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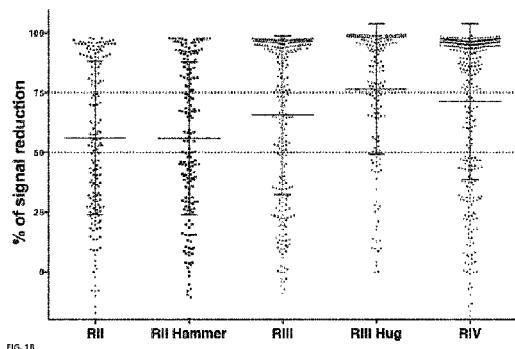
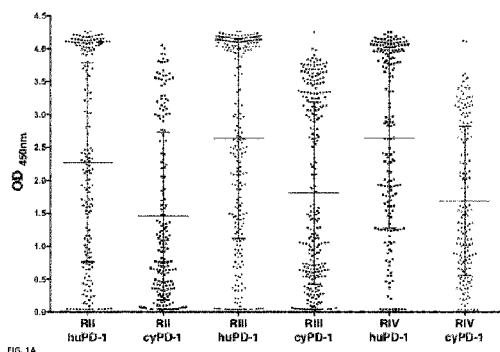
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(54) Title: PD1 BINDING AGENTS



(57) Abstract: Provided herein are antibody molecules that bind specifically to Programmed cell death (PD1) and related nucleic acid molecules, vectors and host cells. Also provided herein are medical uses of such antibody molecules.



PD1 BINDING AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of GB Patent Application No. 1813405.6, filed on August 5 16, 2018, and GB Patent Application No. 1803746.5, filed on March 8, 2018, the disclosure of each of which is hereby incorporated by reference in its entirety.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

The contents of the text file submitted electronically herewith are incorporated herein by 10 reference in their entirety: A computer readable format copy of the Sequence Listing (filename: ULNL_001_00WO_SeqList_ST25.txt, date recorded: March 7, 2019, file size 153,562 bytes).

FIELD OF THE INVENTION

15 The invention relates to antibody molecules binding specifically to PD1 (also known as Programmed cell death 1, PDCD1, CD279, PD-1, SLEB2, PD-I, SLE1) and medical uses thereof.

BACKGROUND OF THE INVENTION

20 PD1 is a cell surface receptor that is a member of the immunoglobulin superfamily and is principally expressed on T cells, but has also been observed on pro-B cells. PD1 binds two known ligands, PD-L1 and PD-L2. The interaction of these ligands with PD1 on T cells down-regulates T cell inflammatory activity, which promotes immune self-tolerance. PD1 is, therefore, described as being an immune 'checkpoint'. This checkpoint activity has been 25 demonstrated to minimise autoimmunity risk by promoting apoptosis (programmed cell death) in lymph node-resident T cells that are reactive to self-antigens. Importantly, PD1 ligation also promotes the survival of regulatory (anti-inflammatory) T cells.

While the role of PD1/PD-L1(2) binding in non-disease states is important for self-tolerance, 30 it is also a key mechanism by which tumour cells escape identification as 'foreign' during immune surveillance. Indeed, PD-L1 has been shown to be highly expressed in several cancers. Monoclonal antibodies that target PD1 and antagonise its function can therefore be of significant potential value in treating cancer, by boosting the immune response against malignant cells with high PD-L1 expression and/or which exhibit high levels of mutation. A 35 significant body of preclinical and clinical evidence suggests that blocking PD1/PD-L1 binding can enhance the anti-tumour activity of T cells and inhibit the growth of both haematological and solid malignancies. As PD1/PD-L1 activity can also be induced in

chronic diseases such as HIV, anti-PD1 antagonistic antibodies may also have therapeutic value in infectious disease settings. Hence, antagonistic anti-PD1 mAbs have the potential to act as immunotherapeutic agents in cancer, immune and infectious disease settings, and to amplify the effectiveness of currently established therapies.

5

The majority of currently approved antibody therapeutics are derived from immunized rodents. Many of those antibodies have undergone a process known as “humanization”, via the “grafting” of murine CDRs into human v-gene framework sequences (see Nelson *et al.*, 2010, *Nat Rev Drug Discov* 9: 767-774). This process is often inaccurate and leads to a reduction in target binding affinity of the resulting antibody. To return the binding affinity of the original antibody, murine residues are usually introduced at key positions in the variable domain frameworks of the grafted v-domains (also known as “back-mutations”).

While antibodies humanized via CDR grafting and back mutations have been shown to induce lower immune response rates in the clinic in comparison to those with fully murine v-domains, antibodies humanized using this basic grafting method still carry significant clinical development risks due to the potential physical instability and immunogenicity motifs still housed in the grafted CDR loops. Antibodies such as PD1 inhibitors that target receptors on immune cells, and whose pharmacological function is to stimulate immune responses, are at heightened risk of provoking anti-drug antibody responses. These anti-drug antibody responses in the patient can reduce drug half-life, potency and safety during clinical use. As animal testing of protein immunogenicity is often non-predictive of immune responses in man, antibody engineering for therapeutic use focuses on minimizing predicted human T-cell epitope content, non-human germline amino acid content and aggregation potential in the purified protein.

The ideal humanized, agonistic anti-PD1 antibody would therefore have as many identical residues as possible in the v-domains to those found in both the frameworks and CDRs of well-characterized human germline sequences. Townsend *et al.* (2015; *PNAS* 112: 15354-15359) describe a method for generating antibodies in which CDRs derived from rat, rabbit and mouse antibodies were grafted into preferred human frameworks and then subjected to a human germ-lining approach termed “Augmented Binary Substitution”. Although the approach demonstrated a fundamental plasticity in the original antibody paratopes, even when an investigator is in possession of highly accurate antibody-antigen co-crystal structural data, it is still not possible to reliably predict which individual residues in the CDR loops of any given antibody can be converted to human germline, and in what combination. Additionally, the Townsend *et al.* study did not address the addition of mutagenesis beyond

the residues found in the human germline at positions where the removal of development risk motifs might be beneficial. This is a technological limitation which renders the process inherently inefficient, requiring an extra stage of modification of the starting antibody sequence. In addition, it cannot currently be accurately predicted what modifications in distal
5 positions of the protein sequence of an individual v-domain, or even on the partner v-domain, might facilitate the removal of risk motifs while maintaining antigen binding affinity and specificity.

CDR germ-lining and development quality optimisation is thus a complex, multifactorial
10 problem, as multiple functional properties of the molecule should preferably be maintained or improved, including in this instance: target binding specificity, PD1/PD-L1 signalling antagonism, affinity to PD1 from both human and animal test species (e.g. cynomolgus monkey, also known as the crab-eating macaque, i.e. *Macaca fascicularis*) should be as similar as possible to facilitate highly accurate preclinical safety testing, v-domain biophysical
15 stability and/or IgG expression yield should be optimal for manufacturing purposes. Antibody engineering studies have shown that mutation of even single residue positions in key CDRs can have dramatic negative effects on all of these desired molecular properties.

WO2015/035606 A1 describes an antagonistic murine anti-PD1 IgG molecule termed
20 "Mu317", and also the preparation of humanized forms of Mu317 (designated hu317). Those humanized forms of Mu317 were produced using classical humanization techniques, i.e. by grafting of Kabat-defined murine CDRs into human heavy and light chain framework sequences, with some of the human framework residues being potentially back-mutated to the correspondingly positioned Mu317 murine residues. For reasons
25 noted above, such humanized forms of Mu317 described in WO2015/035606 A1 are not ideal.

SUMMARY OF THE INVENTION

30 The present invention provides a number of anti-PD1 antibodies and medical uses thereof.

According to one aspect of the invention, there is provided an antibody molecule which specifically binds to human PD1, and optionally also to cynomolgus monkey PD1, or an antigen-binding portion thereof, wherein the antibody molecule or antigen-binding portion
35 comprises a heavy chain variable region with:
an HCDR1 having amino acids in sequence in the following order: G-F-T or a conservative substitution of T (for example S)-F or a conservative substitution of F (for example L)-S or a

conservative substitution of S (for example T)-S-Y-G or any amino acid (for example W)-M or a conservative substitution of M (for example V)-S or any amino acid (for example H) (SEQ ID NO:20);

5 an HCDR2 having amino acids in sequence in the following order: V or a conservative substitution of V (for example L)-A or a conservative substitution of A (for example G)-V/N-I-W/K-Q/A-D/G-G-S-T/E-N/K/S-Y-N/V-D-S-V-K-G (SEQ ID NO:21); and

10 an HCDR3 having amino acids in sequence in the following order: A or any amino acid (for example D/E/G/H/I/K/L/H/Q/S/V/W)-Y or a conservative substitution of Y (for example F/W)-G-N or any amino acid (for example A/E/F/G/H/I/Q/R/S/T/V/W/Y)-Y or a conservative substitution of Y (for example V/W)-W or any amino acid (for example F/H/M/P/Q/S/V)-Y-I or any amino acid (for example L/M/S/T/V/Y)-D or a conservative substitution of D (for example E)-V or any amino acid (for example A/E/F/G/H/I/K/L/M/R/S/T/W/Y) (SEQ ID NO:22).

15 In aspects of the invention, the HCDR1 of the antibody molecule or antigen-binding portion may exclude the sequences GFSLTSYGVH (SEQ ID NO:23; Mu317 murine/humanized antibody HCDR1 disclosed in WO2015/035606 A1; US2015/079109A1), VIWAGGSTNYNSALMS (SEQ ID NO:24; Mu317 murine/humanized antibody HCDR2 disclosed in WO2015/035606 A1; US2015/079109A1), and/or the HCDR3 of the antibody molecule or antigen-binding portion may exclude the sequence AYGNYWYIDV (SEQ ID
20 NO:25; Mu317 murine/humanized antibody HCDR3 disclosed in WO2015/035606 A1; US2015/079109A1).

The antibody molecule or antigen-binding portion may further comprise a light chain variable region with:

25 an LCDR1 having amino acids in sequence in the following order: K-S-S-Q/E-S-V-S or a conservative substitution of S (such as G/T)-N-D-L or a conservative substitution of L (such as V)-A (SEQ ID NO:26);

30 an LCDR2 having amino acids in sequence in the following order: Y-A-F or any amino acid (for example S)-H or any amino acid (for example P/T)-R-F-S or a conservative substitution of S (such as A/T) (SEQ ID NO:27); and

an LCDR3 having amino acids in sequence in the following order: Q or any amino acid (for example H)-Q-A or any amino acid (for example S)-Y-S-T or any amino acid (for example, N/S)-P-Y or any amino acid (for example W)-T (SEQ ID NO:28).

35 In aspects of the invention, the LCDR1 of the antibody molecule or antigen-binding portion may exclude the sequence KASQSVSNDVA / KSSQEVSNDVA (SEQ ID NO:29 / SEQ ID NO:30; Mu317 murine/humanized antibody LCDR1 disclosed in WO2015/035606 A1;

US2015/079109A1), and/or the LCDR2 of the antibody molecule or antigen-binding portion may exclude the sequence YAFHRFT (SEQ ID NO:31; Mu317 murine/humanized antibody LCDR2 disclosed in WO2015/035606 A1; US2015/079109A1) and/or the LCDR3 of the antibody molecule or antigen-binding portion may exclude the sequence HQAYSSPYT (SEQ ID NO:32; Mu317 murine/humanized antibody LCDR3 disclosed in WO2015/035606 A1; US2015/079109A1).

In some aspects, disclosed herein is an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable (VL) region comprising LCDR1, LCDR2, and LCDR3, wherein

(a) the HCDR1 comprises the amino acid sequence G-F-X₁-X₂-X₃-S-Y-X₄-X₅-X₆, wherein X₁ is T or a conservative substitution of T, X₂ is F or a conservative substitution of F, X₃ is S or a conservative substitution of S, X₄ is G or any other amino acid, X₅ is M or a conservative substitution of M, and X₆ is S or any other amino acid (SEQ ID NO:20);

(b) the HCDR2 comprises the amino acid sequence X₁-X₂-X₃-I-X₄-X₅-X₆-G-S-X₇-X₈-Y-X₉-D-S-V-K-G, wherein X₁ is V or a conservative substitution of V, X₂ is A or a conservative substitution of A, X₃ is V or N, X₄ is W or K, X₅ is Q or A, X₆ is D or G, X₇ is T or E, X₈ is N, K, or S, and X₉ is N or V (SEQ ID NO:21);

(c) the HCDR3 comprises the amino acid sequence X₁-X₂-G-X₃-X₄-X₅-Y-X₆-X₇-X₈, wherein X₁ is A or any other amino acid, X₂ is Y or a conservative substitution of Y, X₃ is N or any other amino acid, X₄ is Y or a conservative substitution of Y, X₅ is W or any other amino acid, X₆ is I or any other amino acid, X₇ is D or a conservative substitution of D, and X₈ is V or any other amino acid (SEQ ID NO:22);

(d) the LCDR1 comprises the amino acid sequence K-S-S-X₁-S-V-X₂-N-D-X₃-A, wherein X₁ is Q or E, X₂ is S or a conservative substitution of S, and X₃ is L or a conservative substitution of L (SEQ ID NO:26);

(e) the LCDR2 comprises the amino acid sequence Y-A-X₁-X₂-R-F-X₃, wherein X₁ is F or any other amino acid, X₂ is H or any other amino acid, and X₃ is S or a conservative substitution of S (SEQ ID NO:27); and

(f) the LCDR3 comprises the amino acid sequence X₁-Q-X₂-Y-S-X₃-P-X₄-T, wherein X₁ is Q or any other amino acid, X₂ is A or any other amino acid, X₃ is T or any other amino acid, and X₄ is Y or any other amino acid (SEQ ID NO:28).

