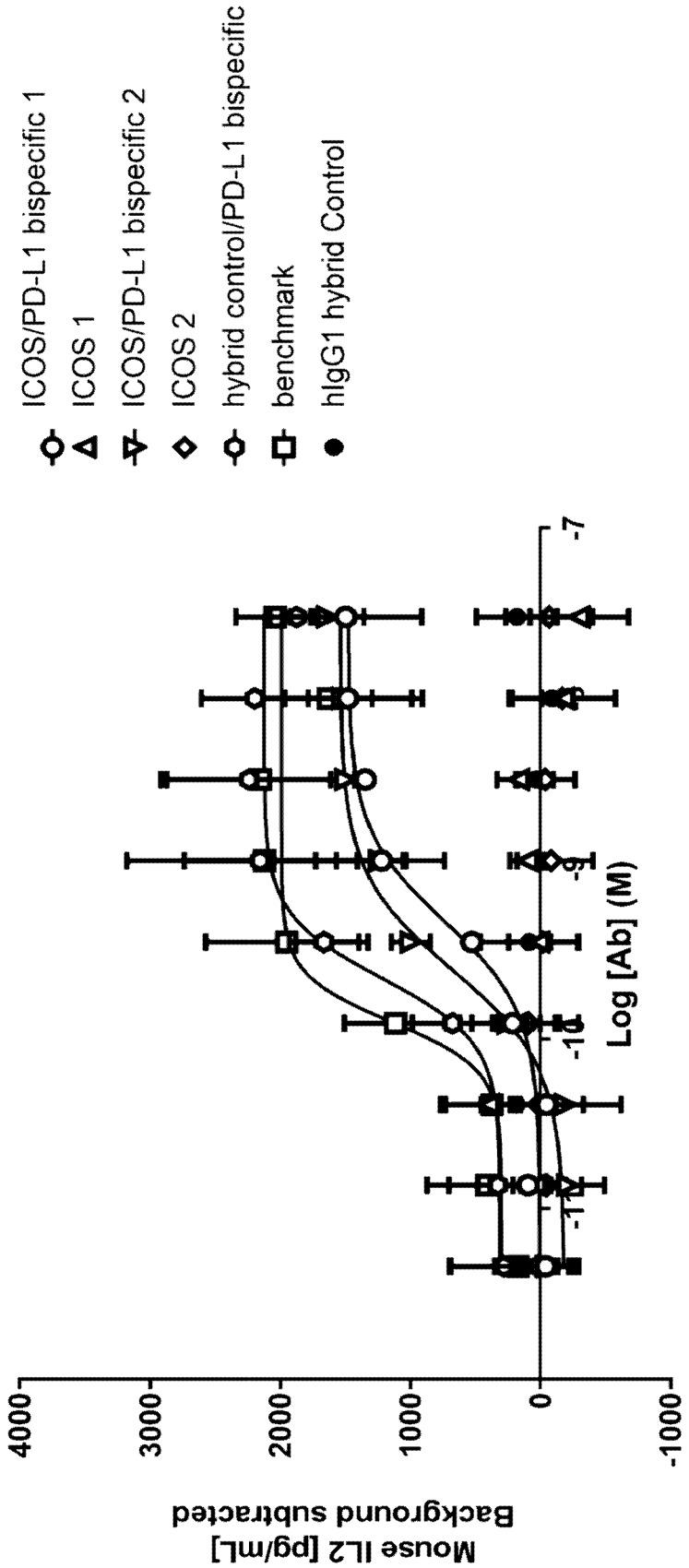

ICOS/PD-L1 bispecific 1
ICOS 1
ICOS/PD-L1 bispecific 2
ICOS 2
hybrid control/PD-L1 bispecific
benchmark
hIgG1 hybrid Control
Mouse IL2 [pg/mL]
Background subtracted
4000
3000
2000
1000
0
-1000
-7
-9
-11
-13
Log [Ab] (M)

Figure 23(b)

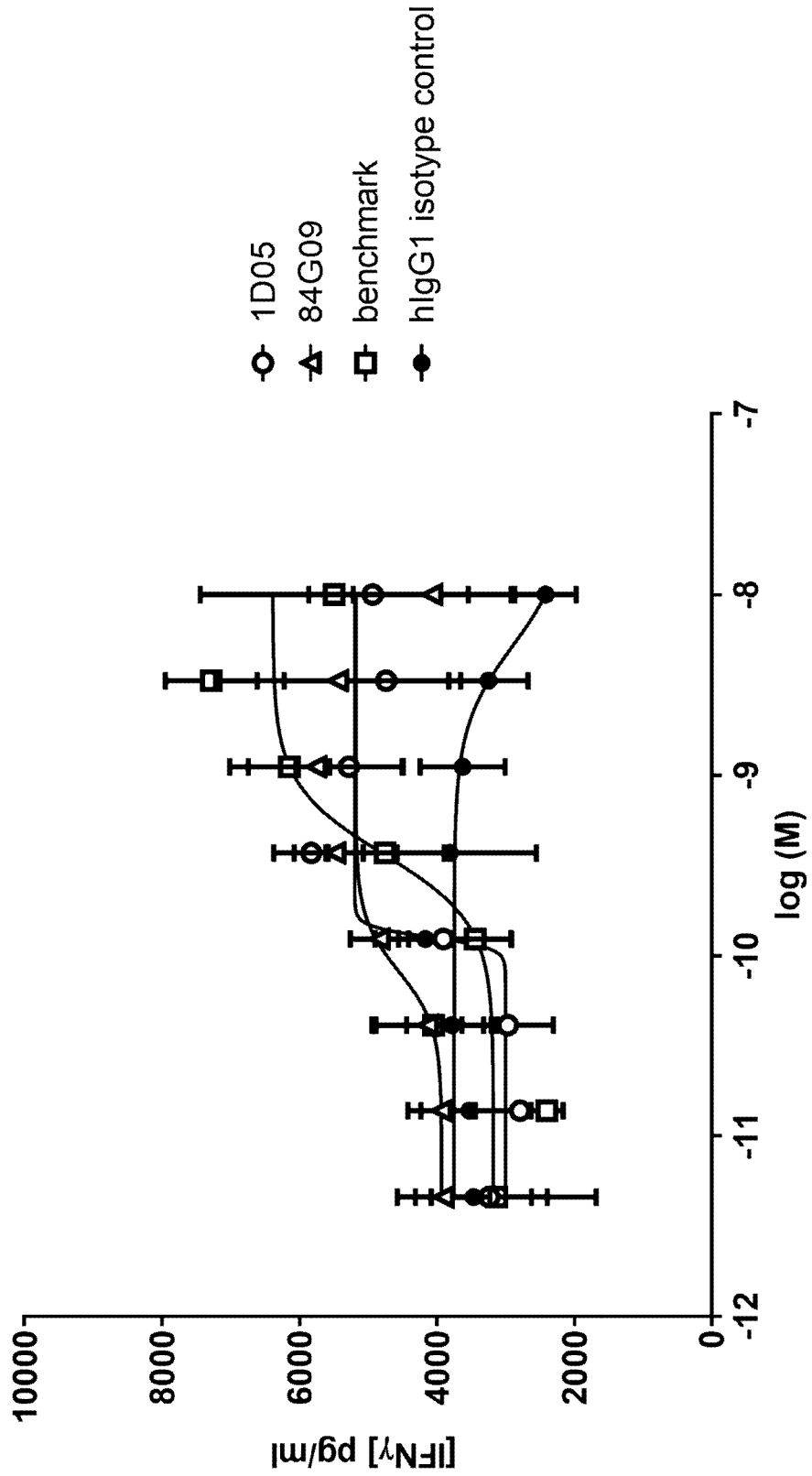

1D05
84G09
benchmark
hIgG1 isotype control
[IFNγ] pg/ml
10000
8000
6000
4000
2000
0
-12
-11
-10
-9
-8
-7
log (M)

Figure 24(a)

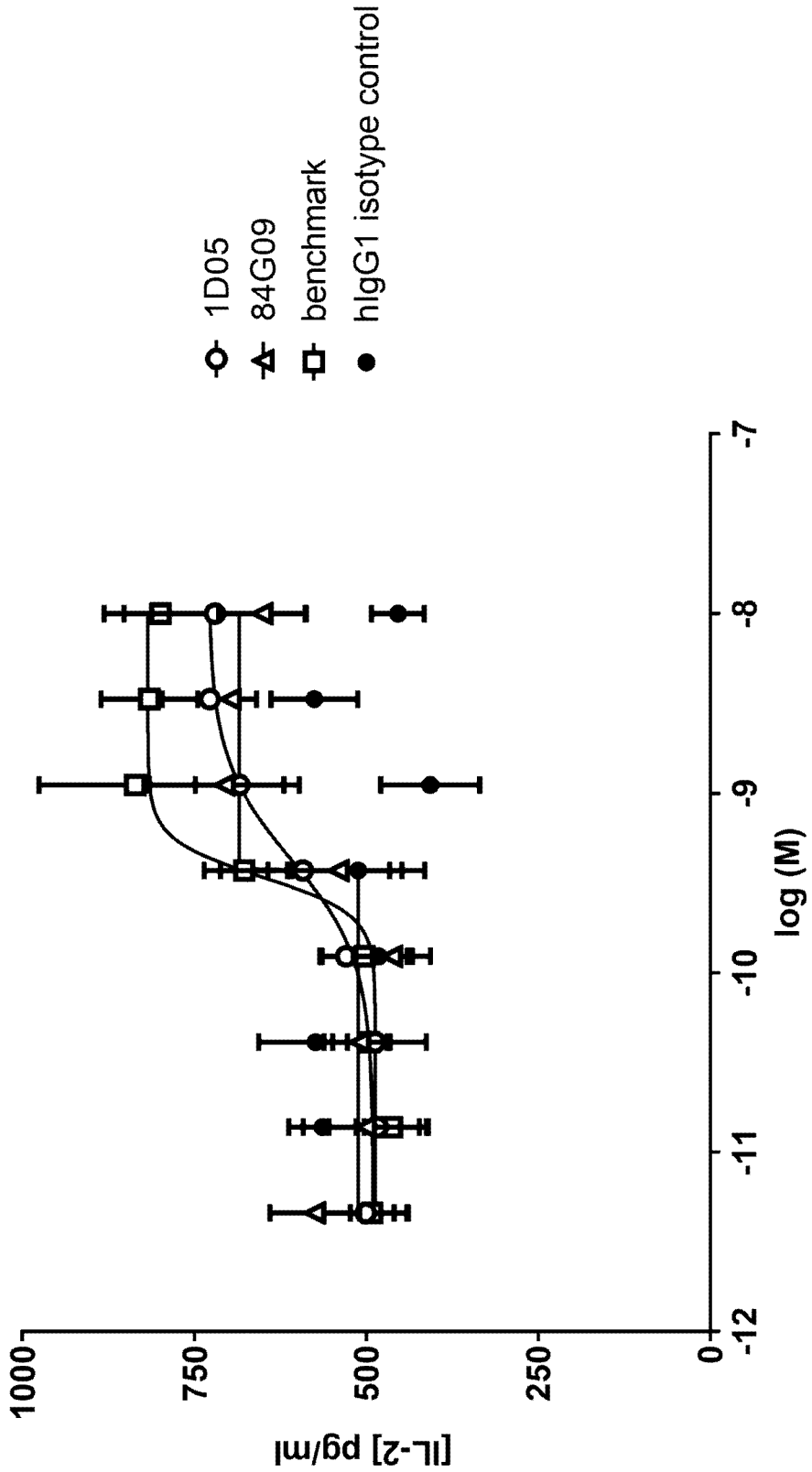

1D05
84G09
benchmark
hIgG1 isotype control
[IL-2] pg/ml
1000
750
500
250
0
-12
-11
-10
-9
-8
-7
log (M)

Figure 24(b)

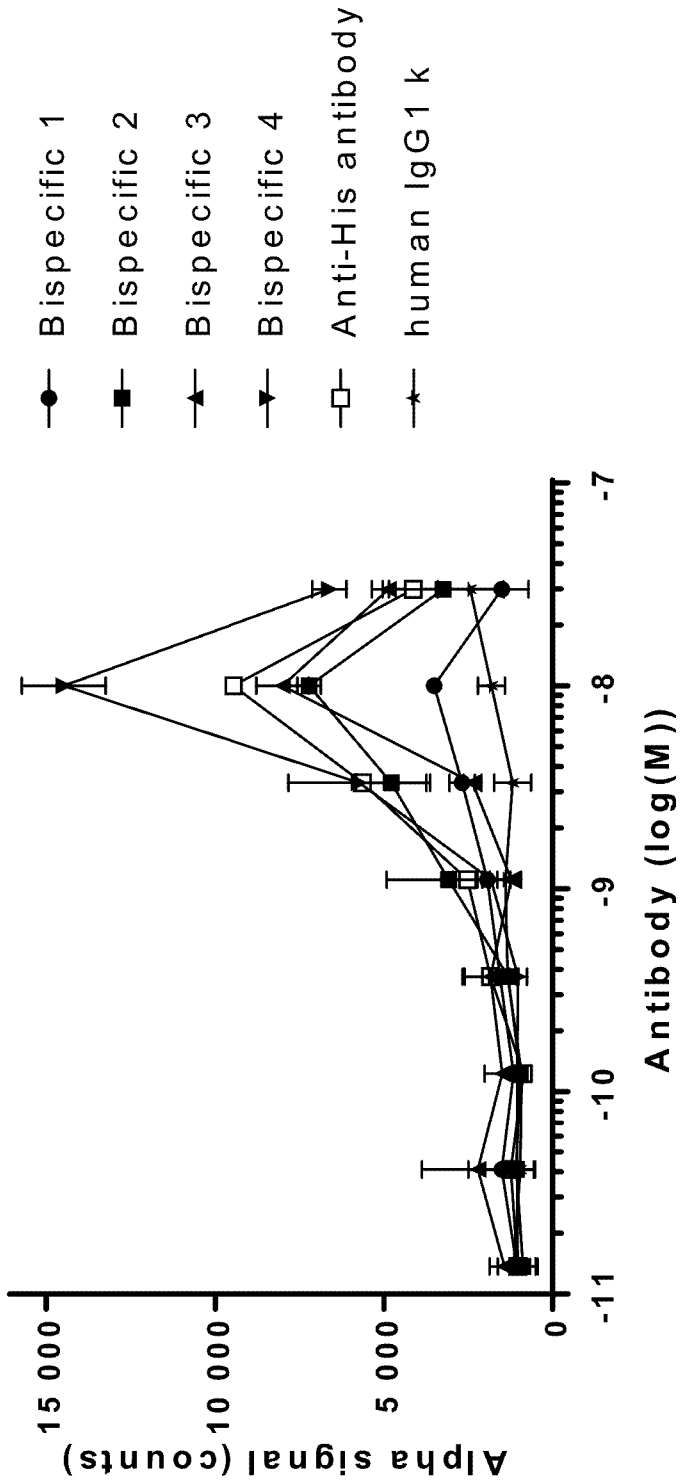

Bispecific 1
Bispecific 2
Bispecific 3
Bispecific 4
Anti-His antibody
human IgG1 k
Alpha signal (counts)
15 000
10 000
5 000
0
-11
-10
-9
-8
-7
Antibody (log(M))