In some aspects, the invention provides an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

- (a) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID NO:33), HCDR2 of VANIWQDGSTKYVDSVKG (SEQ ID NO:34), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);
- (b) the VH region amino acid sequence comprises HCDR1 of GFSLSSYGMS (SEQ ID NO:39), HCDR2 of VAVIWQDGSTNYVDSVKG (SEQ ID NO:40), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);
- (c) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID NO:33), HCDR2 of VANIWQDGSEKYVDSVKG (SEQ ID NO:41), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);
- (d) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
- (e) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of LANIWQDGSTNYVDSVKG (SEQ ID NO:48), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
- (f) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGVH (SEQ ID NO:49), HCDR2 of VGVIWQDGSENYVDSVKG (SEQ ID NO:50), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52);
- (g) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
- (h) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of LANIWQDGSENYVDSVKG (SEQ ID NO:53), and HCDR3 of

AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52);

(i) the VH region amino acid sequence comprises HCDR1 of GFTLSSYGMH (SEQ ID NO: 54), HCDR2 of LAVIWADGSTNYVDSVKG (SEQ ID NO:55), and HCDR3 of AYGNYMYIDV (SEQ ID NO:56); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);

(j) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMH (SEQ ID NO:57), HCDR2 of VGVIKQDGSSENYVDSVKG (SEQ ID NO:58), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46); or

(k) the VH region amino acid sequence comprises HCDR1 of GFSFTSYGMH (SEQ ID NO:59), HCDR2 of VGVIWQDGSTNYVDSVKG (SEQ ID NO:60), and HCDR3 of GYGNYWYIDV (SEQ ID NO:61); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52).

In some aspects, disclosed herein is an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

the VH region amino acid sequence comprises:

(a) HCDR1 of SEQ ID NO: 33, SEQ ID NO: 39, SEQ ID NO: 42, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 54, SEQ ID NO: 57 or SEQ ID NO: 59;

(b) HCDR2 of SEQ ID NO: 34, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 58 or SEQ ID NO: 60; and

(c) HCDR3 of SEQ ID NO: 35, SEQ ID NO: 56 or SEQ ID NO: 61; and

the VL region amino acid sequence comprises:

(a') LCDR1 of SEQ ID NO: 36, SEQ ID NO: 44 or SEQ ID NO: 51;

(b') LCDR2 of SEQ ID NO: 37 or SEQ ID NO: 45; and

(c') LCDR3 of SEQ ID NO: 38, SEQ ID NO: 46 or SEQ ID NO: 52.

In some aspects, the invention provides an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the VH region amino acid sequence comprises SEQ ID NO:1 and the VL region amino acid sequence comprises SEQ ID NO:2;

(b) the VH region amino acid sequence comprises SEQ ID NO:3 and the VL region amino acid sequence comprises SEQ ID NO:4;

5 (c) the VH region amino acid sequence comprises SEQ ID NO:5 and the VL region amino acid sequence comprises SEQ ID NO:6; or

(d) the VH region amino acid sequence comprises SEQ ID NO:7 and the VL region amino acid sequence comprises SEQ ID NO:8.

10 Also provided according to the invention is an immunoconjugate comprising the antibody molecule or antigen-binding portion thereof as defined herein linked, fused or conjugated to a therapeutic agent.

In another aspect the invention provides a nucleic acid molecule encoding the antibody
15 molecule or antigen-binding portion thereof as defined herein.

Further provided is a vector comprising the nucleic acid molecule of the invention.

Also provided is a host cell comprising the nucleic acid molecule or the vector of the invention
20 as defined herein.

In a further aspect there is provided a method of producing an anti-PD1 antibody and/or an antigen-binding portion thereof, comprising culturing the host cell of the invention under conditions that result in expression and/or production of the antibody and/or the antigen-
25 binding portion thereof, and isolating the antibody and/or the antigen-binding portion thereof from the host cell or culture.

In another aspect of the invention there is provided a pharmaceutical composition comprising the antibody molecule or antigen-binding portion thereof of the invention as defined herein,
30 or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein.

Further provided is a method for enhancing an immune response in a subject, comprising administering an effective amount of the antibody molecule or antigen-binding portion thereof
35 of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

In a further aspect there is provided a method for treating or preventing cancer in a subject, comprising administering an effective amount of the antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention
5 as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

Further provided herein is an antibody molecule or antigen-binding portion thereof as defined
10 herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use as a medicament. The invention also provides an antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein,
15 or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein, for use in the treatment of cancer.

In another aspect the invention provides the antibody molecule, or antigen-binding portion thereof, or the immunoconjugate, or the nucleic acid molecule, or the vector for use, or the
20 method of treatment of the invention as defined herein, for separate, sequential or simultaneous use in a combination combined with a second therapeutic agent, for example an anti-cancer agent.

In a further aspect there is provided the use of an antibody molecule or antigen-binding
25 portion thereof of the invention as defined herein, or an immunoconjugate of the invention as defined herein, or a nucleic acid molecule of the invention as defined herein, or a vector of the invention as defined herein, or a pharmaceutical composition of the invention as defined herein, in the manufacture of a medicament for the treatment of cancer.

30 The invention also provides a method for treating or preventing an infectious disease in a subject, comprising administering an effective amount of the antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined here, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.

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The infectious disease may be selected in all aspects from the group consisting of: viral, bacterial, fungal or parasitic. In one embodiment, the infectious disease is human immunodeficiency virus (HIV) infection.

- 5 Also provided is an antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of an infectious disease.
- 10 Further provided is the use of an antibody molecule or antigen-binding portion thereof as defined herein, or an immunoconjugate as defined herein, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of an infectious disease.
- 15 The invention also provides a method for treating or preventing an infectious disease in a subject, comprising administering an effective amount of the antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined here, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.
- 20 The invention also provides a method of producing an antibody molecule which specifically binds to human PD1 and optionally also to cynomolgus monkey PD1, or an antigen-binding portion thereof, comprising the steps of:
- (1) grafting anti-PD1 CDRs from a non-human source into a human v-domain framework to
25 produce a humanized anti-PD1 antibody molecule or antigen-binding portion thereof;
- (2) generating a library of clones of the humanized anti-PD1 antibody molecule or antigen-binding portion thereof comprising one or more mutations in the CDRs;
- (3) screening the library for binding to human PD1 and optionally also to cynomolgus monkey PD1;
- 30 (4) selecting clones from the screening step (3) having binding specificity to human PD1 and optionally also to cynomolgus monkey PD1; and
- (5) producing an antibody molecule which specifically binds to human PD1 and optionally also to cynomolgus monkey PD1, or an antigen-binding portion thereof from clones selected from step (4).
- 35 The method may comprise a further step of producing additional clones based on the clones selected in step (4), for example based on further exploratory mutagenesis at specific

positions in the CDRs of the clones selected in step (4), to enhance humanization and/or minimise human T cell epitope content and/or improve manufacturing properties in the antibody molecule or antigen-binding portion thereof produced in step (5).

5 BRIEF DESCRIPTION OF THE FIGURES

FIG. 1A – FIG. 1B. Direct binding ELISA of library-derived anti-PD1 Fabs against human and cyno PD1-Fc proteins and HTRF competition assay. Clones were derived from multiple phage selection branches where phage populations were selected on biotinylated human, or cynomolgus monkey PD1 proteins in each round. Standard selections are numbered RI-RIV. After each round of selection, library-derived clones were screened as periplasmically-expressed Fab proteins in ELISA (FIG. 1A) against both human (huPD1) and cyno (cyPD1). Fab samples were also tested in parallel for their ability to compete for the binding epitope of mu317 on human PD1 by HTRF (FIG. 1B). Mean \pm SD values in each round are represented in grey bars.

FIG. 2A – FIG. 2B. Analysis of CDR residue tolerance for mutation to germline. A plot of murine amino acid retention frequencies in the CDRs of the ELISA-positive population of 712 unique scFv clones is shown for V_L (SEQ ID NOs: 409-411) (FIG. 2A) and V_H (SEQ ID NOs: 412-414)(FIG. 2B) domains, respectively. Only those residues targeted for human/murine residue mutagenesis are plotted, other than in the HCDR3. CDR residues noted in parentheses on the X-axes were identical to those found in the human germlines used for grafting (IGKV4-1 and IGHV3-7). In both plots the dashed line in grey at 75% represents the cut-off for tolerance of murine residue replacement by human germline.

FIG. 3A – FIG. 3B. Direct titration ELISA for library-derived IgG1null clones binding to human and cyno PD1-Fc proteins. Mu317 and library-derived IgGs were titrated (in nM) in a direct binding ELISA against human (FIG. 3A) and cyno (FIG. 3B) PD1-Fc proteins.

FIG. 4A – FIG. 4B. Flow cytometric binding to human and cyno PD1+ CHO cells. Mu317, lead library-derived and designer IgGs were examined for specific binding on human (FIG. 4A) and cyno (FIG. 4B) CHO cells expressing human PD1. Concentration-dependent binding was observed against human PD1 for all clones, with no binding being observed for isotype control IgG1. No binding signal was observed for any clone against untransfected CHO cells.

FIG. 5. Cell-based PD1/PD-L1 antagonism assay. Analyses of antagonism of human PD1 function at the cell surface, for multiple lead clones in human IgG1null format, showed that all novel clones exhibited strong, concentration-dependent, antagonistic activity.

FIG. 6A – FIG 6C. Cell-based PD1/PD-L1 antagonism assay for maximally humanized lead clones MH4, MH8 AND MH12 versus mu317 and hu317. Analyses of antagonism of

human PD1 function, for multiple lead clones in human IgG1null format. These analyses showed that clones MH4 (FIG. 6A), MH8 (FIG. 6B) and MH12 (FIG. 6C) exhibited antagonistic potency overlapping with both mu317 and hu317. Values expressed as Mean \pm SD fold induction.

5 **FIG. 7A – FIG. 7H. T cell epitope peptide content in lead antibody v-domains.** The v-domains of Hu317 and multiple lead antibodies were examined for the presence of Germline (GE), High Affinity Foreign (HAF), Low Affinity Foreign (LAF) and TCED+ T cell receptor epitopes. Both the VH and VL domains of Hu317 were found to contain multiple high-risk human T cell epitopes and few germline epitopes. In all lead clones, the high-risk epitope
10 content was significantly reduced and germline epitope content significantly improved.

FIG. 8A – FIG. 8C. MLR cell-based PD1/PD-L1 antagonism assay. Effect of anti-PD1 IgGs on IFN- γ Production in an Allogeneic MLR assay. Control analyses (FIG. 8A), 3-point analyses for lead clones 09C06, MH4, MH8, MH12 (FIG. 8B), and multi-point analyses for clones MH4, MH8 and Hu317 (FIG. 8C) are shown. In each case, Isotype controls were used
15 (human IgG4, or IgG1).

FIG. 9. Charge variant profiles of purified IgGs. (1) 09C06, (2) MH4, (3) MH8, (4) MH12 and (5) Hu317 are shown. Y axis signals measured in Fluorescence Units.

FIG. 10. DSC Thermograms of purified IgGs. (1) 09C06, (2) MH4, (3) MH8, (4) MH12 and (5) Hu317 are shown.

20 **FIG. 11. Flow cytometric binding of Hu317, lead and control IgGs to HEK293 cells transfected with PD1 or potential off-target binding proteins.** Analyses of binding specificity were performed on HEK293 cells transiently transfected with plasmids encoding either human PD1, human BTN2A1, human LSAMP, human CD20 or ZS green marker only. Each antibody was used in staining at 2 μ g/ml concentration and histograms are indicated
25 per antibody in this figure. In each panel of this figure, where target binding events were observed (indicated by a movement of all, or the major portion of the requisite histogram towards higher AF647 signal), the peak of interest is named (PD1, CD20, LSAMP). No binding signals were observed for any IgG against BTN2A1.

30 **DETAILED DESCRIPTION OF THE INVENTION**

According to a first aspect of the invention, there is provided an antibody molecule which specifically binds to human PD1 and also to cynomolgus monkey PD1, or an antigen-binding portion thereof, wherein the antibody molecule or antigen-binding portion comprises a heavy chain variable region with:

35 an HCDR1 having amino acids in sequence in the following order: G-F-T or a conservative substitution of T (for example S)-F or a conservative substitution of F (for example L)-S or a conservative substitution of S (for example T)-S-Y-G or any amino acid (for example W)-M

or a conservative substitution of M (for example V)-S or any amino acid (for example H) (SEQ ID NO:20);

an HCDR2 having amino acids in sequence in the following order: V or a conservative substitution of V (for example L)-A or a conservative substitution of A (for example G)-V/N-I-
 5 W/K-Q/A-D/G-G-S-T/E-N/K/S-Y-N/V-D-S-V-K-G (SEQ ID NO:21); and

an HCDR3 having amino acids in sequence in the following order: A or any amino acid (for example D/E/G/H/I/K/L/H/Q/S/V/W)-Y or a conservative substitution of Y (for example F/W)-G-N or any amino acid (for example A/E/F/G/H/I/Q/R/S/T/V/W/Y)-Y or a conservative substitution of Y (for example V/W)-W or any amino acid (for example F/H/M/P/Q/S/V)-Y-I or
 10 any amino acid (for example L/M/S/T/V/Y)-D or a conservative substitution of D (for example E)-V or any amino acid (for example A/E/F/G/H/I/K/L/M/R/S/T/W/Y) (SEQ ID NO:22).

In some aspects an anti-PD1 antibody or antigen-binding portion provided herein specifically binds to a PD1 protein comprising or consisting of SEQ ID NO:16 or SEQ ID NO:17. In some aspects an anti-PD1 antibody or antigen-binding portion provided herein specifically binds to a PD1 protein having an amino acid sequence that is at least about 90%, at least about 91%,
 15 at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:16 or SEQ ID NO:17.

20 In aspects of the invention, the HCDR1 of the antibody molecule or antigen-binding portion may exclude the sequences GFSLTSGYGVH (SEQ ID NO:23; Mu317 murine/humanized antibody HCDR1 disclosed in WO2015/035606 A1; US2015/079109A1), VIWAGGSTNYNSALMS (SEQ ID NO:24; Mu317 murine/humanized antibody HCDR2
 25 disclosed in WO2015/035606 A1; US2015/079109A1), and/or the HCDR3 of the antibody molecule or antigen-binding portion may exclude the sequence AYGNYWYIDV (SEQ ID NO:25; Mu317 murine/humanized antibody HCDR3 disclosed in WO2015/035606 A1; US2015/079109A1).

30 The antibody molecule or antigen-binding portion thereof according to the invention may further comprise a light chain variable region with:

an LCDR1 having amino acids in sequence in the following order: K-S-S-Q/E-S-V-S or a conservative substitution of S (such as G/T)-N-D-L or a conservative substitution of L (such as V)-A (SEQ ID NO:26);

35 an LCDR2 having amino acids in sequence in the following order: Y-A-F or any amino acid (for example S/Y)-H or any amino acid (for example P/T)-R-F-S or a conservative substitution of S (such as A/T) (SEQ ID NO:27); and

an LCDR3 having amino acids in sequence in the following order: Q or any amino acid (for example H)-Q-A or any amino acid (for example S)-Y-S-T or any amino acid (for example, N/S)-P-Y or any amino acid (for example W)-T (SEQ ID NO:28).

- 5 In aspects of the invention, the LCDR1 of the antibody molecule or antigen-binding portion may exclude the sequence KASQSVSNDVA / KSSQEVSNDVA (SEQ ID NO:29 / SEQ ID NO:30; Mu317 murine/humanized antibody LCDR1 disclosed in WO2015/035606 A1; US2015/079109A1), and/or the LCDR2 of the antibody molecule or antigen-binding portion may exclude the sequence YAFHRFT (SEQ ID NO:31; Mu317 murine/humanized antibody
- 10 LCDR2 disclosed in WO2015/035606 A1; US2015/079109A1) and/or the LCDR3 of the antibody molecule or antigen-binding portion may exclude the sequence HQAYSSPYT (SEQ ID NO:32; Mu317 murine/humanized antibody LCDR3 disclosed in WO2015/035606 A1; US2015/079109A1).
- 15 In some aspects, disclosed herein is an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable (VL) region comprising LCDR1, LCDR2, and LCDR3, wherein
- (a) the HCDR1 comprises the amino acid sequence G-F-X₁-X₂-X₃-S-Y-X₄-X₅-X₆,
 20 wherein X₁ is T or a conservative substitution of T (for example, S), X₂ is F or a conservative substitution of F (for example, L), X₃ is S or a conservative substitution of S (for example, T), X₄ is G or any other amino acid (for example, W), X₅ is M or a conservative substitution of M (for example, V), and X₆ is S or any other amino acid (for example, H) (SEQ ID NO:20);
- (b) the HCDR2 comprises the amino acid sequence X₁-X₂-X₃-I-X₄-X₅-X₆-G-S-X₇-X₈-
 25 Y-X₉-D-S-V-K-G, wherein X₁ is V or a conservative substitution of V (for example, L), X₂ is A or a conservative substitution of A (for example, G), X₃ is V or N, X₄ is W or K, X₅ is Q or A, X₆ is D or G, X₇ is T or E, X₈ is N, K, or S, and X₉ is N or V (SEQ ID NO:21);
- (c) the HCDR3 comprises the amino acid sequence X₁-X₂-G-X₃-X₄-X₅-Y-X₆-X₇-X₈,
 30 wherein X₁ is A or any other amino acid (for example, D, E, G, H, I, K, L, H, Q, S, V, or W), X₂ is Y or a conservative substitution of Y (for example, F or W), X₃ is N or any other amino acid (for example, A, E, F, G, H, I, Q, R, S, T, V, W, or Y), X₄ is Y or a conservative substitution of Y (for example, V or W), X₅ is W or any other amino acid (for example, F, H, M, P, Q, S, or V), X₆ is I or any other amino acid (for example, L, M, S, T, V, or Y), X₇ is D or a conservative substitution of D (for example, E), and X₈ is V or any other amino acid (for
 35 example, A, E, F, G, H, I, K, L, M, R, S, T, W, or Y) (SEQ ID NO:22);

(d) the LCDR1 comprises the amino acid sequence K-S-S-X₁-S-V-X₂-N-D-X₃-A, wherein X₁ is Q or E, X₂ is S or a conservative substitution of S (for example, G or T), and X₃ is L or a conservative substitution of L (for example, V) (SEQ ID NO:26);

(e) the LCDR2 comprises the amino acid sequence Y-A-X₁-X₂-R-F-X₃, wherein X₁ is
5 F or any other amino acid (for example, S), X₂ is H or any other amino acid (for example, P or T), and X₃ is S or a conservative substitution of S (for example, A or T) (SEQ ID NO:27);
and

(f) the LCDR3 comprises the amino acid sequence X₁-Q-X₂-Y-S-X₃-P-X₄-T, wherein
10 X₁ is Q or any other amino acid (for example, H), X₂ is A or any other amino acid (for example, S), X₃ is T or any other amino acid (for example, N or S), and X₄ is Y or any other amino acid (for example, W) (SEQ ID NO:28).

In some aspects, disclosed herein is an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region comprising, in
15 amino-terminal to carboxyl-terminal order, FR1-HCDR1-FR2-HCDR2-FR3-HCDR3-FR4 and a light chain variable (VL) region comprising, in amino-terminal to carboxyl-terminal order, FR1-LCDR1-FR2-LCDR2-FR3-LCDR3-FR4, wherein the HCDR1 is SEQ ID NO:20, the HCDR2 is SEQ ID NO:32, the HCDR3 is SEQ ID NO:33, the LCDR1 is SEQ ID NO:26, the LCDR2 is SEQ ID NO:27 and the LCDR3 is SEQ ID NO:28, wherein the heavy chain
20 FR1, FR2, FR3 and FR4 amino acid sequences are the heavy chain FR1, FR2, FR3 and FR4 amino acid sequences in SEQ ID NO: 116 (see Table 2) and wherein the light chain FR1, FR2, FR3 and FR4 amino acid sequences are the light chain FR1, FR2, FR3 and FR4 amino acid sequences in SEQ ID NO: 119 (see Table 2).

25 As elaborated herein, the present inventors have succeeded for the first time in generating a number of optimized anti-PD1 antibody molecules using CDR sequences derived from the murine anti-PD1 antibody Mu317 disclosed in WO2015/035606 A1; US2015/079109A1. Refining of the optimized antibody molecules as described herein has provided improved variable domain stability, high expression yields, and/or reduced immunogenicity potential
30 without compromising binding specificity to both human PD1 as well as cynomolgus monkey PD1 (to facilitate maximally accurate primate toxicology and pk studies) and pharmacological potency in PD1 antagonism assays.

In some aspects, optimized anti-PD1 antibody molecules of the present invention do not
35 necessarily have the maximum number of human germline substitutions at corresponding murine CDR or other (such as framework) amino acid positions. As elaborated in the experimental section below, we have found that "maximally humanized" antibody molecules

are not necessary "maximally optimized" in terms of anti-PD1 binding characteristics and/or other desirable features.

5 The present invention encompasses modifications to the amino acid sequence of the antibody molecule or antigen-binding portion thereof as defined herein. For example, the invention includes antibody molecules and corresponding antigen-binding portions thereof comprising functionally equivalent variable regions and CDRs which do not significantly affect their properties as well as variants which have enhanced or decreased activity and/or affinity. For example, the amino acid sequence may be mutated to obtain an antibody with
10 the desired binding affinity to PD1. Insertions which include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues, are envisaged. Examples of terminal insertions include an antibody molecule with an N-terminal methionyl residue or the antibody molecule fused to an epitope tag. Other insertional variants
15 of the antibody molecule include the fusion to the N- or C-terminus of the antibody of an enzyme or a polypeptide which increases the half-life of the antibody in the blood circulation.

The antibody molecule or antigen-binding portion of the invention may include glycosylated and nonglycosylated polypeptides, as well as polypeptides with other post-translational
20 modifications, such as, for example, glycosylation with different sugars, acetylation, and phosphorylation. The antibody molecule or antigen-binding portion of the invention may be mutated to alter such post-translational modifications, for example by adding, removing or replacing one or more amino acid residues to form or remove a glycosylation site.

25 The antibody molecule or antigen-binding portion of the invention may be modified for example by amino acid substitution to remove potential proteolytic sites in the antibody.

In the antibody molecule or antigen-binding portion thereof, the HCDR1 may have the amino acid sequence: G-F-T-F-S-S-Y-G-M/V-S/H (SEQ ID NO:62); the HCDR2 may have the
30 amino acid sequence: V-A-V/N-I-W/K-Q-D-G-S-E/T-N/K-Y-V/N-D-S-V-K-G (SEQ ID NO:63); and the HCDR3 may have the amino acid sequence: A/D/E/G/H/I/K/L/H/Q/S/V/W-Y/F/W-G-N/A/E/F/G/H/I/Q/R/S/T/V/W/Y-Y/V/W-W/F/H/M/P/Q/S/V-Y-I/L/M/S/T/V/Y-D/E-V/A/E/F/G/H/I/Q/R/S/T/W/Y (SEQ ID NO:64).

35 For example, the HCDR1 may have the amino acid sequence: G-F-T-F-S-S-Y-G-M-S/H (SEQ ID NO:65); the HCDR2 may have the amino acid sequence: V-A-V/N-I-W-Q-D-G-S-

E/T-N/K-Y-V-D-S-V-K-G (SEQ ID NO:66); and the HCDR3 may have the amino acid sequence: A/G-Y-G-N-Y-W/M-Y-I-D-R/V (SEQ ID NO:67).

In the antibody molecule or antigen-binding portion thereof, the LCDR1 may have the amino acid sequence: K-S-S-Q/E-S-V-S/G/T-N-D-L/V-A (SEQ ID NO:68); the LCDR2 may have the amino acid sequence Y-A-F/S/Y-H/P/T-R-F-S/T (SEQ ID NO:69); and the LCDR3 may have the amino acid sequence: Q/H-Q-A/S-Y-S-T/N/S-P-Y-T (SEQ ID NO:70).

For example, the LCDR1 may have the amino acid sequence: K-S-S-Q-S-V-S/G/T-N-D-L/V-A (SEQ ID NO:71); the LCDR2 may have the amino acid sequence Y-A-S/Y-H-R-F-S/T (SEQ ID NO:72); and the LCDR3 may have the amino acid sequence: Q/H-Q-A-Y-S-T/S-P-Y-T (SEQ ID NO:73).