Figure 25(a)

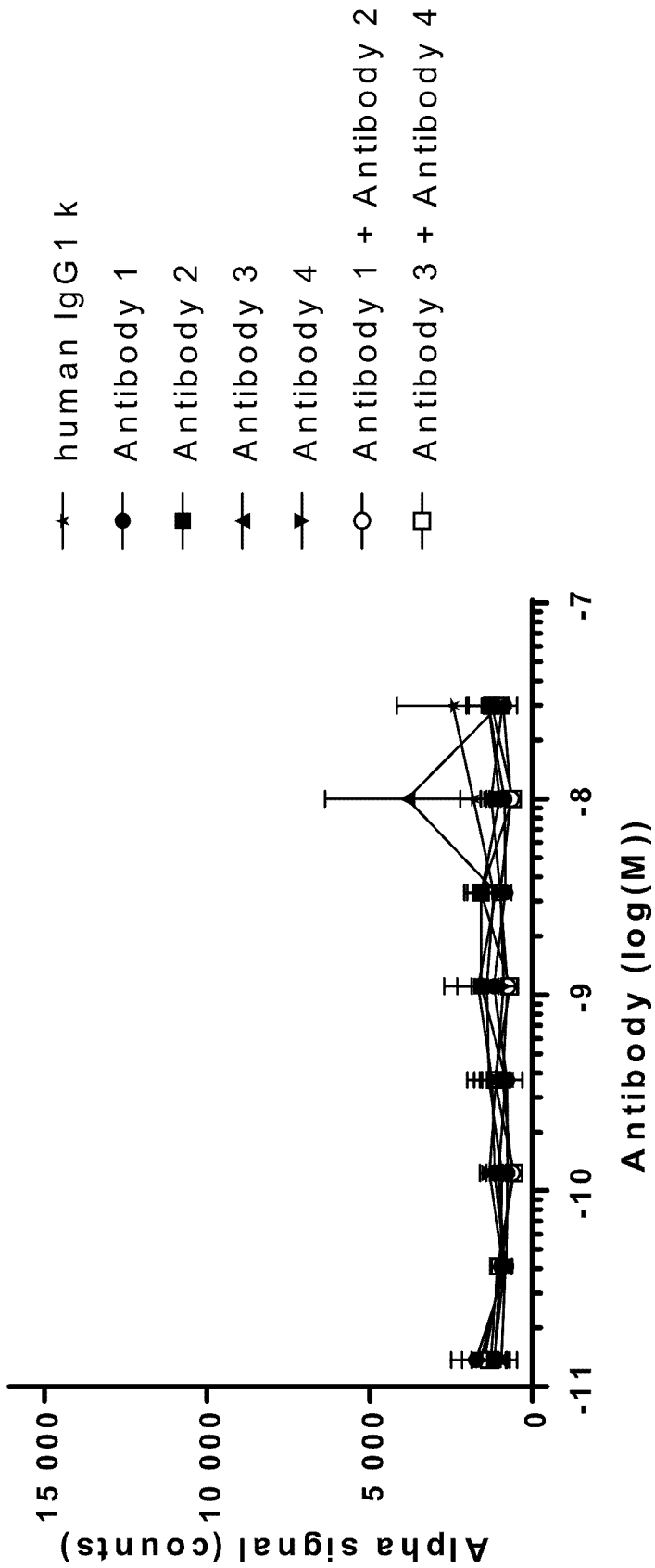

human IgG1 k
Antibody 1
Antibody 2
Antibody 3
Antibody 4
Antibody 1 + Antibody 2
Antibody 3 + Antibody 4
Alpha signal (counts)
15 000
10 000
5 000
0
-11
-10
-9
-8
-7
Antibody (log(M))

Figure 25(b)

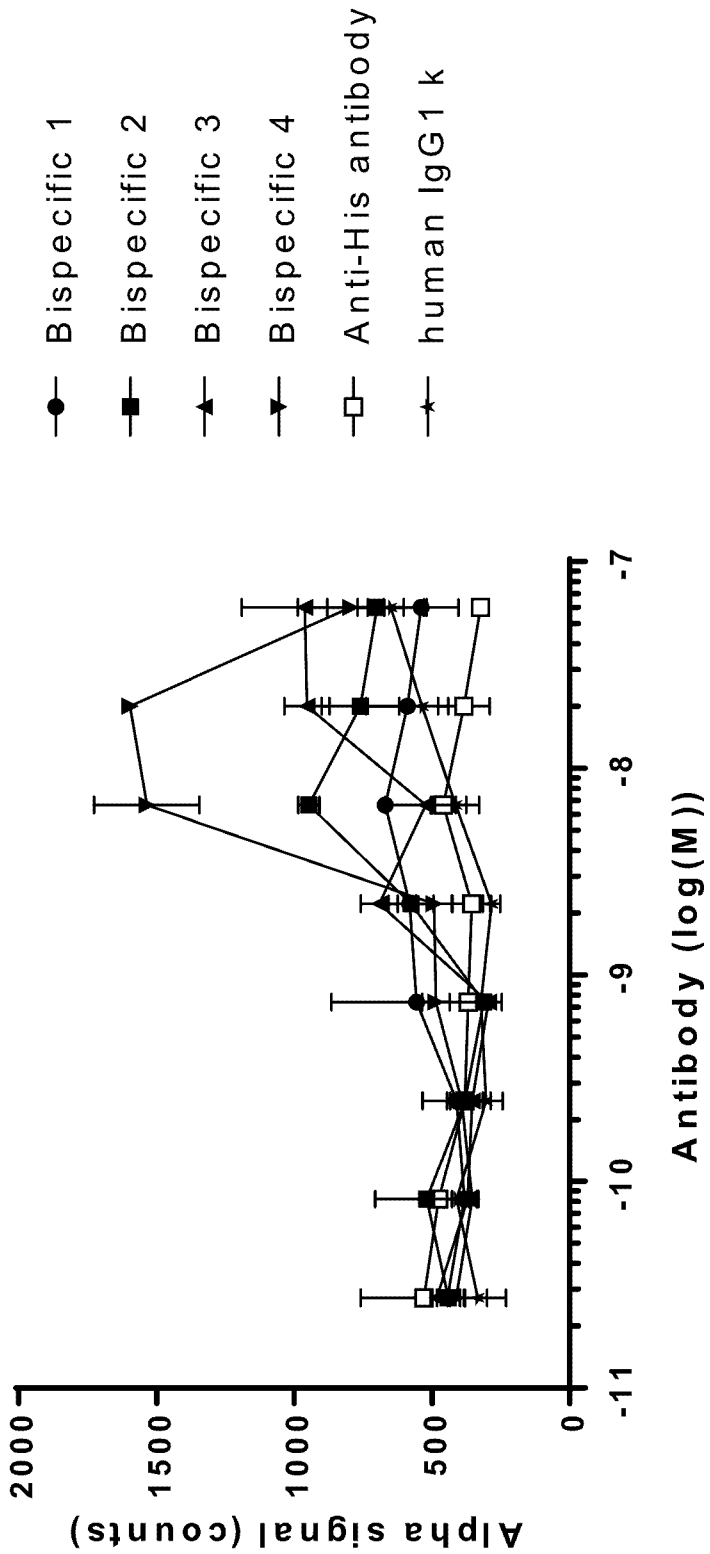

Bispecific 1
Bispecific 2
Bispecific 3
Bispecific 4
Anti-His antibody
human IgG1 k
Alpha signal (counts)
2000
1500
1000
500
0
-11
-10
-9
-8
-7
Antibody (log(M))

Figure 26(a)

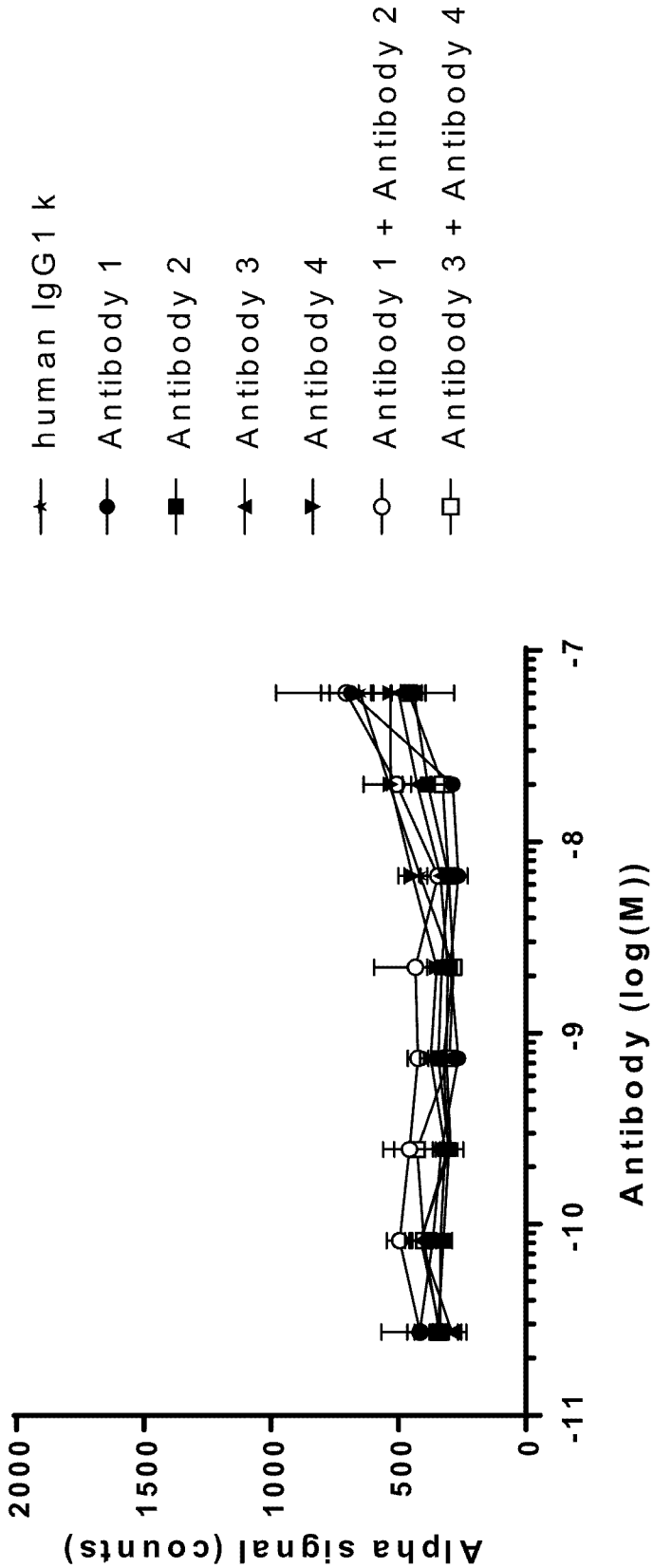

human IgG1 k
Antibody 1
Antibody 2
Antibody 3
Antibody 4
Antibody 1 + Antibody 2
Antibody 3 + Antibody 4
Alpha signal (counts)
2000
1500
1000
500
0
-11
-10
-9
-8
-7
Antibody (log(M))

Figure 26(b)