In specific embodiments of the invention, the antibody molecule or antigen-binding portion may comprise:

(a) the amino acid sequences

GFSFSSYGMS (SEQ ID NO:47; HCDR1), LANIWQDGSTNYVDSVKG (SEQ ID NO:48; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVSNDVA (SEQ ID NO:44; LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and HQAYSTPYT (SEQ ID NO:46; LCDR3)

[Clone 20C07]; or

(b) the amino acid sequences

GFTFSSYGVH (SEQ ID NO:49; HCDR1), VGVIWQDGSENYVDSVKG (SEQ ID NO:50; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVSNDLA (SEQ ID NO:51; LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and QQAYSTPYT (SEQ ID NO:52; LCDR3)

[Clone 11C08];

(c) the amino acid sequences

GFSFSSYGMH (SEQ ID NO:42; HCDR1), VANIWQDGSTNYVDSVKG (SEQ ID NO:43; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVSNDVA (SEQ ID NO:44; LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and HQAYSTPYT (SEQ ID NO:46; LCDR3)

[Clone 09C06];

(d) the amino acid sequences

GFSFSSYGMH (SEQ ID NO:42; HCDR1), LANIWQDGSENYVDSVKG (SEQ ID NO:53; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVSNDVA (SEQ ID NO:44; LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and QQAYSTPYT (SEQ ID NO:52; LCDR3)

[Clone 17A12];

(e) the amino acid sequences

- GFTLSSYGMH (SEQ ID NO:54; HCDR1), LAVIWADGSTNYVDSVKG (SEQ ID NO:55; HCDR2), AYGNYMYIDV (SEQ ID NO:56; HCDR3), KSSQSVSNDVA (SEQ ID NO:44; LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and HQAYSTPYT (SEQ ID NO:46; LCDR3) [Clone 17D08];
- 5 (f) the amino acid sequences
GFTFSSYGMH (SEQ ID NO:57; HCDR1), VGVIKQDGSSENYVDSVKG (SEQ ID NO:58; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVSNDVA (SEQ ID NO:44; LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and HQAYSTPYT (SEQ ID NO:46; LCDR3) [Clone 17G08];
- 10 (g) the amino acid sequences
GFSFTSYGMH (SEQ ID NO:59; HCDR1), VGVIWQDGSTNYVDSVKG (SEQ ID NO:60; HCDR2), GYGNYWYIDV (SEQ ID NO:61; HCDR3), KSSQSVSNDLA (SEQ ID NO:51; LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and QQAYSTPYT (SEQ ID NO:52; LCDR3) [Clone 15D07];
- 15 (h) the amino acid sequences
GFSLSSYGMS (SEQ ID NO:39; HCDR1), VAVIWQDGSTNYVDSVKG (SEQ ID NO:40; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVGNDVA (SEQ ID NO:74; LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and QQAYSSPYT (SEQ ID NO:75; LCDR3) [Clone MH1];
- 20 (i) the amino acid sequences
GFSLSSYGMS (SEQ ID NO:39; HCDR1), VAVIWQDGSTNYVDSVKG (SEQ ID NO:40; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDLA (SEQ ID NO:76; LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and QQAYSSPYT (SEQ ID NO:75; LCDR3) [Clone MH2];
- 25 (j) the amino acid sequences
GFSLSSYGMS (SEQ ID NO:39; HCDR1), VAVIWQDGSTNYVDSVKG (SEQ ID NO:40; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVGNDLA (SEQ ID NO:77; LCDR1), YAYHRFS (SEQ ID NO:78; LCDR2) and QQAYSSPYT (SEQ ID NO:75; LCDR3) [Clone MH3];
- 30 (k) the amino acid sequences
GFSLSSYGMS (SEQ ID NO:39; HCDR1), VAVIWQDGSTNYVDSVKG (SEQ ID NO:40; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDVA (SEQ ID NO:36; LCDR1), YAYHRFT (SEQ ID NO:37; LCDR2) and HQAYSSPYT (SEQ ID NO:38; LCDR3) [Clone MH4];
- 35 (l) the amino acid sequences
GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSTKYVDSVKG (SEQ ID NO:34; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVGNDVA (SEQ ID NO:74;

LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and QQAYSSPYT (SEQ ID NO:75; LCDR3)
[Clone MH5];

(m) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSTKYVDSVKG (SEQ ID NO:34;
5 HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDLA (SEQ ID NO:76;
LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and QQAYSSPYT (SEQ ID NO:75; LCDR3)
[Clone MH6];

(n) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSTKYVDSVKG (SEQ ID NO:34;
10 HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVGNDLA (SEQ ID NO:77;
LCDR1), YAYHRFS (SEQ ID NO:78; LCDR2) and QQAYSSPYT (SEQ ID NO:75; LCDR3)
[Clone MH7];

(o) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSTKYVDSVKG (SEQ ID NO:34;
15 HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDVA (SEQ ID NO:36;
LCDR1), YAYHRFT (SEQ ID NO:37; LCDR2) and HQAYSSPYT (SEQ ID NO:38; LCDR3)
[Clone MH8];

(p) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSEKYVDSVKG (SEQ ID NO:41;
20 HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVGNLVA (SEQ ID NO:74;
LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and QQAYSSPYT (SEQ ID NO:75; LCDR3)
[Clone MH9];

(q) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSEKYVDSVKG (SEQ ID NO:41;
25 HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDLA (SEQ ID NO:76;
LCDR1), YASHRFT (SEQ ID NO:45; LCDR2) and QQAYSSPYT (SEQ ID NO:75; LCDR3)
[Clone MH10];

(r) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSEKYVDSVKG (SEQ ID NO:41;
30 HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVGNDLA (SEQ ID NO:77;
LCDR1), YAYHRFS (SEQ ID NO:78; LCDR2) and QQAYSSPYT (SEQ ID NO:75; LCDR3)
[Clone MH11];

(s) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSEKYVDSVKG (SEQ ID NO:41;
35 HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDVA (SEQ ID NO:36;
LCDR1), YAYHRFT (SEQ ID NO:37; LCDR2) and HQAYSSPYT (SEQ ID NO:38; LCDR3)
[Clone MH12];

(t) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSTKYVDSVKG (SEQ ID NO:34; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDLA (SEQ ID NO:76; LCDR1), YAYHRFT (SEQ ID NO:37; LCDR2) and HQAYSSPYT (SEQ ID NO:38; LCDR3)

5 [Clone MH13];

(u) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSTKYVDSVKG (SEQ ID NO:34; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDLA (SEQ ID NO:76; LCDR1), YAYHRFS (SEQ ID NO:78; LCDR2) and HQAYSSPYT (SEQ ID NO:38; LCDR3)

10 [Clone MH14];

(v) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSTKYVDSVKG (SEQ ID NO:34; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDLA (SEQ ID NO:76; LCDR1), YASHRFS (SEQ ID NO:79; LCDR2) and HQAYSSPYT (SEQ ID NO:38; LCDR3)

15 [Clone MH15];

(w) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSEKYVDSVKG (SEQ ID NO:41; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDLA (SEQ ID NO:76; LCDR1), YAYHRFT (SEQ ID NO:37; LCDR2) and HQAYSSPYT (SEQ ID NO:38; LCDR3)

20 [Clone MH16];

(x) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSEKYVDSVKG (SEQ ID NO:41; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDLA (SEQ ID NO:76; LCDR1), YAYHRFS (SEQ ID NO:78; LCDR2) and HQAYSSPYT (SEQ ID NO:38; LCDR3)

25 [Clone MH17];

(y) the amino acid sequences

GFTFSSYGMS (SEQ ID NO:33; HCDR1), VANIWQDGSEKYVDSVKG (SEQ ID NO:41; HCDR2), AYGNYWYIDR (SEQ ID NO:35; HCDR3), KSSQSVTNDLA (SEQ ID NO:76; LCDR1), YASHRFS (SEQ ID NO:79; LCDR2) and HQAYSSPYT (SEQ ID NO:38; LCDR3)

30 [Clone MH18];

In some aspects, the invention provides an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

35 (a) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID NO:33), HCDR2 of VANIWQDGSTKYVDSVKG (SEQ ID NO:34), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1

of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);

(b) the VH region amino acid sequence comprises HCDR1 of GFSLSSYGMS (SEQ ID NO:39), HCDR2 of VAVIWQDGSTNYVDSVKG (SEQ ID NO:40), and HCDR3 of
5 AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);

(c) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID NO:33), HCDR2 of VANIWQDGSEKYVDSVKG (SEQ ID NO:41), and HCDR3 of
10 AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);

(d) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of
15 AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);

(e) the VH region amino acid sequence comprises HCDR1 of GFSFTSYGMS (SEQ ID NO:47), HCDR2 of LANIWQDGSTNYVDSVKG (SEQ ID NO:48), and HCDR3 of
20 AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);

(f) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGVH (SEQ ID NO:49), HCDR2 of VGVIWQDGSENYVDSVKG (SEQ ID NO:50), and HCDR3 of
25 AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52);

(g) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of
30 AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);

(h) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of LANIWQDGSENYVDSVKG (SEQ ID NO:53), and HCDR3 of
35 AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52);

- (i) the VH region amino acid sequence comprises HCDR1 of GFTLSSYGMH (SEQ ID NO:54), HCDR2 of LAVIWADGSTNYVDSVKG (SEQ ID NO:55), and HCDR3 of AYGNYMYIDV (SEQ ID NO:56); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
- (j) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMH (SEQ ID NO:57), HCDR2 of VGVIKQDGSENYVDSVKG (SEQ ID NO:58), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46); or
- (k) the VH region amino acid sequence comprises HCDR1 of GFSFTSYGMH (SEQ ID NO:59), HCDR2 of VGVIWQDGSTNYVDSVKG (SEQ ID NO:60), and HCDR3 of GYGNYWYIDV (SEQ ID NO:61); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52).

In some aspects, disclosed herein is anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH region comprises any one of the VH region amino acid sequences in Table 9 and the VL region comprises any one of the VL region amino acid sequences in Table 9.

In some aspects, the invention provides an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

- (a) the VH region amino acid sequence comprises SEQ ID NO:1 and the VL region amino acid sequence comprises SEQ ID NO:2;
- (b) the VH region amino acid sequence comprises SEQ ID NO:3 and the VL region amino acid sequence comprises SEQ ID NO:4;
- (c) the VH region amino acid sequence comprises SEQ ID NO:5 and the VL region amino acid sequence comprises SEQ ID NO:6; or
- (d) the VH region amino acid sequence comprises SEQ ID NO:7 and the VL region amino acid sequence comprises SEQ ID NO:8.

In some aspects, disclosed herein is an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the VH region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:1 and the VL region amino acid sequence is at least about 90%, at least about 91%,
5 at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:2;

(b) the VH region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least
10 about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:3 and the VL region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:4;

(c) the VH region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:5 and the VL region amino acid sequence is at least about 90%, at least about 91%,
15 at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:6; or

(d) the VH region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ
25 ID NO:7 and the VL region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:8. In some aspects, the CDR amino acid sequences of an anti-PD1 antibody are 100% identical to the CDR amino acid sequences in the recited sequences while the FR
30 amino acid sequences are less than 100% identical to the FR amino acid sequences in the recited sequences.

In some aspects, the antibody or antigen-binding portion as defined herein may be isolated.

35 The antibody molecule or antigen-binding portion as defined herein may cross-compete for binding to PD1 with an antibody or antigen-binding portion thereof comprising the sets of CDRs disclosed herein. In some embodiments, the invention provides an anti-PD1 antibody

or an antigen-binding portion thereof, wherein the antibody or antigen-binding portion cross-competes for binding to PD1 with the antibody or antigen-binding portion comprising the sets of CDRs disclosed herein; and (a) comprises fully germline human framework amino acid sequences; and/or (b) binds specifically to human PD1 and cynomolgus PD1; and/or (c) does not comprise an oxidation site in the LCDR2; and/or (d) comprises a human germline peptide sequence with high MHC class II binding affinity (e.g., VKGRFTISR (SEQ ID NO:81)) in the HCDR2/framework 3 region of the VH domain; and/or (e) does not comprise a human T cell epitope sequence in the HCDR1/framework 2 region of the VH domain; and/or (f) does not comprise a human T cell epitope sequence in the HCDR3/framework 4 region of the VH domain; and/or (g) exhibits reduced charge species heterogeneity compared to antibody Hu317, when in IgG1 effector null antibody format. In some embodiments, a KD value of an antibody or antigen-binding portion may be determined by Biacore analysis. In some embodiments, an EC50 value of an antibody or antigen-binding portion may be determined by flow cytometric staining of PD-1 expressing cells (e.g., CHO cells).

The terms "cross-compete", "cross-competition", "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of an antibody or portion thereof to interfere with the binding directly or indirectly through allosteric modulation of the anti-PD1 antibodies of the invention to the target PD1 (e.g., human PD1). The extent to which an antibody or portion thereof is able to interfere with the binding of another to the target, and therefore whether it can be said to cross-block or cross-compete according to the invention, can be determined using competition binding assays. One example of a binding competition assay is Homogeneous Time Resolved Fluorescence (HTRF). One particularly suitable quantitative cross-competition assay uses a FACS- or an AlphaScreen-based approach to measure competition between the labelled (e.g. His tagged, biotinylated or radioactive labelled) antibody or portion thereof and the other antibody or portion thereof in terms of their binding to the target. In general, a cross-competing antibody or portion thereof is, for example, one which will bind to the target in the cross-competition assay such that, during the assay and in the presence of a second antibody or portion thereof, the recorded displacement of the immunoglobulin single variable domain or polypeptide according to the invention is up to 100% (e.g. in a FACS based competition assay) of the maximum theoretical displacement (e.g. displacement by cold (e.g. unlabeled) antibody or fragment thereof that needs to be cross-blocked) by the potentially cross-blocking antibody or fragment thereof that is present in a given amount. Preferably, cross-competing antibodies or portions thereof have a recorded displacement that is between 10% and 100%, or between 50% and 100%.

The antibody molecule or antigen-binding portion as defined herein may comprise one or more substitutions, deletions and/or insertions which remove a post-translational modification (PTM) site, for example a glycosylation site (N-linked or O-linked), a deamination site, a phosphorylation site or an isomerisation/fragmentation site.

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More than 350 types of PTM are known. Key forms of PTM include phosphorylation, glycosylation (*N*- and *O*-linked), sumoylation, palmitoylation, acetylation, sulfation, myristoylation, prenylation and methylation (of K and R residues). Statistical methods to identify putative amino acid sites responsible for specific PTMs are well known in the art (see Zhou *et al.*, 2016, Nature Protocols 1: 1318-1321). Removal of such a site for example by substitution, deletion and/or insertion and then optionally testing (experimentally and/or theoretically) for (a) binding activity and/or (b) loss of the PTM is contemplated.

For example, the Mu317 murine LCDR2 (as defined herein, i.e. the amino acid sequence YAFHRFT (SEQ ID NO:31)) has been identified to have a putative oxidation site at residue 3 (F). Removal of this site at equivalent positions in an LCDR2 of the invention, for example by conservative or non-conservative substitution (such as to S or Y), is envisaged (as for example in clones 09C06 and other clones in Tables 3 and 4).

20 The antibody molecule or antigen-binding portion thereof may be human, humanized or chimeric.

The antibody molecule or antigen-binding portion thereof may comprise one or more human variable domain framework scaffolds into which the CDRs have been inserted. For example, 25 the VH region, the VL region, or both the VH and the VL region may comprise one or more human framework region amino acid sequences.

The antibody molecule or antigen-binding portion thereof may comprise an IGHV3-7 human germline scaffold into which the corresponding HCDR sequences have been inserted. The 30 antibody molecule or antigen-binding portion thereof may comprise a VH region that comprises an IGHV3-7 human germline scaffold amino acid sequence into which a set of corresponding HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted.

The antibody molecule or antigen-binding portion thereof may comprise an IGKV4-1 human germline scaffold into which the corresponding LCDR sequences have been inserted. The 35 antibody molecule or antigen-binding portion thereof may comprise a VL region that

comprises an IGKV4-1 human germline scaffold amino acid sequence into which a set of corresponding LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted.

5 The antibody molecule or antigen-binding portion thereof may comprise an IGHV3-7 human germline scaffold into which the corresponding HCDR sequences have been inserted and an IGKV4-1 human germline scaffold into which the corresponding LCDR sequences have been inserted. The antibody molecule or antigen-binding portion thereof may comprise a VH region that comprises an IGHV3-7 human germline scaffold amino acid sequence into which a set of corresponding HCDR1, HCDR2 and HCDR3 amino acid sequences have been
10 inserted and a VL region that comprises an IGKV4-1 human germline scaffold amino acid sequence into which a set of corresponding LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted. The HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 amino acid sequences may be the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 amino acid sequences of any one of the clones in Table 4 (with all six CDR sequences being
15 from the same clone).

In some aspects, the antibody molecule or antigen-binding portion thereof may comprise an immunoglobulin constant region. In some embodiments, the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2. In additional embodiments, the
20 immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2. The antibody molecule or antigen-binding portion thereof may comprise an immunologically inert constant region. In some aspects, an anti-PD1 antibody or antigen-binding portion thereof may comprise an immunoglobulin constant region comprising a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A
25 and G237A or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S. In some aspects, an anti-PD1 antibody or antigen-binding portion thereof may comprise an immunoglobulin constant region comprising a wild-type human IgG2 constant region or a wild-type human IgG4 constant region. In some aspects, an anti-PD1 antibody may comprise an immunoglobulin constant region comprising any one
30 of the amino acid sequences in Table 10. The Fc region sequences in Table 10 begin at the CH1 domain. In some aspects, an anti-PD1 antibody may comprise an immunoglobulin constant region comprising an amino acid sequence of an Fc region of human IgG4, human IgG4(S228P), human IgG2, human IgG1, human IgG1-3M or human IgG1-4M. For example, the human IgG4(S228P) Fc region comprises the following substitution compared to the wild-
35 type human IgG4 Fc region: S228P. For example, the human IgG1-3M Fc region comprises the following substitutions compared to the wild-type human IgG1 Fc region: L234A, L235A and G237A, while the human IgG1-4M Fc region comprises the following substitutions

compared to the wild-type human IgG1 Fc region: L234A, L235A, G237A and P331S. In some aspects, a position of an amino acid residue in a constant region of an immunoglobulin molecule is numbered according to EU nomenclature (Ward *et al.*, 1995 *Therap. Immunol.* 2:77-94). In some aspects, an immunoglobulin constant region may comprise an RDEL
5 (SEQ ID NO:18) motif or an REEM (SEQ ID NO:19) motif (underlined in Table 18). The REEM (SEQ ID NO:19) allotype is found in a smaller human population than the RDEL (SEQ ID NO:18) allotype. In some aspects, an anti-PD1 antibody may comprise an immunoglobulin constant region comprising any one of SEQ ID NOS:9-15. In some aspects, an anti-PD1 antibody may comprise the six CDR amino acid sequences of any one of the
10 clones in Table 4 and any one of the Fc region amino acid sequences in Table 10. In some aspects, an anti-PD1 antibody may comprise an immunoglobulin heavy chain constant region comprising any one of the Fc region amino acid sequences in Table 10 and an immunoglobulin light chain constant region that is a kappa light chain constant region or a lambda light chain constant region.

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In some aspects, disclosed herein is an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region, a light chain variable (VL) region and a heavy chain constant region, wherein

(a) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID
20 NO:33), HCDR2 of VANIWQDGSTKYVDSVKG (SEQ ID NO:34), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;

25 (b) the VH region amino acid sequence comprises HCDR1 of GFSLSSYGMS (SEQ ID NO:39), HCDR2 of VAVIWQDGSTNYVDSVKG (SEQ ID NO:40), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38); and the heavy chain constant region comprises any one of
30 SEQ ID NOS: 9-15;

(c) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID NO:33), HCDR2 of VANIWQDGSEKYVDSVKG (SEQ ID NO:41), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of
35 HQAYSSPYT (SEQ ID NO:38); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;

- (d) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;
- (e) the VH region amino acid sequence comprises HCDR1 of GFSFTSYGMS (SEQ ID NO:47), HCDR2 of LANIWQDGSTNYVDSVKG (SEQ ID NO:48), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;
- (f) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGVH (SEQ ID NO:49), HCDR2 of VGVIWQDGSENYVDSVKG (SEQ ID NO:50), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;
- (g) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;
- (h) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of LANIWQDGSENYVDSVKG (SEQ ID NO:53), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;
- (i) the VH region amino acid sequence comprises HCDR1 of GFTLSSYGMH (SEQ ID NO:54), HCDR2 of LAVIWADGSTNYVDSVKG (SEQ ID NO:55), and HCDR3 of AYGNYMYIDV (SEQ ID NO:56); the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;

(j) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMH (SEQ ID NO:57), HCDR2 of VGVIKQDGSENYVDSVKG (SEQ ID NO:58), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15; or

(k) the VH region amino acid sequence comprises HCDR1 of GFSFTSYGMH (SEQ ID NO:59), HCDR2 of VGVIWQDGSTNYVDSVKG (SEQ ID NO:60), and HCDR3 of GYGNYWYIDV (SEQ ID NO:61); the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52); and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15.

In some aspects, disclosed herein is an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region, a light chain variable (VL) region and a heavy chain constant region, wherein

(a) the VH region amino acid sequence comprises or consists of SEQ ID NO:1; the VL region amino acid sequence comprises or consists of SEQ ID NO:2; and the heavy chain constant region comprises a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG2 constant region; a wild-type human IgG1 constant region or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A;

(b) the VH region amino acid sequence comprises or consists of SEQ ID NO:3; the VL region amino acid sequence comprises or consists of SEQ ID NO:4; and the heavy chain constant region comprises a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG2 constant region; a wild-type human IgG1 constant region or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A;

(c) the VH region amino acid sequence comprises or consists of SEQ ID NO:5; the VL region amino acid sequence comprises or consists of SEQ ID NO:6; and the heavy chain constant region comprises a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG2 constant region; a wild-type human IgG1 constant region or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A; or

(d) the VH region amino acid sequence comprises or consists of SEQ ID NO:7; the VL region amino acid sequence comprises or consists of SEQ ID NO:8; and the heavy chain constant region comprises a wild-type human IgG4 constant region, a human IgG4

constant region comprising the amino acid substitution S228P, a wild-type human IgG2 constant region; a wild-type human IgG1 constant region or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A.

- 5 In some aspects, disclosed herein is an anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region, a light chain variable (VL) region and a heavy chain constant region, wherein
- (a) the VH region amino acid sequence comprises or consists of SEQ ID NO:1; the VL region amino acid sequence comprises or consists of SEQ ID NO:2; and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;
- 10 (b) the VH region amino acid sequence comprises or consists of SEQ ID NO:3; the VL region amino acid sequence comprises or consists of SEQ ID NO:4; and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15;
- (c) the VH region amino acid sequence comprises or consists of SEQ ID NO:5; the VL region amino acid sequence comprises or consists of SEQ ID NO:6; and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15; or
- 15 (d) the VH region amino acid sequence comprises or consists of SEQ ID NO:7; the VL region amino acid sequence comprises or consists of SEQ ID NO:8; and the heavy chain constant region comprises any one of SEQ ID NOS: 9-15.

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In some aspects, an anti-PD1 antibody may be immune effector null. In some aspects, an anti-PD1 antibody or an antigen-binding portion thereof does not induce immune effector function and, optionally, suppresses immune effector function. In some aspects, an anti-PD1 antibody may lack measurable binding to human Fc γ RI, Fc γ RIIa, Fc γ RIIIa and Fc γ RIIIb receptors but maintain binding to human Fc γ RIIIb receptor and optionally maintain binding to human FcRn receptor. Fc γ RI, Fc γ RIIa, Fc γ RIIIa and Fc γ RIIIb are examples of activating receptors. Fc γ RIIIb is an example of an inhibitory receptor. FcRn is an example of a recycling receptor. In some aspects, binding affinity of an anti-PD1 antibody or an antigen-binding portion thereof for human Fc receptors may be measured by BIACORE[®] analysis. In some aspects, Homogeneous Time Resolved Fluorescence (HTRF) can be used to study binding of an anti-PD1 antibody to human Fc receptors. In one example of HTRF, human IgG1 (wild type) is labelled, as is the full suite of Fc gamma receptors and then antibodies with engineered Fc fragments are used in titration competition. In some aspects, PD1-positive cells may be mixed with human white blood cells and anti-PD1 antibodies, and cell killing by CDC, ADCC and/or ADCP may be measured. In some aspects, an anti-PD1 antibody comprising an amino acid sequence of an Fc region of human IgG1-3M (see Table 10) is

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effector null. In some aspects, an anti-PD1 antibody comprising an amino acid sequence of an Fc region of human IgG1-3M (see Table 10) is not effector null.

5 The antibody molecule or antigen-binding portion thereof may be a Fab fragment, a F(ab)₂ fragment, an Fv fragment, a tetrameric antibody, a tetravalent antibody, a multispecific antibody (for example, a bivalent antibody), a domain-specific antibody, a single domain antibody, a monoclonal antibody or a fusion protein. In one embodiment, an antibody may be a bispecific antibody that binds specifically to a first antigen and a second antigen, wherein the first antigen is PD1 and the second antigen is not PD1. Antibody molecules and methods
10 for their construction and use are described, in for example Holliger & Hudson (2005, Nature Biotechnol. 23(9): 1126-1136).

In another aspect of the invention, there is provided an immunoconjugate comprising the antibody molecule or antigen-binding portion thereof of the invention as defined herein linked
15 a therapeutic agent.

Examples of suitable therapeutic agents include cytotoxins, radioisotopes, chemotherapeutic agents, immunomodulatory agents, anti-angiogenic agents, antiproliferative agents, pro-apoptotic agents, and cytostatic and cytolytic enzymes (for example RNAses). Further
20 therapeutic agents include a therapeutic nucleic acid, such as a gene encoding an immunomodulatory agent, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent. These drug descriptors are not mutually exclusive, and thus a therapeutic agent may be described using one or more of the above terms.

25 Examples of suitable therapeutic agents for use in immunoconjugates include the taxanes, maytansines, CC-1065 and the duocarmycins, the calicheamicins and other enediynes, and the auristatins. Other examples include the anti-folates, vinca alkaloids, and the anthracyclines. Plant toxins, other bioactive proteins, enzymes (i.e., ADEPT), radioisotopes, photosensitizers may also be used in immunoconjugates. In addition, conjugates can be
30 made using secondary carriers as the cytotoxic agent, such as liposomes or polymers. Suitable cytotoxins include an agent that inhibits or prevents the function of cells and/or results in destruction of cells. Representative cytotoxins include antibiotics, inhibitors of tubulin polymerization, alkylating agents that bind to and disrupt DNA, and agents that disrupt protein synthesis or the function of essential cellular proteins such as protein kinases,
35 phosphatases, topoisomerases, enzymes, and cyclins.

Representative cytotoxins include, but are not limited to, doxorubicin, daunorubicin, idarubicin, aclarubicin, zorubicin, mitoxantrone, epirubicin, carubicin, nogalamycin, menogaril, pitarubicin, valrubicin, cytarabine, gemcitabine, trifluridine, ancitabine, enocitabine, azacitidine, doxifludine, pentostatin, broxuhdine, capecitabine, cladhbine, 5 decitabine, floxuhdine, fludarabine, gougertin, puromycin, tegafur, tiazofuhn, adhamycin, cisplatin, carboplatin, cyclophosphamide, dacarbazine, vinblastine, vincristine, mitoxantrone, bleomycin, mechlorethamine, prednisone, procarbazine, methotrexate, flurouracils, etoposide, taxol, taxol analogs, platins such as cis-platin and carbo-platin, mitomycin, thiotepa, taxanes, vincristine, daunorubicin, epirubicin, actinomycin, authramycin, 10 azaserines, bleomycins, tamoxifen, idarubicin, dolastatins/auristatins, hemiasterlins, esperamicins and maytansinoids.

Suitable immunomodulatory agents include anti-hormones that block hormone action on tumors and immunosuppressive agents that suppress cytokine production, down-regulate 15 self-antigen expression, or mask MHC antigens.

Also provided is a nucleic acid molecule encoding the antibody molecule or antigen-binding portion thereof of the invention as defined herein. A nucleic acid molecule may encode (a) the VH region amino acid sequence; (b) the VL region amino acid sequence; or (c) both the 20 VH and the VL region amino acid sequences of an anti-PD1 antibody or an antigen-binding portion thereof described herein. In some aspects, the nucleic acid molecule as defined herein may be isolated.