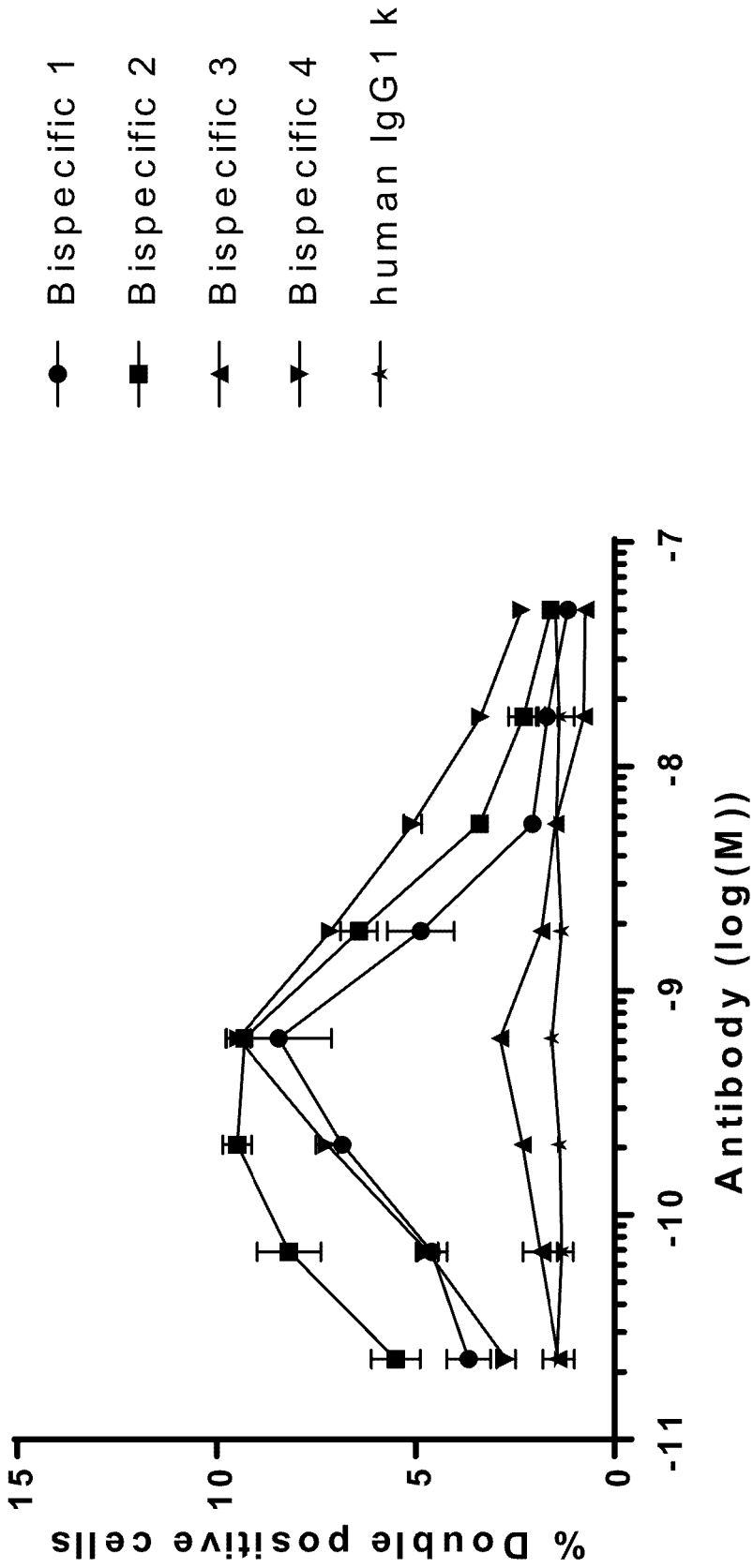

Bispecific 1
Bispecific 2
Bispecific 3
Bispecific 4
human IgG1 k
% Double positive cells
15
10
5
0
-11
-10
-9
-8
-7
Antibody (log(M))

Figure 27

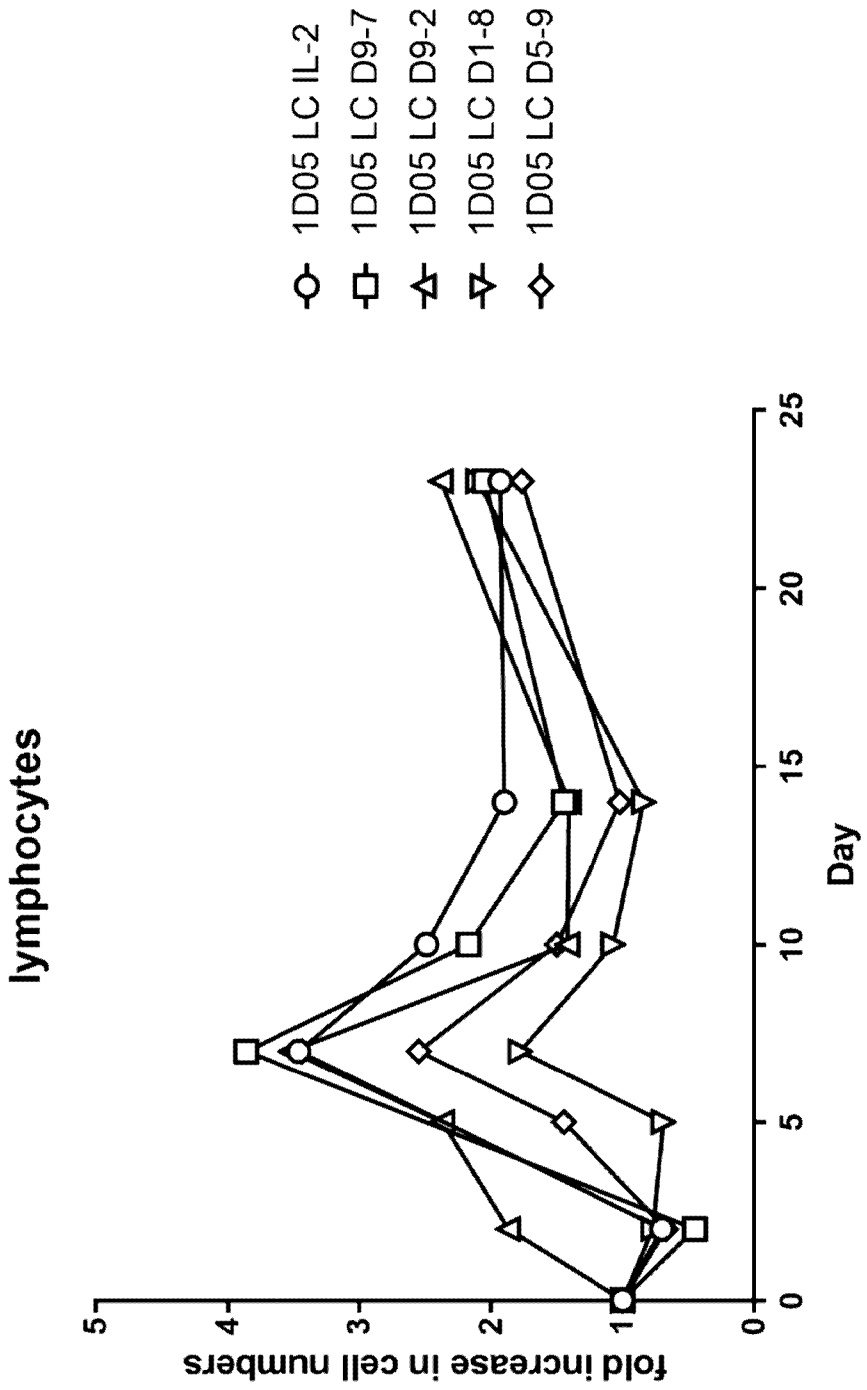

lymphocytes
fold increase in cell numbers
0
1
2
3
4
5
0
5
10
15
20
25
Day
1D05 LC IL-2
1D05 LC D9-7
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D5-9

Figure 28

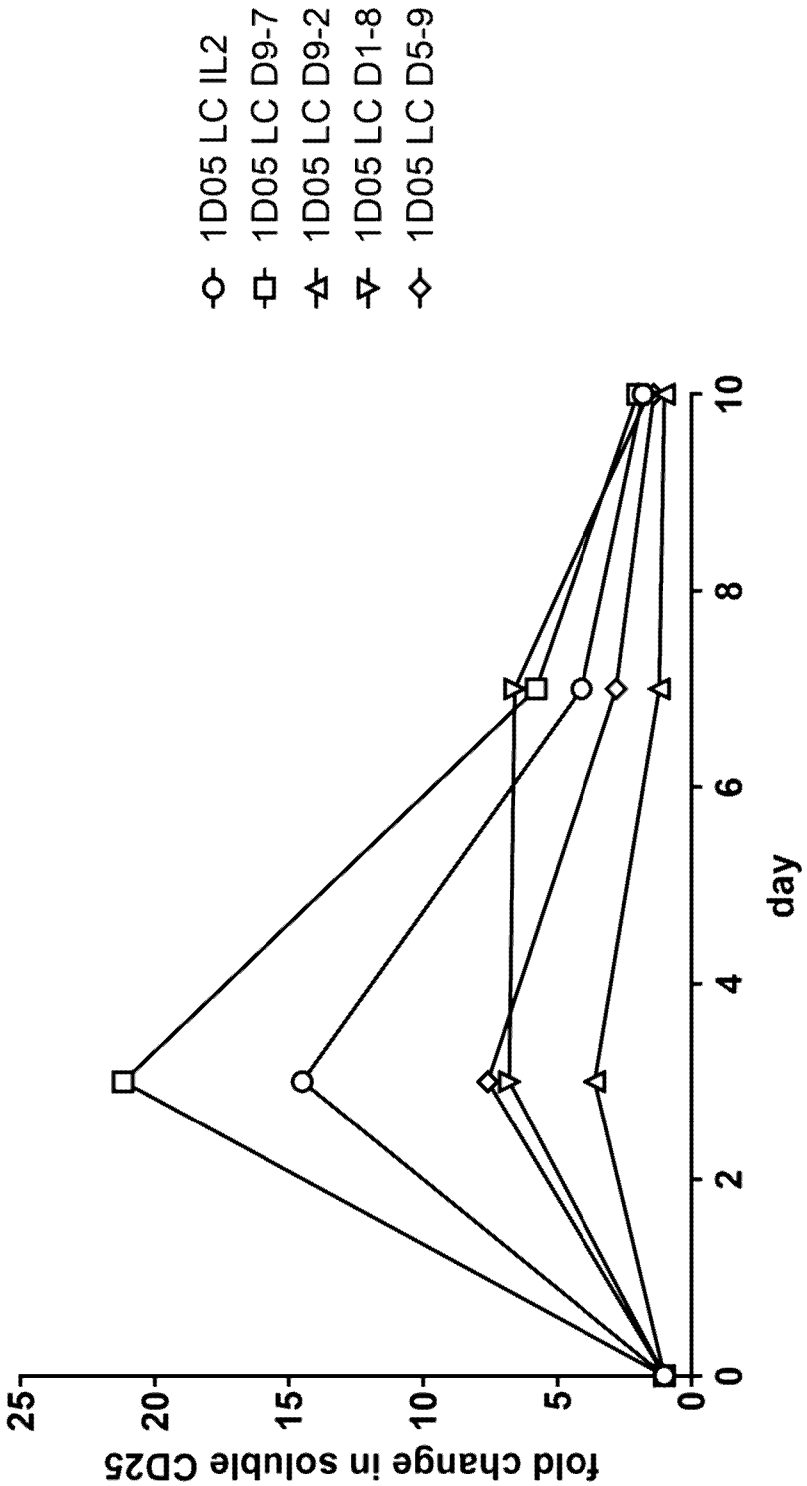

1D05 LC IL2
1D05 LC D9-7
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D5-9
fold change in soluble CD25
0
5
10
15
20
25
0
2
4
6
8
10
day

Figure 29

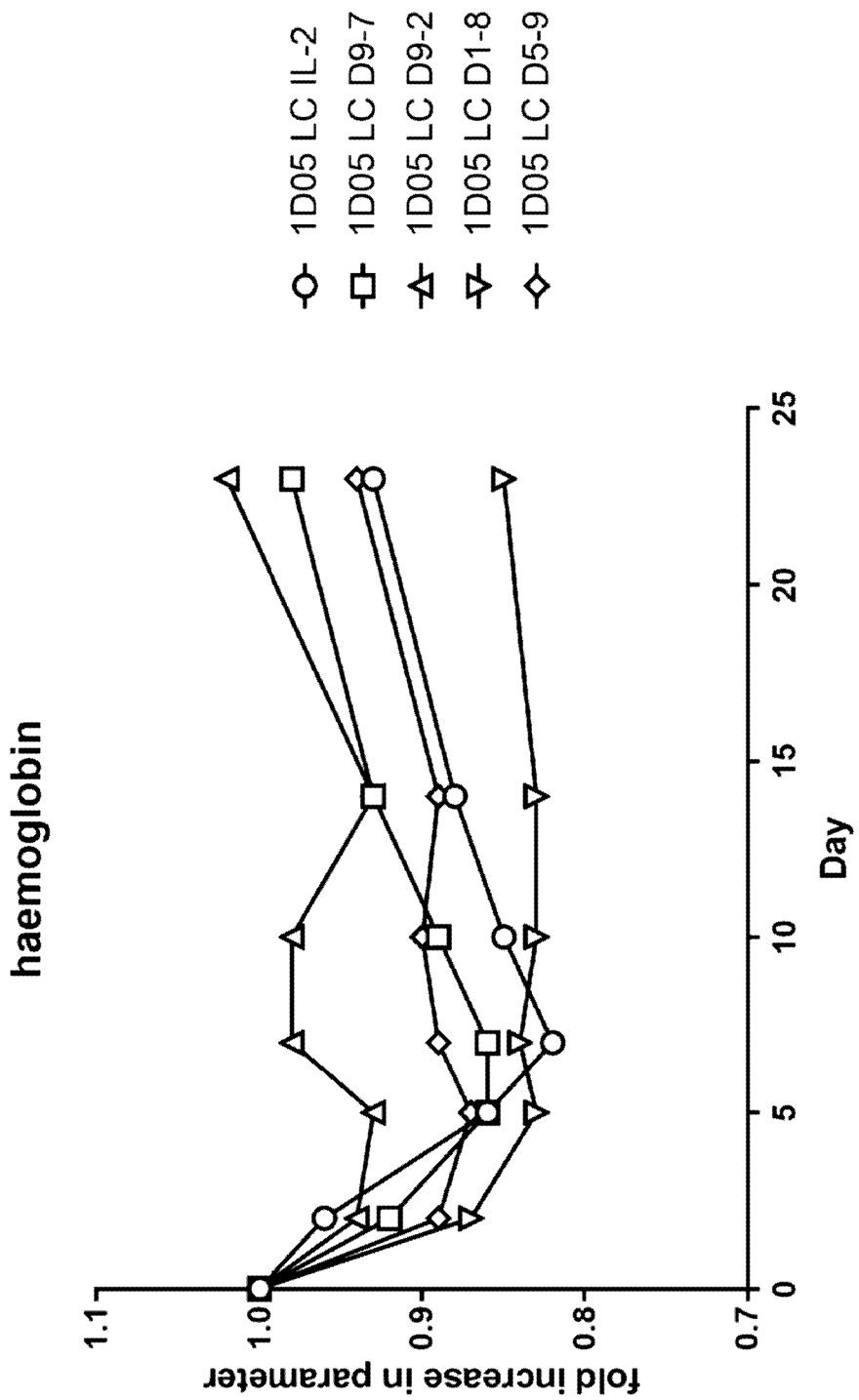

haemoglobin
1D05 LC IL-2
1D05 LC D9-7
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D5-9
fold increase in parameter
1.1
1.0
0.9
0.8
0.7
0
5
10
15
20
25
Day