Further provided is a vector comprising the nucleic acid molecule of the invention as defined 25 herein. The vector may be an expression vector.

Also provided is a host cell comprising the nucleic acid molecule or the vector of the invention as defined herein. The host cell may be a recombinant host cell.

30 In a further aspect there is provided a method of producing an anti-PD1 antibody and/or an antigen-binding portion thereof, comprising culturing the host cell of the invention under conditions that result in expression and/or production of the antibody and/or the antigen-binding portion thereof, and isolating the antibody and/or the antigen-binding portion thereof from the host cell or culture.

35 In another aspect of the invention there is provided a pharmaceutical composition comprising the antibody molecule or antigen-binding portion thereof of the invention as defined herein,

or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein.

5 Further provided is a method for enhancing an immune response in a subject, comprising administering to the subject an effective amount of the antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

10

In a further aspect there is provided a method for treating or preventing cancer in a subject, comprising administering to the subject an effective amount of the antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

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For example, the cancer may be pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

25

The invention also provides an antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein, for use in the treatment of cancer.

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In another aspect the invention provides the antibody molecule, or antigen-binding portion thereof, or the immunoconjugate, or the nucleic acid molecule, or the vector for use, or the method of treatment of the invention as defined herein, for separate, sequential or simultaneous use in a combination combined with a second therapeutic agent, for example an anti-cancer agent.

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In a further aspect there is provided the use of an antibody molecule or antigen-binding portion thereof of the invention as defined herein, or an immunoconjugate of the invention as defined herein, or a nucleic acid molecule of the invention as defined herein, or a vector of the invention as defined herein, or a pharmaceutical composition of the invention as defined herein, in the manufacture of a medicament for the treatment of cancer.

The invention also provides a method for treating or preventing an infectious or immune disease in a subject, comprising administering to the subject an effective amount of the antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined here, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.

In one embodiment, the invention provides an anti-PD1 antibody or an antigen-binding portion thereof comprising the amino acid sequences disclosed herein for use in therapy.

The pharmaceutical composition of the invention may comprise a pharmaceutically acceptable excipient, carrier, or diluent. A pharmaceutically acceptable excipient may be a compound or a combination of compounds entering into a pharmaceutical composition which does not provoke secondary reactions and which allows, for example, facilitation of the administration of the anti-PD1 antibody molecule, an increase in its lifespan and/or in its efficacy in the body or an increase in its solubility in solution. These pharmaceutically acceptable vehicles are well known and will be adapted by the person skilled in the art as a function of the mode of administration of the anti-PD1 antibody molecule.

In some embodiments, the anti-PD1 antibody molecule may be provided in a lyophilised form for reconstitution prior to administration. For example, lyophilised antibody molecules may be re-constituted in sterile water and mixed with saline prior to administration to an individual.

The anti-PD1 antibody molecules will usually be administered in the form of a pharmaceutical composition, which may comprise at least one component in addition to the antibody molecule. Thus pharmaceutical compositions may comprise, in addition to the anti-PD1 antibody molecule, a pharmaceutically acceptable excipient, carrier, buffer, stabilizer or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the anti-PD1 antibody molecule. The precise nature of the carrier or other material will depend on the route of administration, which may be by bolus, infusion, injection or any other suitable route, as discussed below.

For parenteral, for example sub-cutaneous or intra-venous administration, e.g. by injection, the pharmaceutical composition comprising the anti-PD1 antibody molecule may be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilizers, buffers, antioxidants and/or other additives may be employed as required including buffers such as phosphate, citrate and other organic acids; antioxidants, such as ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens, such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3'-pentanol; and m-cresol); low molecular weight polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers, such as polyvinylpyrrolidone; amino acids, such as glycine, glutamine, asparagines, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose or dextrans; chelating agents, such as EDTA; sugars, such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions, such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants, such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

A pharmaceutical composition comprising an anti-PD1 antibody molecule may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

An anti-PD1 antibody molecule as described herein may be used in a method of treatment of the human or animal body, including prophylactic or preventative treatment (e.g. treatment before the onset of a condition in an individual to reduce the risk of the condition occurring in the individual; delay its onset; or reduce its severity after onset). The method of treatment may comprise administering the anti-PD1 antibody molecule to an individual in need thereof.

Administration is normally in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the composition, the method of administration, the scheduling of administration and other factors known to medical practitioners. Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors and may depend

on the severity of the symptoms and/or progression of a disease being treated. Appropriate doses of antibody molecules are well known in the art (Ledermann J.A. *et al.*, 1991, *Int. J. Cancer* 47: 659-664; Bagshawe K.D. *et al.*, 1991, *Antibody, Immunoconjugates and Radiopharmaceuticals* 4: 915-922). Specific dosages may be indicated herein or in the
5 Physician's Desk Reference (2003) as appropriate for the type of medicament being administered may be used. A therapeutically effective amount or suitable dose of an antibody molecule may be determined by comparing its *in vitro* activity and *in vivo* activity in an animal model. Methods for extrapolation of effective dosages in mice and other test animals to humans are known. The precise dose will depend upon a number of factors,
10 including whether the antibody is for prevention or for treatment, the size and location of the area to be treated, the precise nature of the antibody (e.g. whole antibody, fragment) and the nature of any detectable label or other molecule attached to the antibody.

A typical antibody dose will be in the range 100 μ g to 1 g for systemic applications, and 1 μ g
15 to 1 mg for topical applications. An initial higher loading dose, followed by one or more lower doses, may be administered. Typically, the antibody will be a whole antibody, e.g. the IgG1 or IgG4 isotype. This is a dose for a single treatment of an adult patient, which may be proportionally adjusted for children and infants, and also adjusted for other antibody formats in proportion to molecular weight. Treatments may be repeated at daily, twice-weekly,
20 weekly or monthly intervals, at the discretion of the physician. The treatment schedule for an individual may be dependent on the pharmacokinetic and pharmacodynamic properties of the antibody composition, the route of administration and the nature of the condition being treated.

25 Treatment may be periodic, and the period between administrations may be about two weeks or more, e.g. about three weeks or more, about four weeks or more, about once a month or more, about five weeks or more, or about six weeks or more. For example, treatment may be every two to four weeks or every four to eight weeks. Treatment may be given before, and/or after surgery, and/or may be administered or applied directly at the anatomical site of
30 surgical treatment or invasive procedure. Suitable formulations and routes of administration are described above.

In some embodiments, anti-PD1 antibody molecules as described herein may be administered as sub-cutaneous injections. Sub-cutaneous injections may be administered
35 using an auto-injector, for example for long term prophylaxis/treatment.

In some embodiments, the therapeutic effect of the anti-PD1 antibody molecule may persist for several half-lives, depending on the dose. For example, the therapeutic effect of a single dose of the anti-PD1 antibody molecule may persist in an individual for 1 month or more, 2 months or more, 3 months or more, 4 months or more, 5 months or more, or 6 months or more.

The invention also provides a method of producing an antibody molecule which specifically binds to human PD1 and optionally also to cynomolgus monkey PD1, or an antigen-binding portion thereof, comprising the steps of:

- 10 (1) grafting anti-PD1 CDRs from a non-human source into a human v-domain framework to produce a humanized anti-PD1 antibody molecule or antigen-binding portion thereof;
- (2) generating a library of clones of the humanized anti-PD1 antibody molecule or antigen-binding portion thereof comprising one or more mutations in the CDRs;
- (3) screening the library for binding to human PD1 and optionally also to cynomolgus monkey
15 PD1;
- (4) selecting clones from the screening step (3) having binding specificity to human PD1 and optionally also to cynomolgus monkey PD1; and
- (5) producing an antibody molecule which specifically binds to human PD1 and optionally also to cynomolgus monkey PD1, or an antigen-binding portion thereof from clones selected
20 from step (4).

The method may comprise a further step of producing additional clones based on the clones selected in step (4), for example based on further exploratory mutagenesis at specific positions in the CDRs of the clones selected in step (4), to enhance humanization and/or
25 minimise human T cell epitope content and/or improve manufacturing properties in the antibody molecule or antigen-binding portion thereof produced in step (5).

Refinements applicable to the above method are as described in Example 1 below.

30 As used herein, the term "PD1" refers to Programmed Cell Death Protein 1 and variants thereof that retain at least part of the biological activity of PD1. As used herein, PD1 includes all species of native sequence PD1, including human, rat, mouse and chicken. The term "PD1" is used to include variants, isoforms and species homologs of human PD1. Antibodies of the invention may cross-react with PD1 from species other than human, in particular PD1
35 from cynomolgus monkey (*Macaca fascicularis*). Examples of human and cynomolgus PD1 amino acid sequences are provided in Table 11. In certain embodiments, the antibodies may be completely specific for human PD1 and may not exhibit non-human cross-reactivity.

As used herein, an “antagonist” as used in the context of the antibody of the invention or an “anti-PD1 antagonist antibody” (interchangeably termed “anti-PD1 antibody”) refers to an antibody which is able to bind to PD1 and inhibit PD1 biological activity and/or downstream pathway(s) mediated by PD1 signalling. An anti-PD1 antagonist antibody encompasses antibodies that can block, antagonize, suppress or reduce (including significantly) PD1 biological activity, including downstream pathways mediated by PD1 signalling, such as receptor binding and/or elicitation of a cellular response to PD1. For the purposes of the present invention, it will be explicitly understood that the term “anti- PD1 antagonist antibody” encompass all the terms, titles, and functional states and characteristics whereby PD1 itself, and PD1 biological activity (including but not limited to its ability to suppress the activation of anti-tumour cell activity of T cells), or the consequences of the activity or biological activity, are substantially nullified, decreased, or neutralized in any meaningful degree.

PD1 “specifically binds” “specifically interacts”, “preferentially binds”, “binds” or “interacts” with PD1 if it binds with greater affinity, avidity, more readily and/or with greater duration than it binds to other receptors.

An “antibody molecule” is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term “antibody molecule” encompasses not only intact polyclonal or monoclonal antibodies, but also any antigen binding fragment (for example, an “antigen-binding portion”) or single chain thereof, fusion proteins comprising an antibody, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site including, for example without limitation, scFv, single domain antibodies (for example, shark and camelid antibodies), maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv.

An “antibody molecule” encompasses an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), for example IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta,

epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

5 The term “antigen binding portion” of an antibody molecule, as used herein, refers to one or more fragments of an intact antibody that retain the ability to specifically bind to PD1. Antigen binding functions of an antibody molecule can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term “antigen binding portion” of an antibody molecule include Fab; Fab'; F(ab')₂; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm
10 of an antibody; a single domain antibody (dAb) fragment, and an isolated complementarity determining region (CDR).

The term “Fc region” is used to define a C-terminal region of an immunoglobulin heavy chain. The “Fc region” may be a native sequence Fc region or a variant Fc region. Although the
15 boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The numbering of the residues in the Fc region is that of the EU index as in Kabat. The Fc region of an immunoglobulin generally comprises two constant domains, CH2 and CH3. As is known in the art, an Fc
20 region can be present in dimer or monomeric form.

A “variable region” of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. As known in the art, the variable regions of the heavy and light chain each consist of four framework
25 regions (FRs) connected by three complementarity determining regions (CDRs) also known as hypervariable regions, contribute to the formation of the antigen binding site of antibodies. When choosing FR to flank CDRs, for example when humanizing or optimizing an antibody, FRs from antibodies which contain CDR sequences in the same canonical class are preferred.

30 The CDR definitions used in the present application combine the domains used in the many disparate, often conflicting schemes that have been created in the field, which are based on the combination of immunoglobulin repertoire analyses and structural analyses of antibodies in isolation and in their co-crystals with antigens (see review by Swindells *et al.*, 2016, abYsis:
35 Integrated Antibody Sequence and Structure-Management, Analysis, and Prediction. J Mol Biol. [PMID: 27561707; Epub 22 August 2016]). The CDR definition used herein (a “Unified” definition) incorporates the lessons of all such prior insights and includes all appropriate loop

positions required to sample the full residue landscape that potentially mediates target-binding complementarity.

Table 1 shows the amino acid sequences of the Mu317 murine anti-PD1 antibody CDRs as defined herein (a “Unified” scheme), in comparison to well-known alternative systems for defining the same CDRs.

As used herein the term “conservative substitution” refers to replacement of an amino acid with another amino acid which does not significantly deleteriously change the functional activity. A preferred example of a “conservative substitution” is the replacement of one amino acid with another amino acid which has a value ≥ 0 in the following BLOSUM 62 substitution matrix (see Henikoff & Henikoff, 1992, PNAS 89: 10915-10919):

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V	
15	A	4	-1	-2	-2	0	-1	-1	0	-2	-1	-1	-1	-2	-1	1	0	-3	-2	0	
	R	-1	5	0	-2	-3	1	0	-2	0	-3	2	-1	-3	-2	-1	-1	-3	-2	-3	
	N	-2	0	6	1	-3	0	0	0	1	-3	-3	0	-2	-3	-2	1	0	-4	-2	-3
	D	-2	-2	1	6	-3	0	2	-1	-1	-3	-4	-1	-3	-3	-1	0	-1	-4	-3	-3
	C	0	-3	-3	-3	9	-3	-4	-3	-3	-1	-1	-3	-1	-2	-3	-1	-1	-2	-2	-1
20	Q	-1	1	0	0	-3	5	2	-2	0	-3	-2	1	0	-3	-1	0	-1	-2	-1	-2
	E	-1	0	0	2	-4	2	5	-2	0	-3	-3	1	-2	-3	-1	0	-1	-3	-2	-2
	G	0	-2	0	-1	-3	-2	-2	6	-2	-4	-4	-2	-3	-3	-2	0	-2	-2	-3	-3
	H	-2	0	1	-1	-3	0	0	-2	8	-3	-3	-1	-2	-1	-2	-1	-2	-2	2	-3
	I	-1	-3	-3	-3	-1	-3	-3	-4	-3	4	2	-3	1	0	-3	-2	-1	-3	-1	3
25	L	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4	-2	2	0	-3	-2	-1	-2	-1	1
	K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5	-1	-3	-1	0	-1	-3	-2	-2
	M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5	0	-2	-1	-1	-1	-1	1
	F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6	-4	-2	-2	1	3	-1
	P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7	-1	-1	-4	-3	-2
30	S	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4	1	-3	-2	-2
	T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5	-2	-2	0
	W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11	2	-3
	Y	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	-1
35	V	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4.

The term “monoclonal antibody” (Mab) refers to an antibody, or antigen-binding portion thereof, that is derived from a single copy or clone, including for example any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. Preferably, a monoclonal antibody of the invention exists in a homogeneous or substantially homogeneous population.

A “humanized” antibody molecule refers to a form of non-human (for example, murine) antibody molecules, or antigen-binding portion thereof, that are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-

human immunoglobulin. Humanized antibodies may be human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity.

5

“Human antibody or fully human antibody” refers to an antibody molecule, or antigen-binding portion thereof, derived from transgenic mice carrying human antibody genes or from human cells.

10 The term “chimeric antibody” is intended to refer to an antibody molecule, or antigen-binding portion thereof, in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody molecule in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

15

“Antibody-drug conjugate” and “immunoconjugate” refer to an antibody molecule, or antigen-binding portion thereof, including antibody derivatives that binds to PD1 and is conjugated to cytotoxic, cytostatic and/or therapeutic agents.

20 Antibody molecules of the invention, or antigen-binding portion thereof, can be produced using techniques well known in the art, for example recombinant technologies, phage display technologies, synthetic technologies or combinations of such technologies or other technologies readily known in the art.

25 The term “isolated molecule” (where the molecule is, for example, a polypeptide, a polynucleotide, or an antibody) is a molecule that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other molecules from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a molecule that is
30 chemically synthesized, or expressed in a cellular system different from the cell from which it naturally originates, will be “isolated” from its naturally associated components. A molecule also may be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art. Molecule purity or homogeneity may be assayed by a number of means well known in the art. For example, the purity of a polypeptide
35 sample may be assayed using polyacrylamide gel electrophoresis and staining of the gel to visualize the polypeptide using techniques well known in the art. For certain purposes, higher

resolution may be provided by using HPLC or other means well known in the art for purification.

5 The term "epitope" refers to that portion of a molecule capable of being recognized by and bound by an antibody molecule, or antigen-binding portion thereof, at one or more of the antibody molecule's antigen-binding regions. Epitopes can consist of defined regions of primary secondary or tertiary protein structure and includes combinations of secondary structural units or structural domains of the target recognised by the antigen binding regions of the antibody, or antigen-binding portion thereof. Epitopes can likewise consist of a defined
10 chemically active surface grouping of molecules such as amino acids or sugar side chains and have specific three-dimensional structural characteristics as well as specific charge characteristics. The term "antigenic epitope" as used herein, is defined as a portion of a polypeptide to which an antibody molecule can specifically bind as determined by any method well known in the art, for example, by conventional immunoassays, antibody
15 competitive binding assays or by x-ray crystallography or related structural determination methods (for example NMR).

The term "binding affinity" or "KD" refers to the dissociation rate of a particular antigen-antibody interaction. The KD is the ratio of the rate of dissociation, also called the "off-rate
20 (k_{off})", to the association rate, or "on-rate (k_{on})". Thus, K_D equals $k_{\text{off}} / k_{\text{on}}$ and is expressed as a molar concentration (M). It follows that the smaller the K_D , the stronger the affinity of binding. Therefore, a K_D of 1 μM indicates weak binding affinity compared to a K_D of 1 nM. KD values for antibodies can be determined using methods well established in the art. One method for determining the KD of an antibody is by using surface plasmon resonance (SPR),
25 typically using a biosensor system such as a Biacore® system.

The term "potency" is a measurement of biological activity and may be designated as IC_{50} , or effective concentration of an antibody or antibody drug conjugate to the antigen PD1 to inhibit 50% of activity measured in a PD1 activity assay as described herein.

30 The phrase "effective amount" or "therapeutically effective amount" as used herein refers to an amount necessary (at dosages and for periods of time and for the means of administration) to achieve the desired therapeutic result. An effective amount is at least the minimal amount, but less than a toxic amount, of an active agent which is necessary to impart
35 therapeutic benefit to a subject.

The term “inhibit” or “neutralize” as used herein with respect to bioactivity of an antibody molecule of the invention means the ability of the antibody to substantially antagonize, prohibit, prevent, restrain, slow, disrupt, eliminate, stop, reduce or reverse for example progression or severity of that which is being inhibited including, but not limited to, a biological activity or binding interaction of the antibody molecule to PD1.

A “host cell” includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) of this invention.

As used herein, “vector” means a construct, which is capable of delivering, and, preferably, expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

The term “treating”, as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, delaying the progression of, delaying the onset of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term “treatment”, as used herein, unless otherwise indicated, refers to the act of treating as defined above. The term “treating” also includes adjuvant and neoadjuvant treatment of a subject. For the avoidance of doubt, reference herein to “treatment” includes reference to curative, palliative and prophylactic treatment. For the avoidance of doubt, references herein to “treatment” also include references to curative, palliative and prophylactic treatment.

It is understood that wherever embodiments are described herein with the language “comprising,” otherwise analogous embodiments described in terms of “consisting of” and/or “consisting essentially of” are also provided.

Where aspects or embodiments of the invention are described in terms of a Markush group or other grouping of alternatives, the present invention encompasses not only the entire group listed as a whole, but each member of the group individually and all possible

subgroups of the main group, but also the main group absent one or more of the group members. The present invention also envisages the explicit exclusion of one or more of any of the group members in the claimed invention.

- 5 Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In case of conflict, the present specification, including definitions, will control. Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or
- 10 group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Any example(s) following the term "e.g." or "for example" is not meant to be exhaustive or limiting.
- 15 The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art.

20 Particular non-limiting embodiments of the present invention will now be described with reference to accompanying drawings.

EXAMPLE 1. Generation of optimized anti-PD1 therapeutic antibodies**Introduction**

In this example, we successfully generate a panel of agonistic, optimized anti-PD1 antibodies. These anti-PD1 antibodies are well expressed, biophysically stable, highly soluble and of maximized identity to preferred human germlines.

Materials and methods**PD1 library generation and selection**

10 The PD1 Fab library was assembled by mass oligo synthesis and PCR. The amplified Fab repertoire was then cloned via restriction-ligation into a phagemid vector, transformed into *E.coli* TG-1 cells, and the phage repertoire rescued essentially as previously described in detail (Finlay *et al.*, 2011, Methods Mol Biol 681: 383-401).

15 Phage selections were performed by coating streptavidin magnetic microbeads with biotinylated PD1 target protein (either human or cyno), washing the beads thrice with PBS and resuspending in PBS pH7.4 plus 5% skim milk protein. These beads were coated at 100 nM target protein in round 1 of selection, followed by reduced antigen concentrations in three successive rounds. In each round, phage were eluted using trypsin before re-infection into
20 TG1 cells.

Periplasmic extracts production (small-scale)

Production of soluble Fabs in individual *E. coli* clones was performed. *E. coli* TG1 cells in logarhythmic growth phase were induced with isopropyl 1-thio- β -D-galactopyranoside.
25 Periplasmic extracts containing soluble Fab were generated by a freeze/thaw cycle: BacteriaL cell pellets were frozen at -20 °C for overnight and then thawed at room temperature and resuspended in PBS pH 7.4. The supernatants containing the soluble Fab were collected after shaking at room temperature and centrifugation.

30 IgG expression and purification

Mammalian codon-optimized synthetic genes encoding the heavy and light chain variable domains of the lead panel anti-PD1 antibodies plus the Mu317 and hu317 were cloned into mammalian expression vectors comprising effector function null human IgG1 ('IgG1null'; human IgG1 containing L234A, L235A, G237A mutations in the lower hinge that abrogate
35 normal immunoglobulin Fc γ R interactions) and human C κ domains, respectively. Co-transfection of heavy and light chain containing vector in mammalian expression system was

performed, followed by protein A-based purification of the IgG, quantification and QC on denaturing and non-denaturing SDS-PAGE.

Direct binding ELISA for Fab and IgG

5 Binding and cross-reactivity of the lead panel to the recombinant proteins was initially assessed by binding ELISA. The human PD1 human Fc tagged recombinant protein and the cynomolgus monkey PD1 human Fc tagged recombinant protein were coated to the surface of MaxiSorp™ flat-bottom 96 well plate at 1 µg/ml. The Fab samples were applied at 1:5
10 serial dilutions starting from 500 nM to 0.98 nM and allowed to bind to the coated antigens. The Fabs were detected using mouse anti-c-myc antibody followed by donkey anti-mouse IgG conjugated to horseradish peroxidase. The IgGs were detected using the mouse anti-human IgG conjugated to horseradish peroxidase. Binding signals were visualized with 3,3',5,5'-Tetramethylbenzidine Substrate Solution (TMB) and the absorbance measured at
15 450 nm.

Alphascreen epitope competition assay for IgG1null antibodies

The AlphaScreen assay (Perkin Elmer) was performed in a 25 µl final volume in 384-well white microtiter plates (Greiner). The reaction buffer contained 1xPBS pH 7.3 (Oxoid, Cat.
20 nr. BR0014G) and 0.05 % (v/v) Tween® 20 (Sigma, Cat. nr. P9416). Purified IgG samples were titrated in three fold serial dilutions starting at 500 nM final concentration and incubated with biotinylated human PD1-His/AviTag at 0.6 nM final concentration for 20 minutes at room temperature. The parental IgG at 0.3 nM and the anti-human IgG1 Acceptor beads at 20 µg/ml (final concentrations) were added and the mix was incubated for 1 hour at room
25 temperature. Followed by addition of the Streptavidin Donor beads at 20 µg/ml (final concentration) and incubation for 30 minutes at room temperature. The emission of light was measured in the EnVision multilabel plate reader (Perkin Elmer) and analysed using the EnVision manager software. Values were reported as Counts Per Second (CPS) and corrected for crosstalk.

30

Flow cytometry of IgGs

Purified IgGs were tested in FACs for binding to CHO-K1 stable cell lines expressing human (Genscript, Cat. nr. M00529), and cyno (Genscript, Cat. nr. M00572) PD1, and CHO-K1 wild-type cells. The IgG samples were titrated in three-fold serial dilutions starting at 500 nM to
35 0.98 nM. Binding of IgGs was detected with a mouse anti-human IgG conjugated to FITC. Results were analyzed by examining the Mean Fluorescence Intensity (MFI) of 10000 cells per sample in the BL-1 channel detector of a flow cytometer (Attune™ NxT Acoustic

Focusing Cytometer, Invitrogen/ ThermoFisher Scientific). The EC50 values were calculated using the MFI values in GraphPad Prism software (GraphPad Software, La Jolla, CA) and 4 parameters.

5 **PD1/PD-L1 cell-based antagonism assay**

The PD1/PD-L1 blockade cell-based bioassay (Promega), was used to measure the potency of antibodies in blocking the PD1/PD-L1 interaction. On the day before the assay, PD-L1 aAPC/CHO-K1 cells were thawed and transferred into cell recovery medium (90% Ham's F12/10% FBS). The cell suspension was dispensed to each of the inner 60 wells of two 96-
10 well, white, flat-bottom assay plates, at 100 µl per well. Cell recovery medium was added to each of the outside wells and the assay plates and incubated overnight at 37 °C/5% CO₂. On the day of the assay the sample IgGs were diluted 4-fold in assay buffer (99% RPMI 1640/1% FBS) from 300 nM to 0,04 nM and 40 µl per dilution added to the assay plates containing the PD-L1 aAPC/CHO-K1 cells. Positive inhibition controls included the human
15 PD1 Antibody AF1086 (R&D systems), mu317 in IgG1 null form and a pembrolizumab mab analogue in IgG1 null form. As a negative inhibition control, an irrelevant IgG was included. PD1 Effector Cells were then thawed in assay buffer (99% RPMI 1640/1% FBS) and the cell suspension added to the wells of the assay plates containing the PD-L1 aAPC/CHO-K1 cells and the IgG titration samples. The assay plates were incubated for six hours in a 37 °C/5 %
20 CO₂ incubator, allowed to equilibrate to ambient temperature for 5–10 minutes, then 80 µl of Bio-Glo™ Reagent (Promega) was added. Assay plates were incubated at ambient temperature for a further 5–30 minutes and luminescence signals subsequently measured at 10, 20 and 30 minutes.