Figure 30(a)

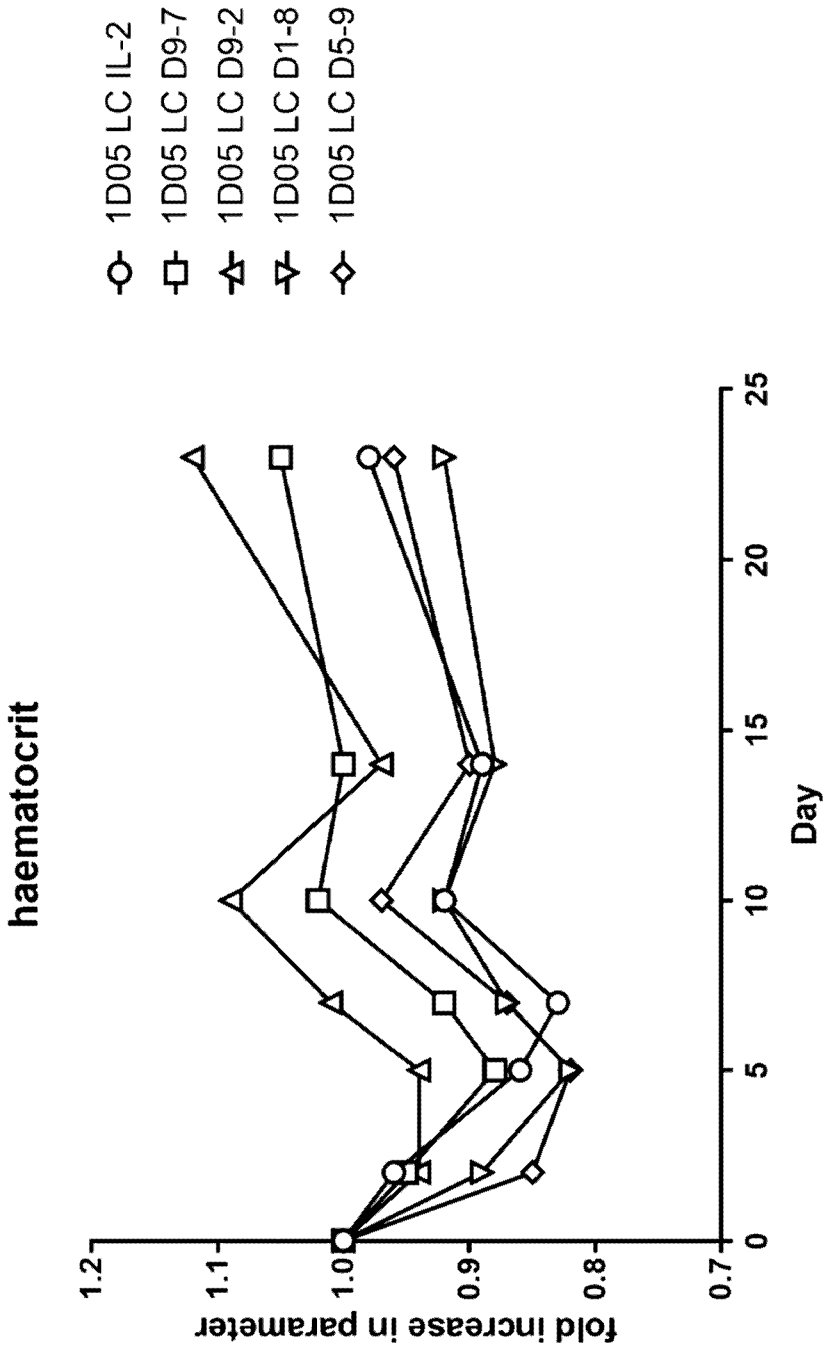

haematocrit
1D05 LC IL-2
1D05 LC D9-7
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D5-9
fold increase in parameter
1.2
1.1
1.0
0.9
0.8
0.7
0
5
10
15
20
25
Day

Figure 30(b)

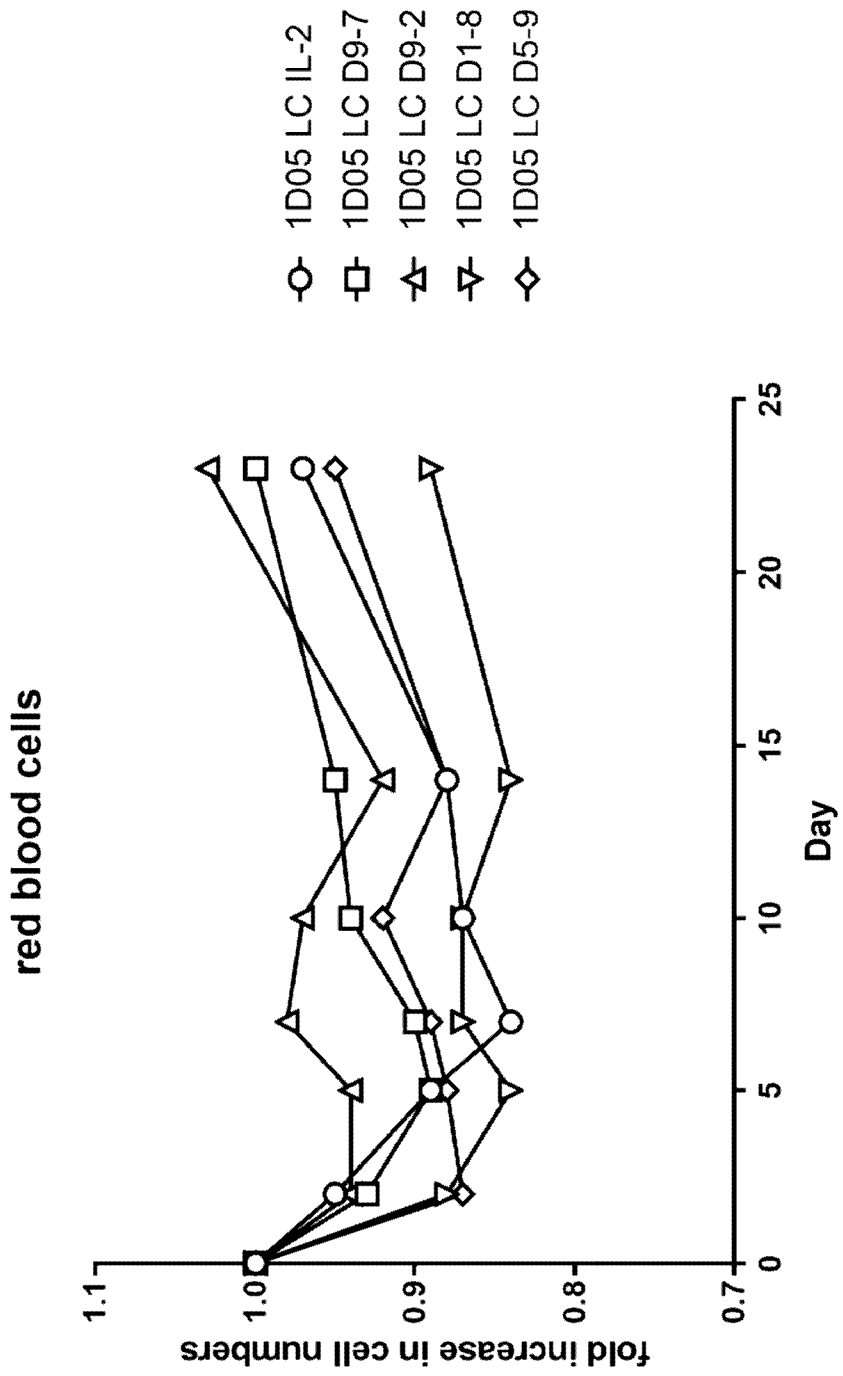

red blood cells
1D05 LC IL-2
1D05 LC D9-7
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D5-9
fold increase in cell numbers
1.1
1.0
0.9
0.8
0.7
0
5
10
15
20
25
Day

Figure 30(c)

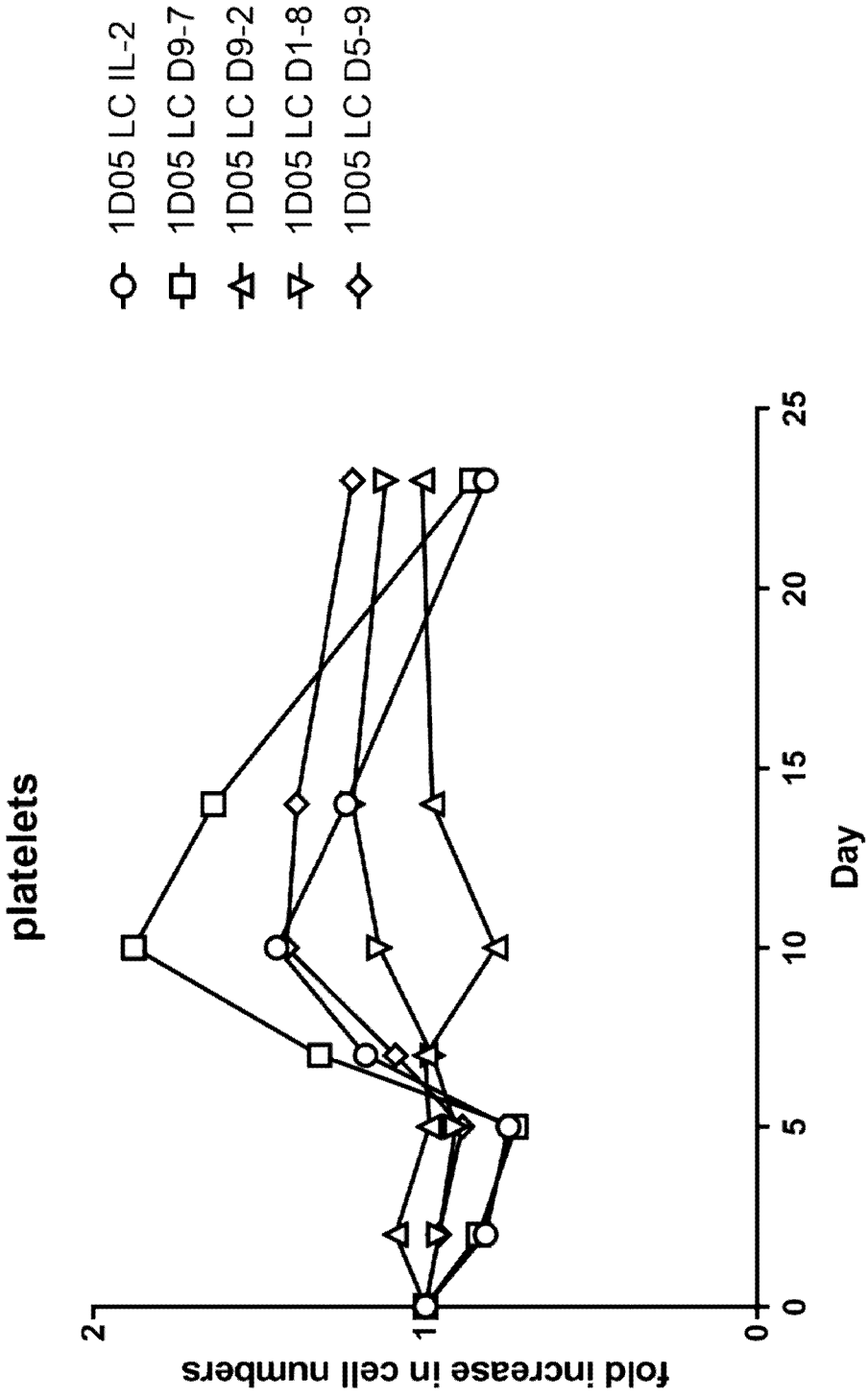

platelets
1D05 LC IL-2
1D05 LC D9-7
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D5-9
fold increase in cell numbers
0
1
2
0
5
10
15
20
25
Day

Figure 30(d)

Figure 31(a)

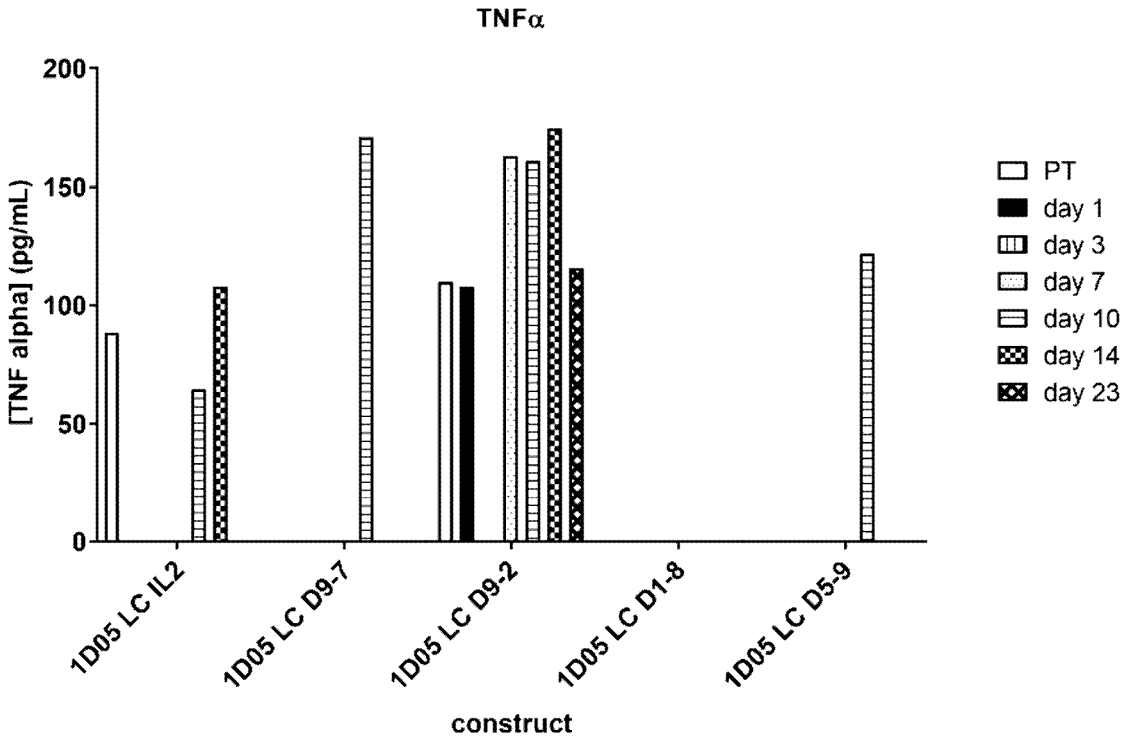


Figure 31(b)

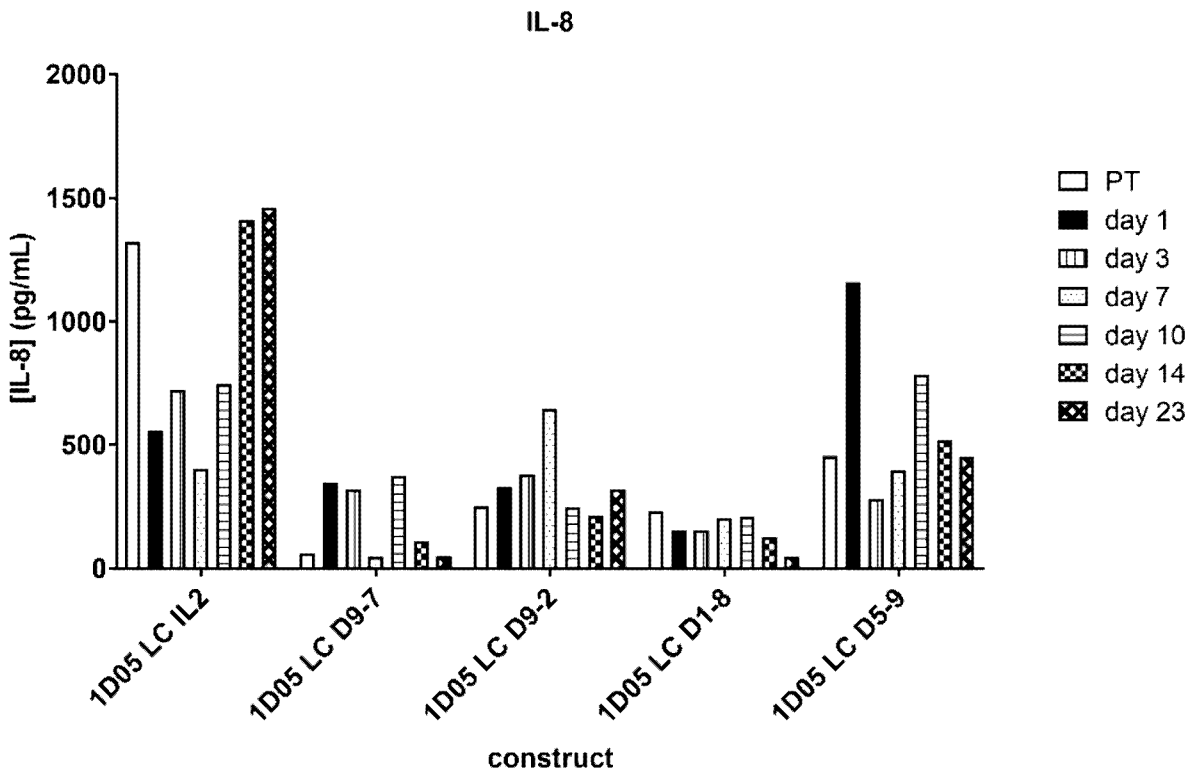


Figure 31(c)

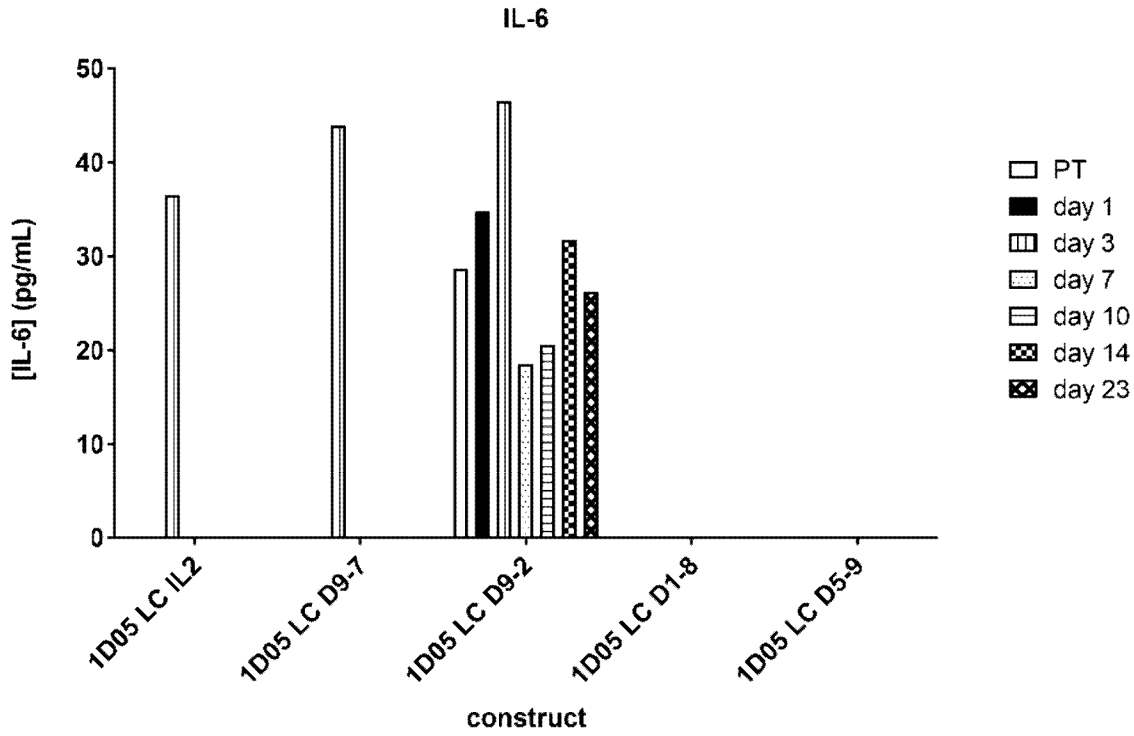


Figure 31(d)

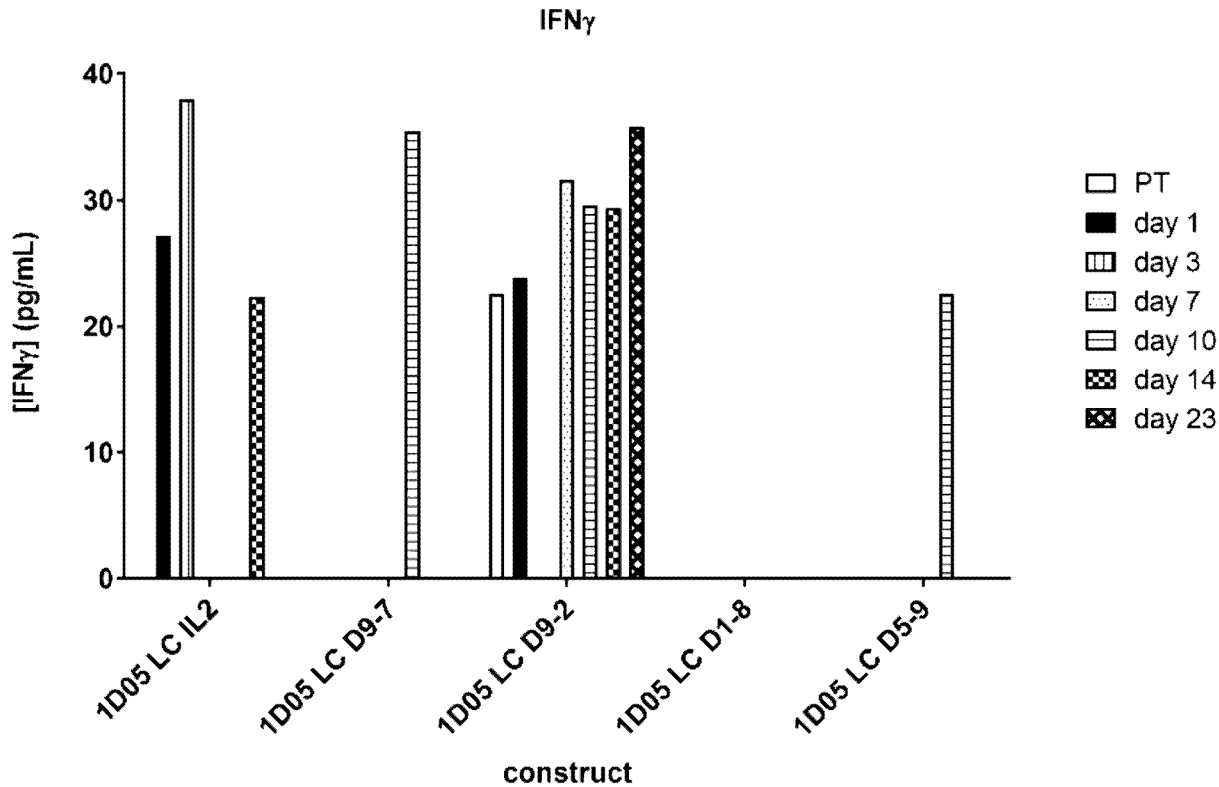


Figure 31 (e)

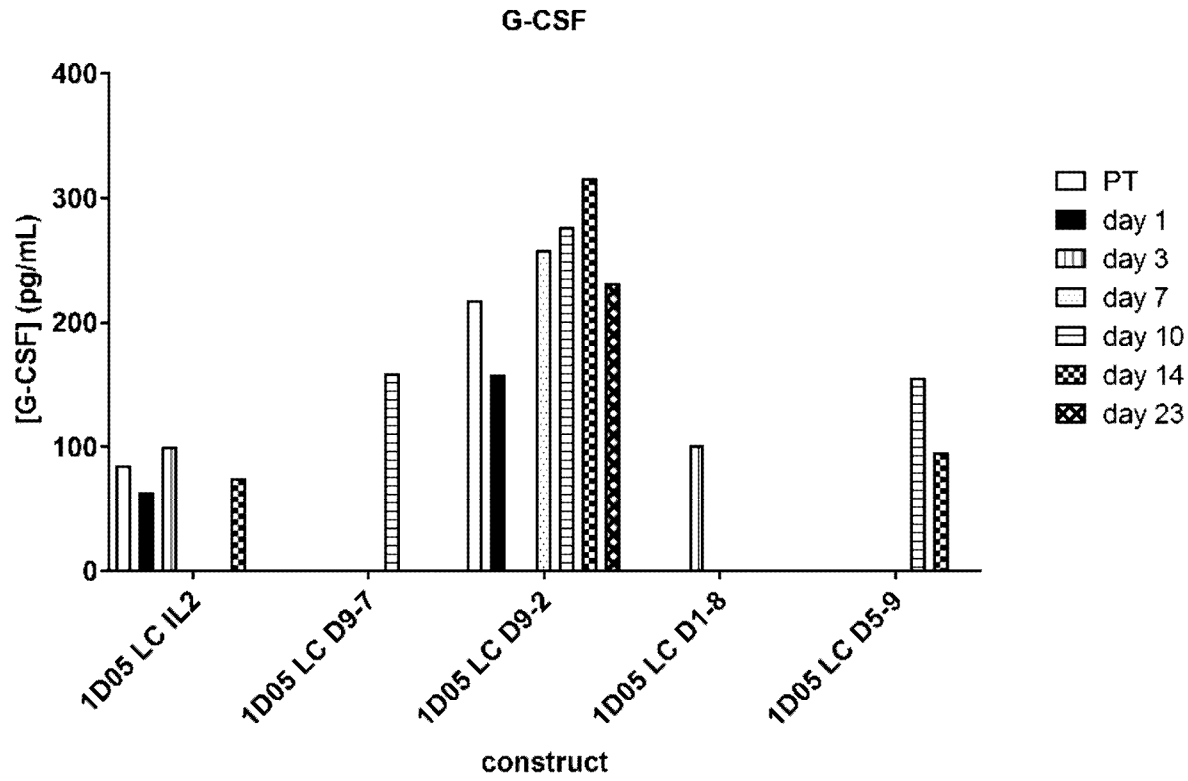


Figure 31(f)

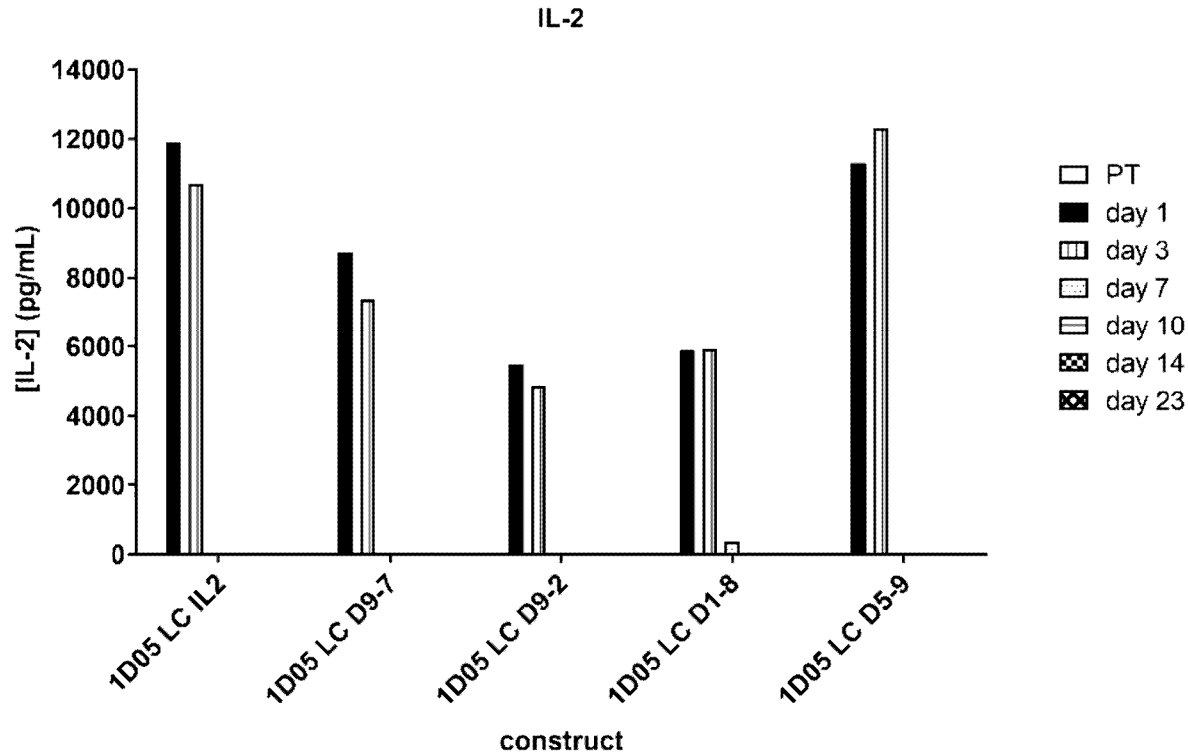


Figure 31(g)

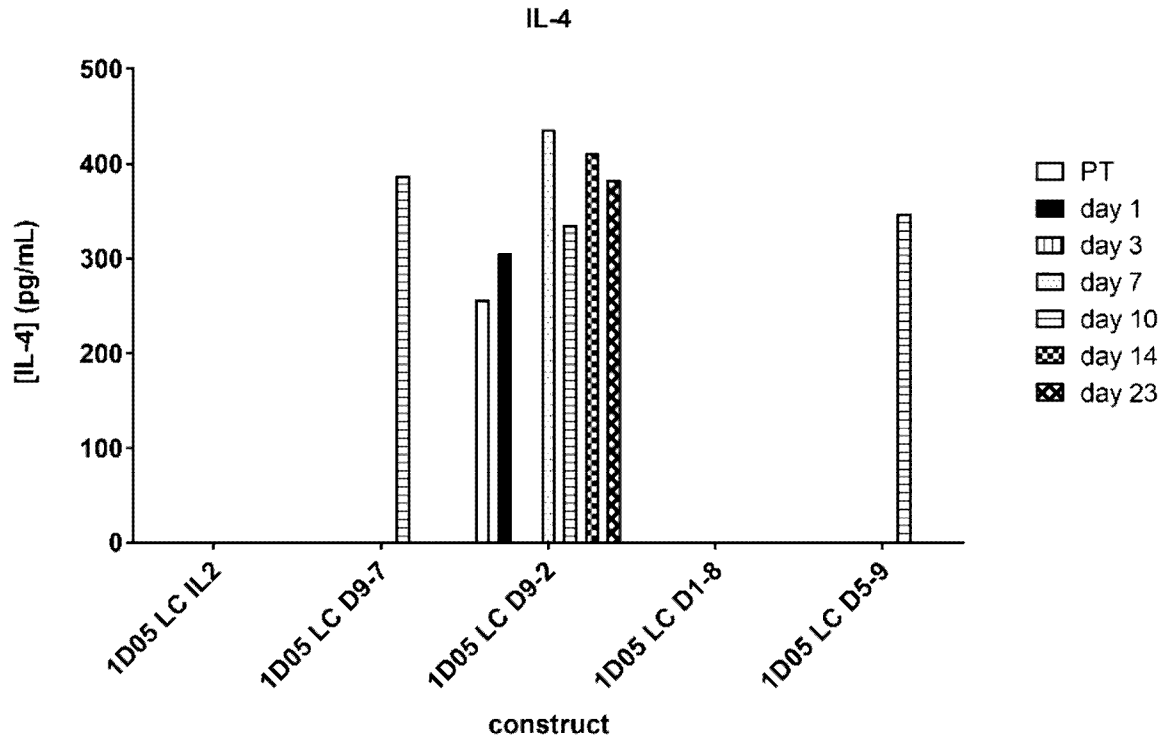
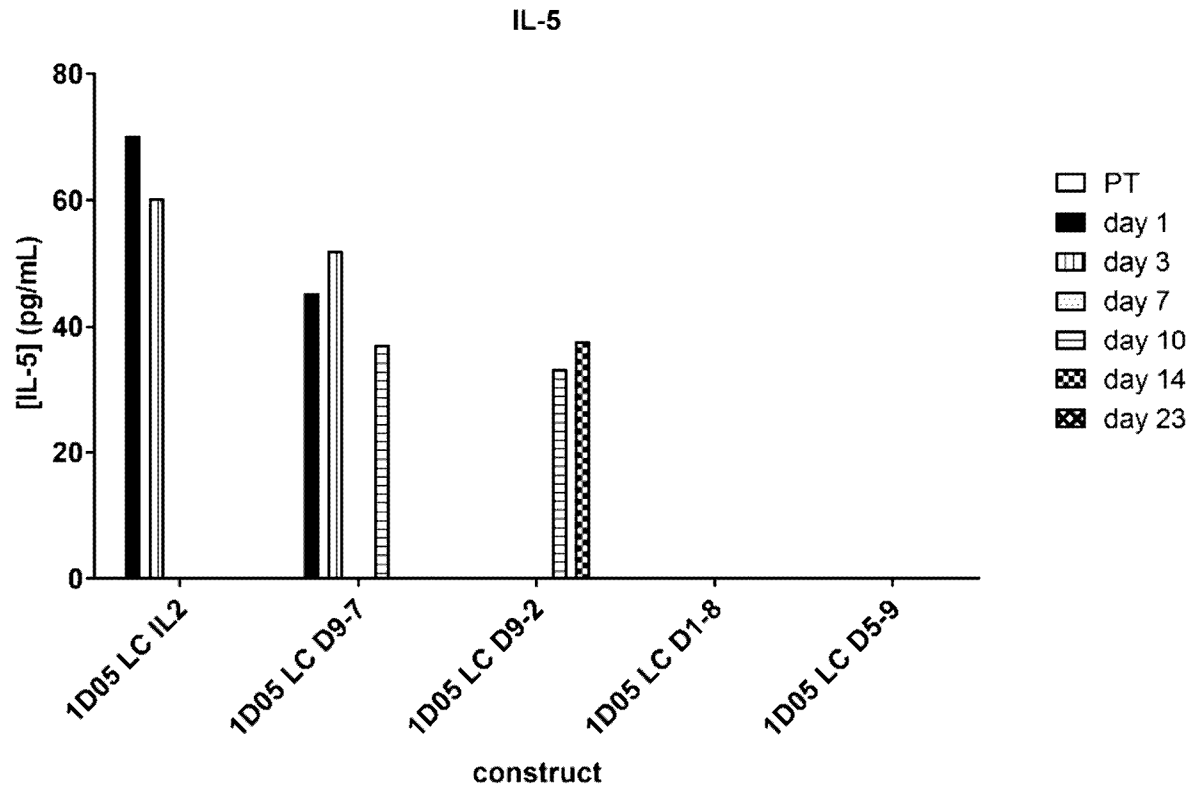


Figure 31(h)



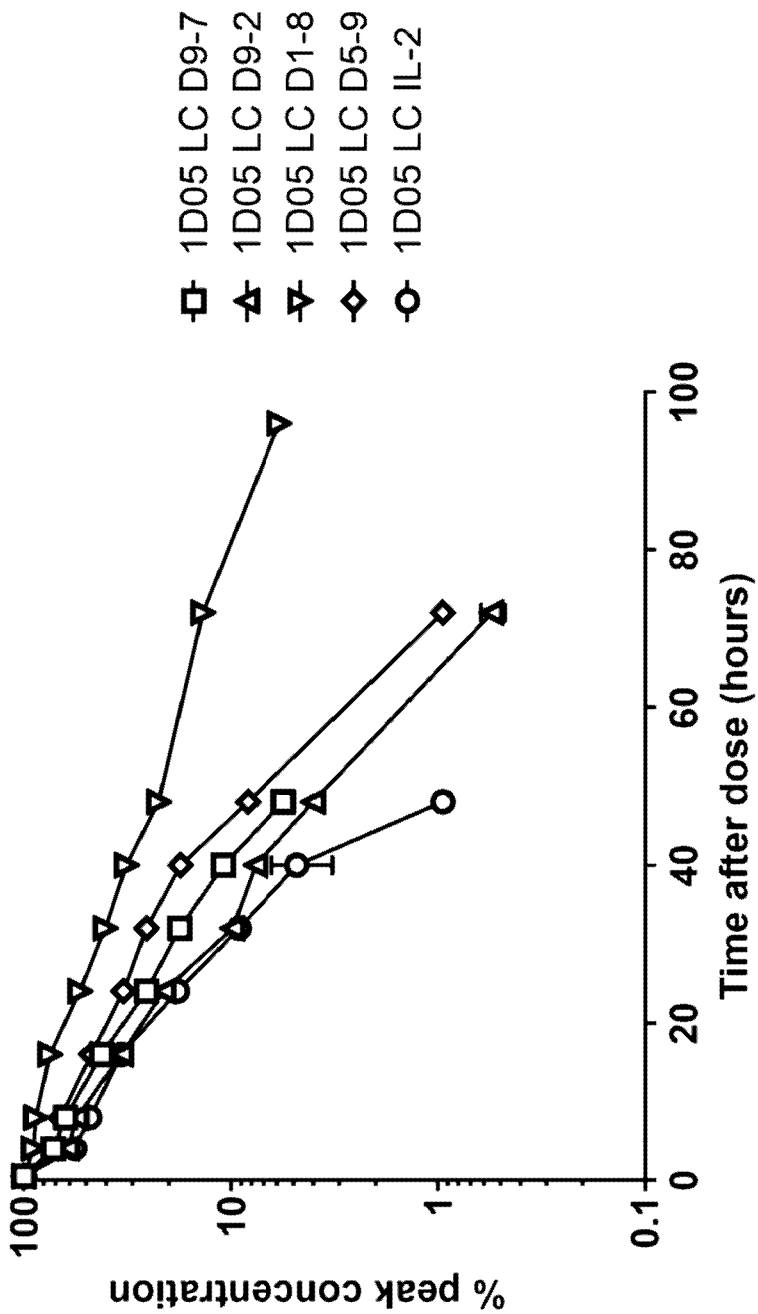

1D05 LC D9-7
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D5-9
1D05 LC IL-2
% peak concentration
100
10
1
0.1
0
20
40
60
80
100
Time after dose (hours)

Figure 32

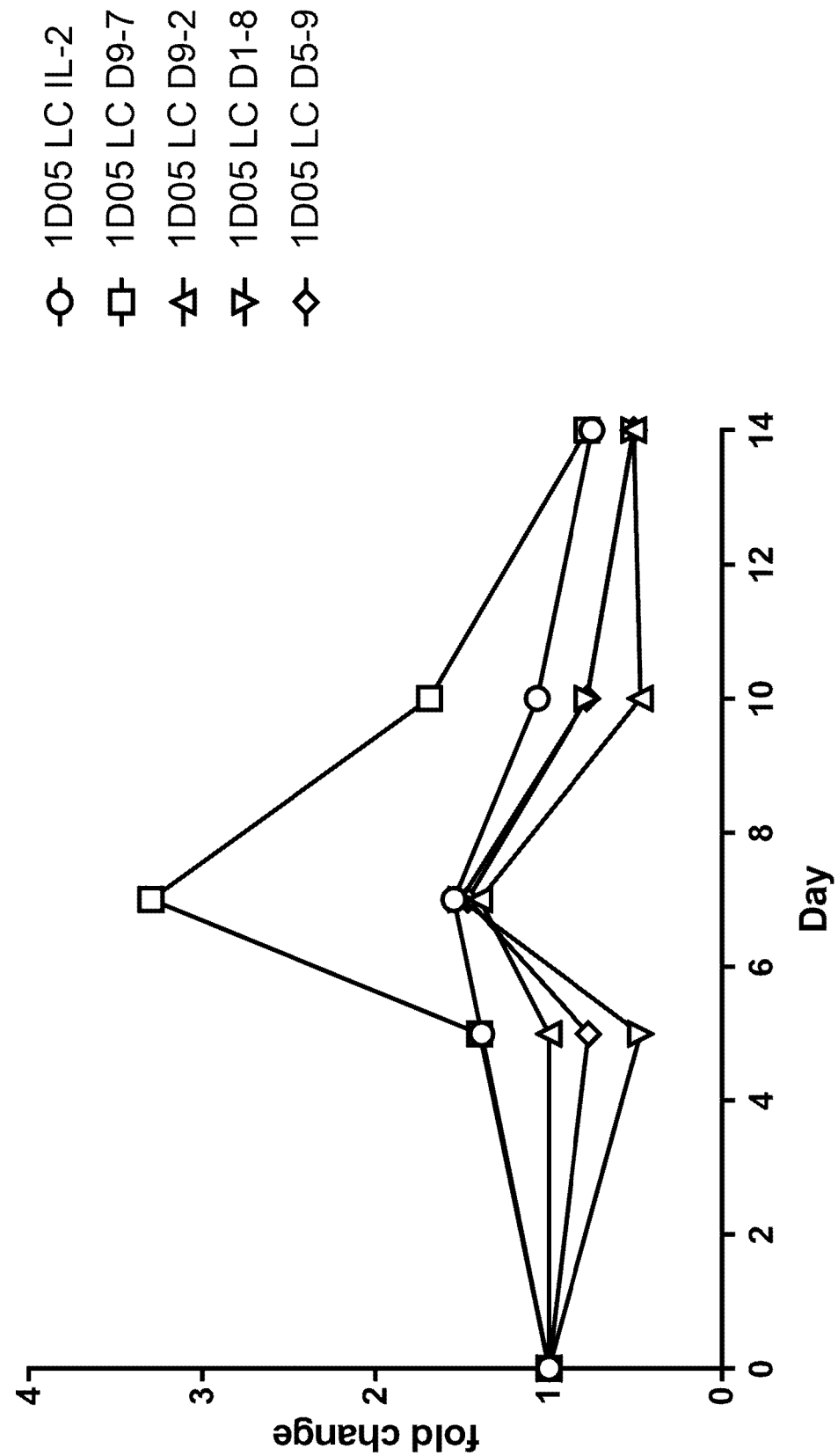

1D05 LC IL-2
1D05 LC D9-7
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D5-9
fold change
Day
0
1
2
3
4
0
2
4
6
8
10
12
14

Figure 33(a)

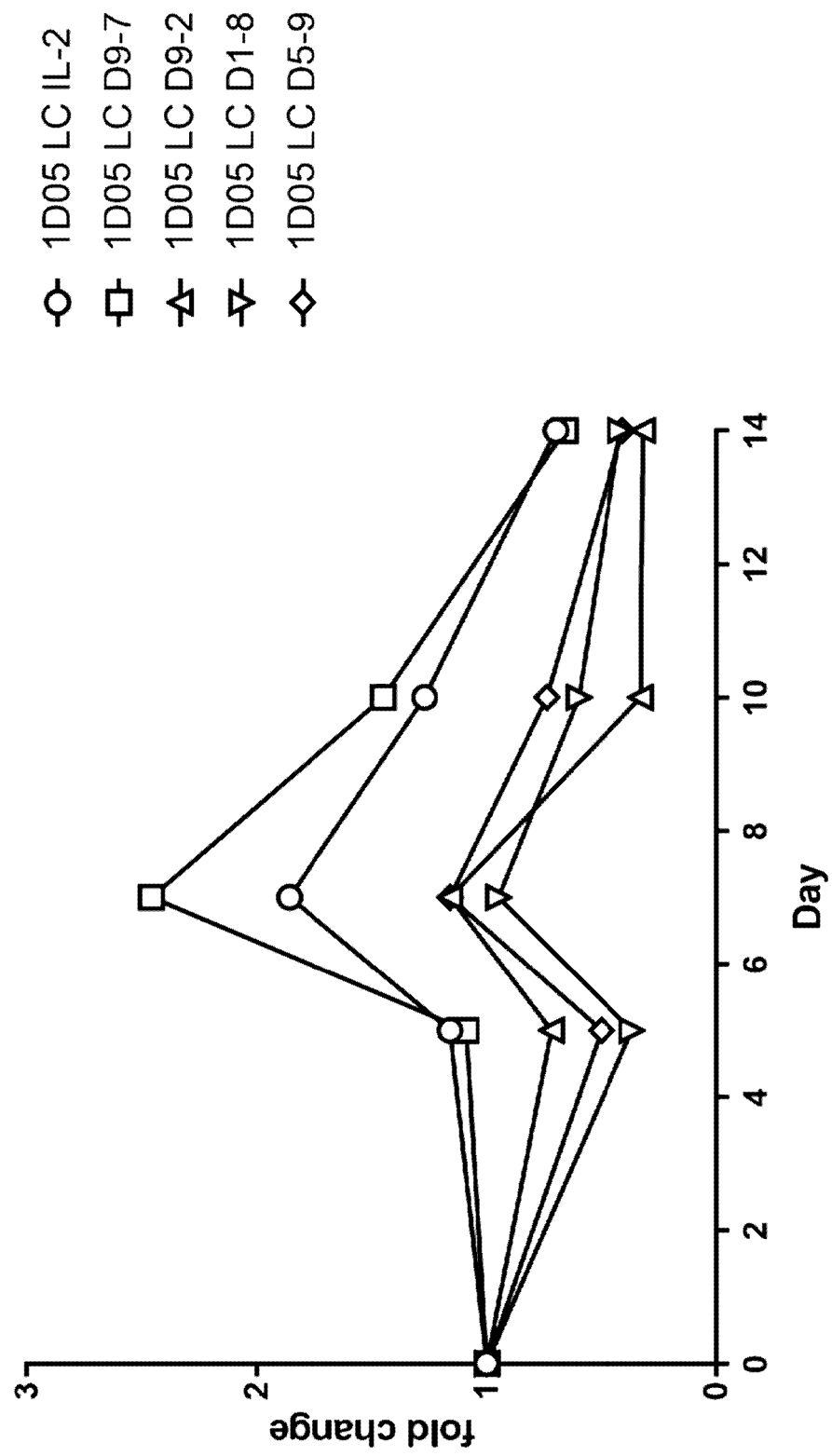

1D05 LC IL-2
1D05 LC D9-7
1D05 LC D9-2
1D05 LC D1-8
1D05 LC D5-9
fold change
Day
0
1
2
3
0
2
4
6
8
10
12
14

Figure 33(b)

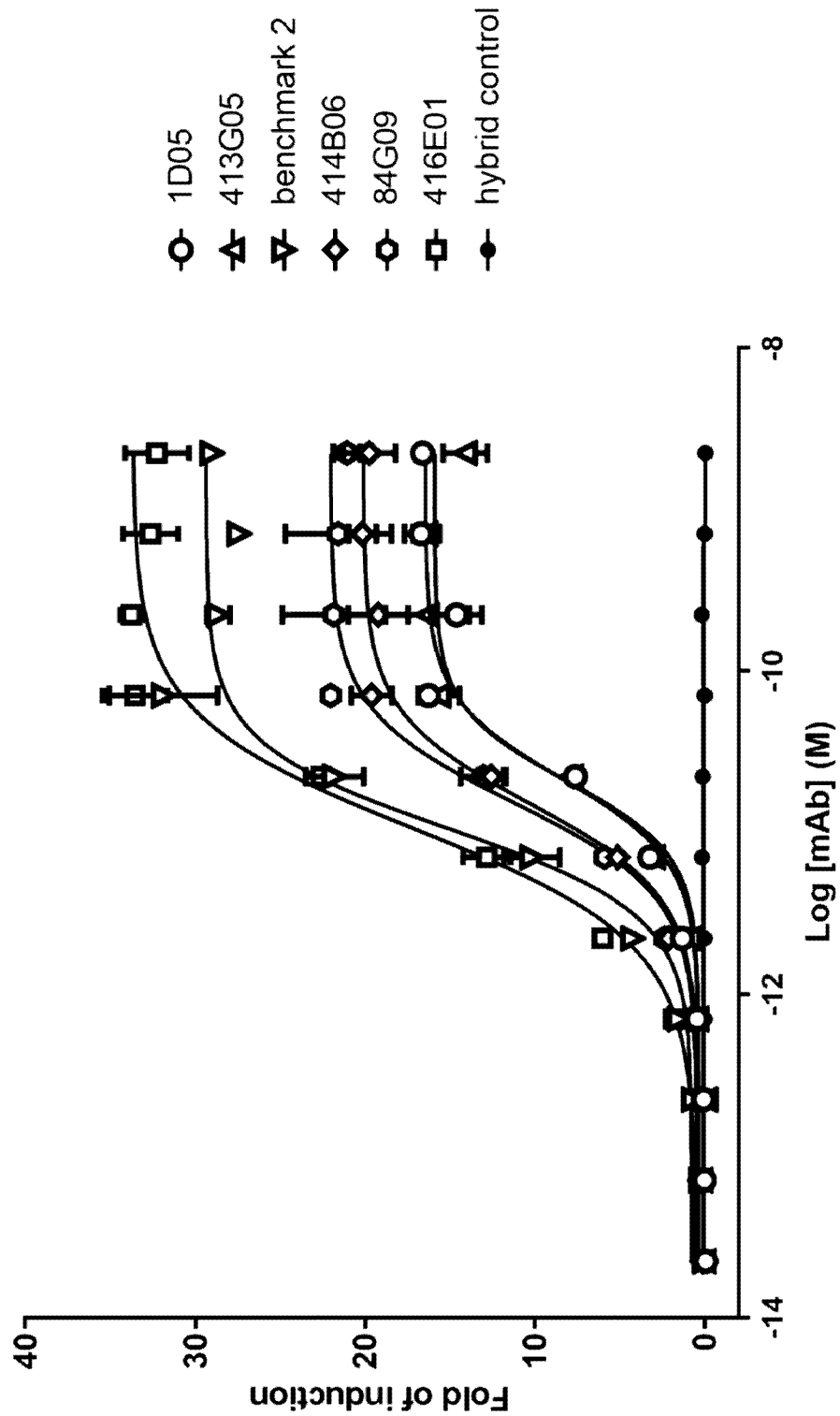

1D05
413G05
benchmark 2
414B06
84G09
416E01
hybrid control
Fold of induction
0
10
20
30
40
-14
-12
-10
-8
Log [mAb] (M)

Figure 34

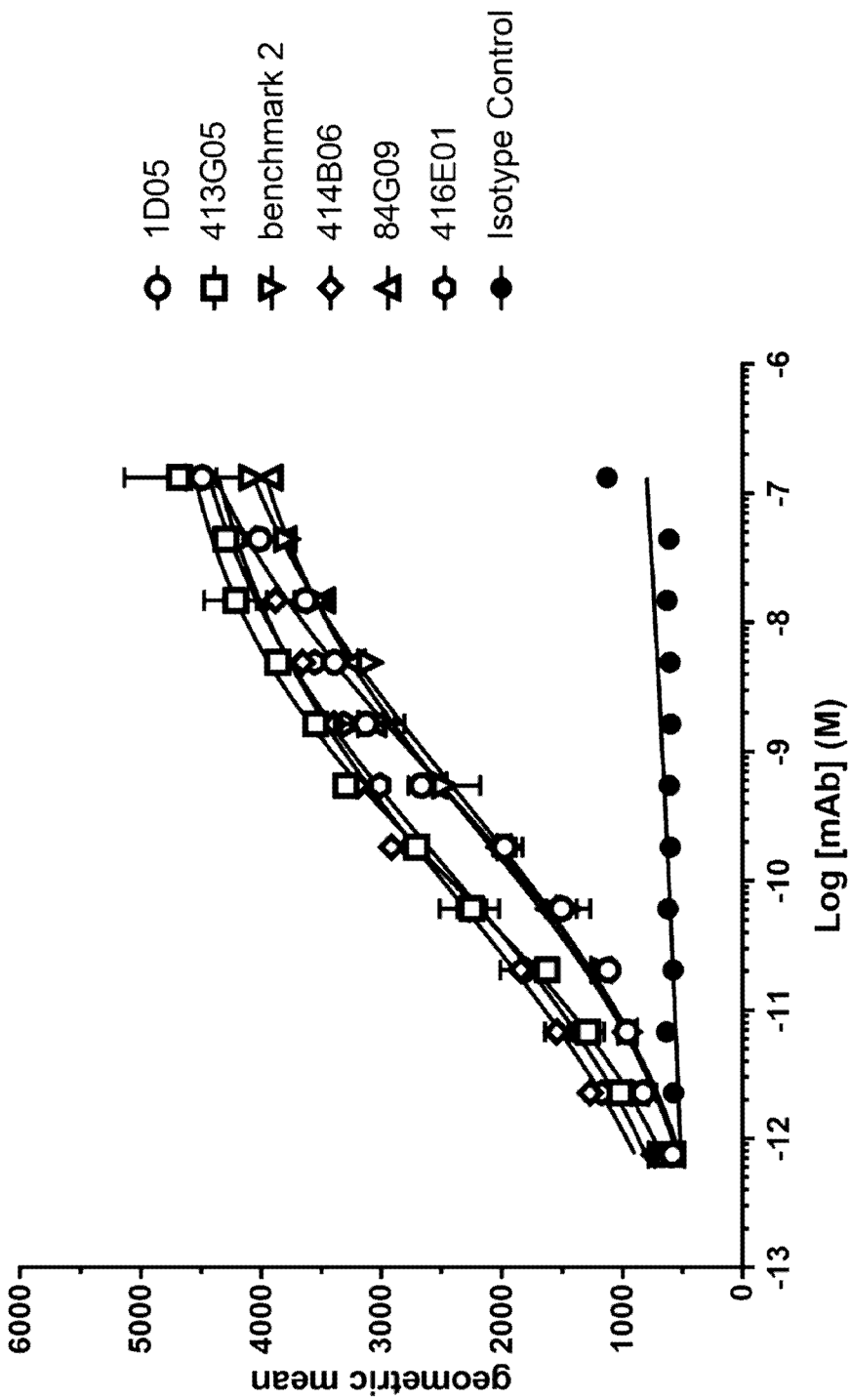

1D05
413G05
benchmark 2
414B06
84G09
416E01
Isotype Control
geometric mean
6000
5000
4000
3000
2000
1000
0
-13
-12
-11
-10
-9
-8
-7
-6
Log [mAb] (M)

Figure 35

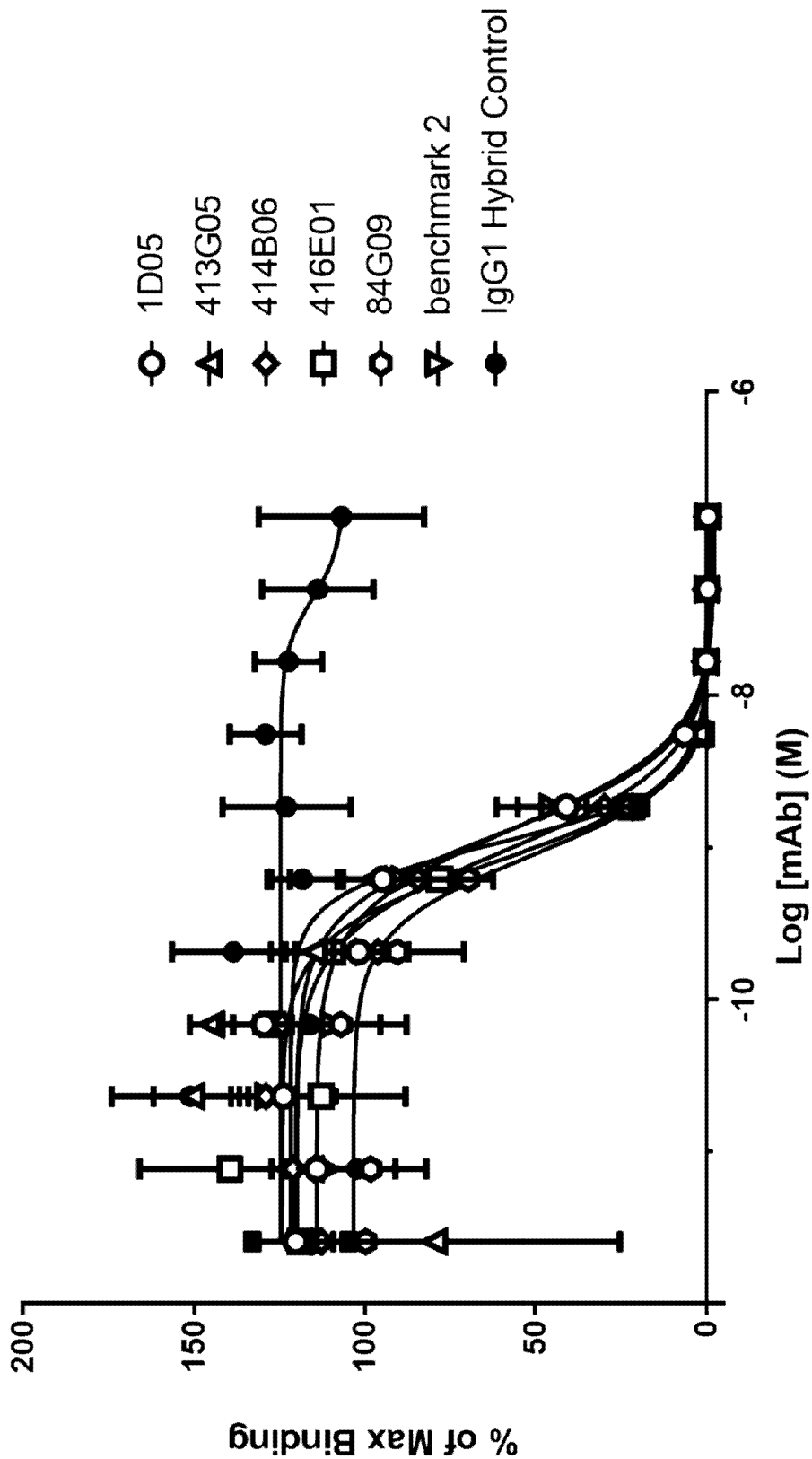

% of Max Binding
200
150
100
50
0
-10
-8
-6
Log [mAb] (M)
1D05
413G05
414B06
416E01
84G09
benchmark 2
IgG1 Hybrid Control

Figure 36(a)

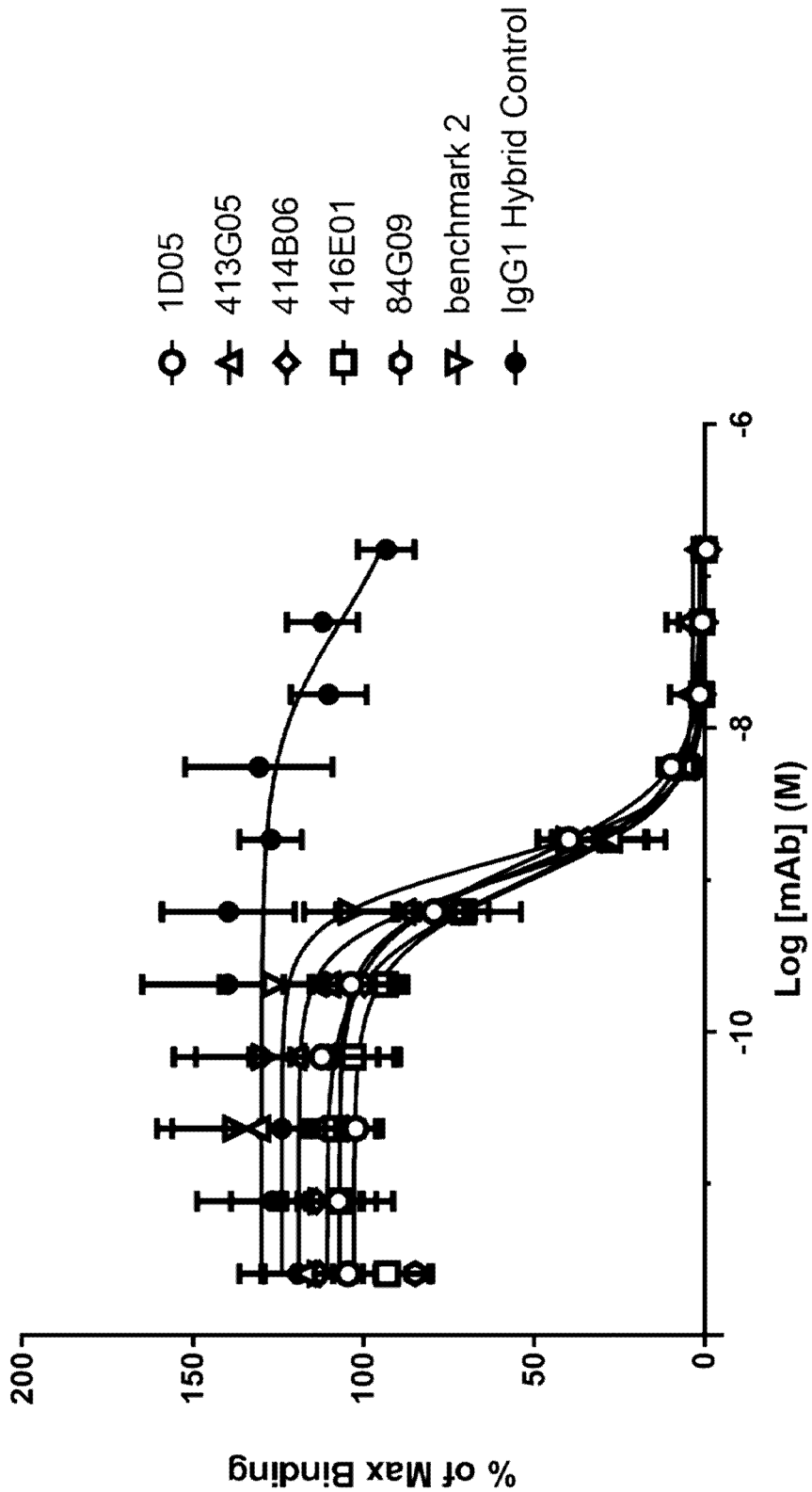

1D05
413G05
414B06
416E01
84G09
benchmark 2
IgG1 Hybrid Control
% of Max Binding
200
150
100
50
0
-6
-8
-10
Log [mAb] (M)

Figure 36(b)

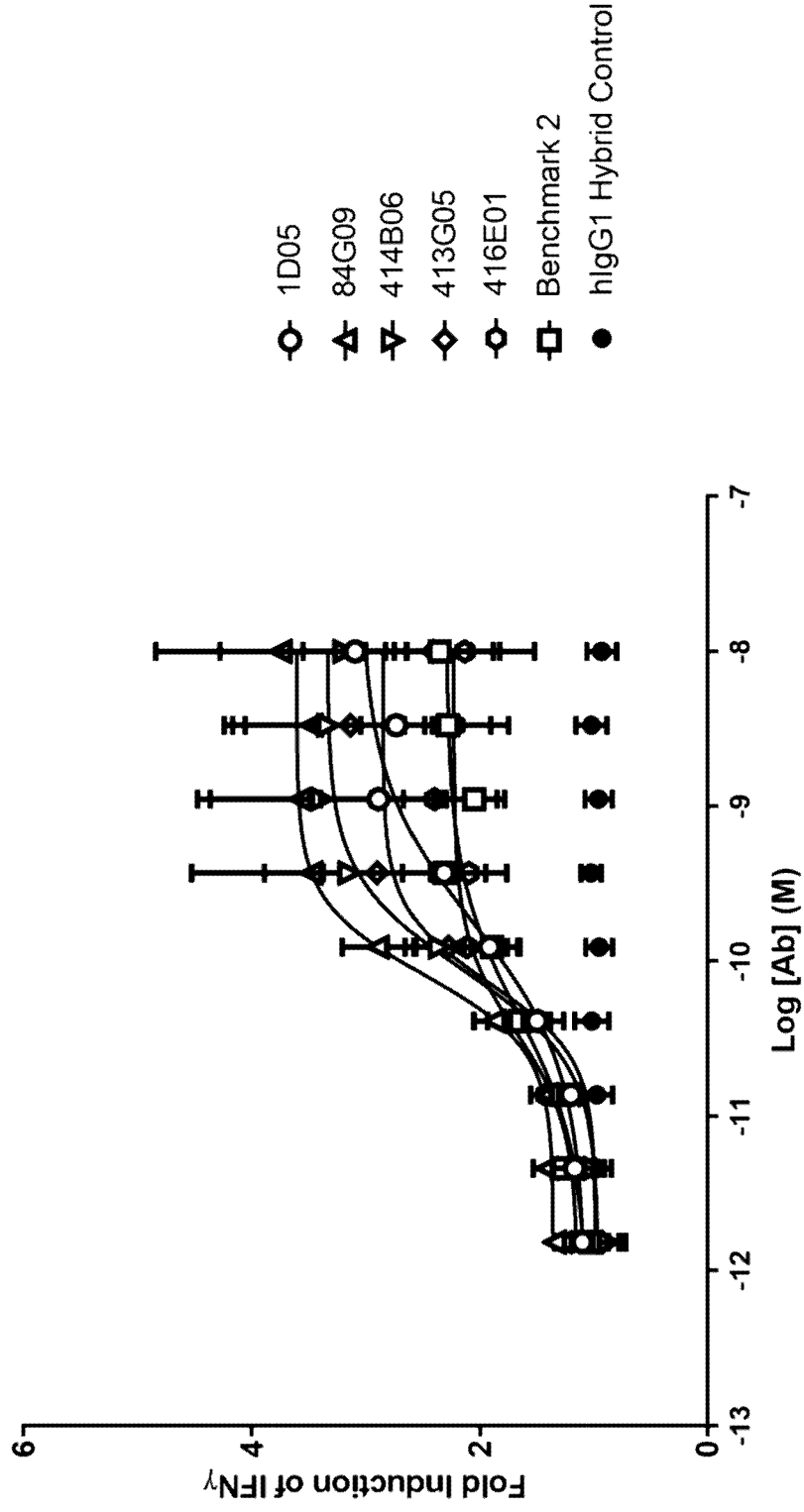

1D05
84G09
414B06
413G05
416E01
Benchmark 2
hIgG1 Hybrid Control
Fold Induction of IFNγ
0
2
4
6
-13
-12
-11
-10
-9
-8
-7
Log [Ab] (M)

Figure 37

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/051796

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/20 C07K14/55 A61K39/395 C07K16/28
ADD.

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)
A61K C07K

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)
EPO-Internal, EMBASE, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ERIN E. WEST ET AL: "PD-L1 blockade synergizes with IL-2 therapy in reinvigorating exhausted T cells", JOURNAL OF CLINICAL INVESTIGATION, vol. 123, no. 6, 15 May 2013 (2013-05-15), pages 2604-2615, XP055404072, US ISSN: 0021-9738, DOI: 10.1172/JCI67008 Abstract, discussion ----- -/--	1-61

[X] Further documents are listed in the continuation of Box C. [X] 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
12 September 2017	04/10/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rojo Romeo, Elena

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2017/051796

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☒ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/051796

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	C. WANG ET AL: "In Vitro Characterization of the Anti-PD-1 Antibody Nivolumab, BMS-936558, and In Vivo Toxicology in Non-Human Primates", CANCER IMMUNOLOGY RESEARCH, vol. 2, no. 9, 28 May 2014 (2014-05-28), pages 846-856, XP055206944, ISSN: 2326-6066, DOI: 10.1158/2326-6066.CIR-14-0040 the whole document	1-60
A	NERI DARIO ET AL: "Immunocytokines for cancer treatment: past, present and future", CURRENT OPINION IN IMMUNOLOGY, ELSEVIER, OXFORD, GB, vol. 40, 6 April 2016 (2016-04-06), pages 96-102, XP029551352, ISSN: 0952-7915, DOI: 10.1016/J.COI.2016.03.006 the whole document	1-61
X	WO 2016/030350 A1 (HOFFMANN LA ROCHE [CH]; HOFFMANN LA ROCHE [US]) 3 March 2016 (2016-03-03) Examples	1-61
T	RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity", PROCEEDINGS NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 79, 1 March 1982 (1982-03-01), pages 1979-1983, XP007901436, ISSN: 0027-8424, DOI: 10.1073/PNAS.79.6.1979 the whole document	
X,P	VAZQUEZ-LOMBARDI RODRIGO ET AL: "Potent antitumour activity of interleukin-2-Fc fusion proteins requires Fc-mediated depletion of regulatory T-cells", NATURE COMMUNICATIONS, vol. 8, 12 May 2017 (2017-05-12), pages 1-12, XP002773463, ISSN: 2041-1723 page 9, left-hand column, paragraph 3	1-61

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2017/051796

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016030350 A1	03-03-2016	AR 101697 A1	04-01-2017
		AU 2015308527 A1	15-12-2016
		CA 2951604 A1	03-03-2016
		CN 106794245 A	31-05-2017
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