25 **Allogeneic mixed leucocyte reaction (MLR) assay**

Human PBMCs from healthy donors were prepared from buffy coats. Immature monocyte-derived dendritic cells (Mo-DCs) were prepared by isolating CD14+ cells using magnetic-activated cell sorting (MACs, Stemcell) and cultured with differentiation medium (Miltenyi) for 7 days. At the end of this 7-day period the Mo-DCs were classed as 'immature' and are ready
30 to use in an immature MLR. Responder T cells (using cryopreserved PBMCs) were prepared on the day required, from a different donor to that used for the Mo-DCs, using a T cell isolation kit (Stemcell). Under each experimental condition (immature and MoDCs) 6 separate MLRs were performed to provide biological variation, all conditions were prepared in technical triplicate. Cells were co-cultured: 1x10⁴ Mo-DC and 1x10⁵ CD4+ T cell per well
35 +/- test IgG antibodies for 4 days. Single cell type (T cell/Mo-DC) controls were included in each assay. Supernatants were collected at the end of culture period and assessed for IFN-γ by ELISA.

Charge variant Analyses

Charge variant profiling of test articles was determined by Protein Charge Variant Assay on a LabChip GXII Touch HT (PerkinElmer, Beaconsfield, UK), according to the manufacturer's protocol.

5

DSC Analyses

The T_m of test articles was analysed using a MicroCal PEAQ-DSC (Malvern Instruments, Malvern, UK) running version 1.22 software. The samples were heated at a rate of 200 °C/hour over a range of 20-110 °C. Thermal data was normalised based on protein concentration. The T_m of the protein was determined from the heating scan data.

10

Forced Oxidation Analyses

For forced oxidation analysis, test articles in PBS were treated with 0.5 % H₂O₂ at room temperature for 2 hours and then stored at - 80 °C prior to SEC, HIC and RP analysis (intact antibodies and subunits) on a Dionex Ultimate 3000RS HPLC system (ThermoFisher Scientific, Hemel Hempstead, UK), as detailed below. For intact antibody reduction, DTT was added to a final concentration of 0.33 M and samples were incubated for 1 hour at room temperature and immediately analysed by RP.

15

RP analysis of intact antibodies and subunits - Chromatographic separation was performed using a PLRP-S 1000, 5 µm, 2.1mm x 50 mm column (Agilent Technologies, Stockport, UK) connected to a Dionex Ultimate 3000RS HPLC system (ThermoFisher Scientific, Hemel Hempstead, UK). The method consisted of a linear gradient from 75% buffer A (0.075% TFA, 7.5% acetonitrile in H₂O) to 50% buffer B (0.075% TFA, 7.5% H₂O in acetonitrile) for mAbs 1-4, or 90% buffer B for mAb 5, over 24 minutes. The flow rate was 0.5 mL/minute and the temperature was maintained at 70°C throughout the analysis. Detection was carried out by UV absorption at 280 nm.

25

SEC Analysis - Chromatographic separation was performed using an Acquity UPLC Protein BEH SEC Column, 200Å, 1.7 µm, 4.6 mm X 150 mm (Waters, Elstree, UK) and an Acquity UPLC Protein BEH SEC guard column 30 x 4.6 mm, 1.7 µm, 200 Å (Waters, Elstree, UK) connected to a Dionex Ultimate 3000RS HPLC system (ThermoFisher Scientific, Hemel Hempstead, UK). The method consisted of an isocratic elution over 15 minutes and the mobile phase was 0.2 M potassium phosphate pH 6.8, 0.2 M potassium chloride. The flow rate was 0.25 mL/minute. Detection was carried out by UV absorption at 280 nm.

30

HIC Analysis - Chromatographic separation was performed using a TSKgel Butyl-NPR 4.6 mm x 35 mm HIC column (TOSOH Bioscience Ltd., Reading, UK) connected to a Dionex Ultimate 3000RS HPLC system (ThermoFisher Scientific, Hemel Hempstead, UK). The method consisted of a linear gradient from 60% Buffer A (100 mM sodium phosphate pH 7.0,

35

2 M ammonium sulphate) to 90% Buffer B (100 mM sodium phosphate pH 7.0) over 9 minutes. The flow rate was 1.2 mL/minute. Detection was carried out by UV absorption at 280 nm.

5 **Antibody v-domain specificity testing: human receptor array analyses**

Human cell membrane receptor proteome arrays were performed at Retrogenix Ltd. Primary screens: 2 µg/ml of each antibody was screened for binding against fixed HEK293 cells/slides expressing 5528 human plasma membrane and tethered secreted proteins individually. All transfection efficiencies exceeded the minimum threshold. Antibody binding
10 was detected using AF647 fluorescent secondary anti-human IgG1 antibody. Primary hits (duplicate spots) were identified by analysing fluorescence (AF647 and ZsGreen1) on ImageQuant. Confirmation/specificity screens: Expression vectors encoding ZsGreen1 only, or ZsGreen1 and CD20, PD1, BTN2A1, or LSAMP were transfected into human HEK293 cells. Each live transfectant was incubated with 2 µg/ml of each of the test antibodies, the
15 positive control antibody Rituximab, or no primary antibody. Cells were washed, and incubated with the same AF647 anti-human IgG Fc detection antibody as used in the cell microarray screens. Cells were again washed, and analysed by flow cytometry using an Accuri flow cytometer (BD). A 7AAD live/dead dye was used to exclude dead cells, and ZsGreen1-positive cells (i.e. transfected cells) were selected for analyses.

20

Results and Discussion

CDR grafting onto preferred human germline v-genes

The CDRs of an agonistic murine anti-PD1 IgG Mu317 (WO2015/035606 A1 and Table 2)
25 were initially introduced to human germline immunoglobulin v-domain framework sequence scaffolds using CDR grafting. To bias our engineering efforts towards final lead therapeutic IgG compounds with optimal drug-like properties, we chose to graft the CDRs of the parental antibody onto "preferred" germline scaffolds IGHV3-7 and IGKV4-1, which are known to have good solubility and drug development qualities, and are used at high frequency in the
30 expressed human antibody repertoire.

Those scaffolds and grafted CDR definitions are outlined in Table 2. The heavy and light chain sequences for hu317 anti-PD1 antibody are also shown in Table 2. While this process of CDR grafting is well known, it is still problematic to predict whether a given set of human
35 v-domain sequences will act as suitable acceptor frameworks for non-human CDR grafting. The use of unsuitable frameworks can lead to the loss of target binding function, protein stability issues or even impaired expression of the final IgG. The IGHV3-7/IGKV4-1 graft was

therefore taken forward as the template for CDR mutagenesis and selection of improved clones.

Library generation and screening

5 The CDR-grafted IGHV3-7/IGKV4-1 v-domain sequences were combined into a Fab phage display format and a mutagenesis library cassette was generated by oligo synthesis and assembly. Two separate Fab libraries were initially constructed that sampled mutational diversity in either the heavy or light chain v-domain sequences in combination with the cognate paired grafted v-domain. Both VH and VL libraries were separately ligated into a
10 phage display vector and transformed into *E. coli* via electroporation to generate 3.15×10^9 and 2.27×10^9 independent clones, respectively. Library build quality was verified by sequencing 96 clones per library. This sequencing data showed that the positions encoding either the murine or human germline residue at each position of variance had been effectively sampled at a frequency of approximately 50% and that positions sampled with non-binary
15 amino acid content sampled the position in question with the intended amino acids. Libraries were rescued using helper phage M13 and selections performed on biotinylated human and cynomolgus monkey PD1-Fc proteins. After an initial round of selection, the two pools of mutated VH and VL domains were recombined into a secondary library and three further rounds of standard selection, plus two 'hammer-hug' rounds performed.

20 Post-selection screening (Fig. 1A, 1B) and DNA sequencing revealed the presence of 712 Fab clones that exhibited strong binding to human and cyno PD1 in ELISA and >50% inhibition of Mu317 IgG1 binding to human and cyno PD1 in Alphascreen assay. Amongst these 712 clones, germlining mutations were observed in all CDRs (Table 3). Lead clones
25 were ranked based on level of CDR germ-lining versus ELISA signals for binding to both human and cyno PD1-Fc. The v-domains of the 7 top clones from this ranking were then sub-cloned into IgG expression vectors for further testing as below (Table 4).

30 While germ-lining mutations were observed in all CDRs for the lead clones derived directly from library selections, it remained possible that sequence analyses might allow further clones to be designed to have maximal humanization. The 712 hits with binding signals against human and cyno protein were therefore used to analyse the retention frequency for murine amino acids in the CDRs of this functionally characterized population. Positional amino acid retention frequency was expressed as a percentage found in the V_L and V_H
35 domains (Fig. 2A, 2B). Murine residues with RF < 75% were regarded as positions that are possibly not essential to the target-binding paratope and are likely to be open to germ-lining, in a series of combinatorial designs (Table 4). In the V_H domain (excluding the CDR-H3),

only 5 of 15 murine residues in the CDR-H1 and H2 exhibited retention frequency above 75% (Fig. 2B). In the V_L domain, only 6 of 12 murine CDR residues derived from the Mu317 sequence were retained with frequencies >75% (Fig. 2A). This analysis strongly suggested that the LCDR1 and LCDR3 sequences could be rendered close to germline identity to
5 IGKV4-1.

Designs containing combination of those murine residues with RF > 75% were given the prefix "MH" (MH = Maximally Humanized). In total 12 initial designer V_H and V_L designer domain combinations were generated: MH1-MH12 (Table 4). The MH clones were generated
10 by gene synthesis and (along with the 7 library-derived clones outlined above and positive controls Mu317 and hu317), cloned into human expression vectors for production in IgG1 null format. All IgGs were readily expressed and purified from transient transfections of mammalian cells.

15 **Lead IgG specificity and potency characteristics**

The purified IgGs described above were then tested for binding to human and cyno PD1-Fc in direct titration ELISA format. This analysis demonstrated that all library-derived clones and a select subset of designer clones (MH4, MH8, MH12) had human and cyno PD1 binding profiles similar to, or improved over, Mu317 (Fig. 3A, 3B). The majority of designer clones
20 (MH1, MH2, MH3, MH5, MH6, MH7, MH9, MH19, MH11) exhibited reduced binding to one or both orthologs of PD1, demonstrating that the mutations found in these clones are disruptive to binding when used in combination. This finding highlighted the inability to predict precisely which combinations of mutations will lead to an optimal outcome, even in the possession of the mutational map outlined in Figs 2A and 2B.

25 An Alphascreen assay was established to allow the testing of designer IgGs for PD1 binding affinity and epitope competition with mu317 IgG binding to biotinylated monomeric human PD1. In this assay, while all 3 clones exhibited full epitope competition with Mu317, clone MH8 exhibited an IC₅₀ value closest to mu317 (mu317 – 0.37 nM, MH8 – 0.39 nM, MH12
30 0.624 nM, MH4, 0.630 nM).

Flow cytometric analyses of lead IgG binding specificity at the cell membrane

Antibodies to PD1 were analysed for concentration-dependent binding at the cell surface via flow cytometry. Initial analyses were performed on CHO cells stably-transfected with
35 human or cyno PD1. These analyses showed that lead library-derived and designer clones exhibit concentration-dependent binding to membrane-presented human or cyno PD1 (Fig.

4A, 4B) with potencies similar to, or improved over, the hu317. No binding signals were observed for any clone, even at the highest concentrations, on untransfected CHO cells.

Lead IgG analyses in PD1-PDL1 blockade assay

5 In a cell-based PD1/PD-L1 blockade reporter assay, all clones tested exhibited concentration-dependent antagonism of PD1. Lead clones MH4, MH8, MH12, 09C06, 17A12 and 20C07 demonstrated fold induction curves and maximal signal values highly similar to mu317 (Fig. 5). Maximally humanized clones MH4, MH8 and MH12 (Fig 6A, 6B, 6C, respectively) were then re-examined in this assay, being run alongside both mu317 and
10 hu317 IgG1. These analyses showed that these three clones had fully maintained the potency of both mu317 and hu317, with concentration-dependent fold induction curves that are overlapping.

Antibody v-domain T cell epitope analyses

15 *In silico* technologies (Abzena, Ltd.), which are based on identifying the location of T cell epitopes in therapeutic antibodies and proteins, were used for assessing the immunogenicity of both the Hu317 and lead antibody v-domains. Analysis of the v-domain sequences was performed with overlapping 9mer peptides (with each overlapping the last peptide by 8 residues) which were tested against each of the 34 MHC class II allotypes.
20 Each 9mer was scored based on the potential 'fit' and interactions with the MHC class II molecules. The peptide scores calculated by the software lie between 0 and 1. Peptides that produced a high mean binding score (>0.55 in the iTope™ scoring function) were highlighted and, if >50% of the MHC class II binding peptides (i.e. 17 out of 34 alleles) had a high binding affinity (score >0.6), such peptides were defined as 'high affinity' MHC class
25 II binding peptides which are considered a high risk for containing CD4+ T cell epitopes. Low affinity MHC class II binding peptides bind a high number of alleles (>50%) with a binding score >0.55 (but without a majority >0.6). Further analysis of the sequences was performed using the TCED™. The sequences were used to interrogate the TCED™ by
30 BLAST search in order to identify any high sequence homology between peptides (T cell epitopes) from unrelated proteins/antibodies that stimulated T cell responses in previous *in vitro* T cell epitope mapping studies performed at Abzena Ltd.

Peptides were grouped into four classes: High Affinity Foreign ('HAF' – high immunogenicity risk), Low Affinity Foreign ('LAF' – lower immunogenicity risk), TCED+
35 (previously identified epitope in TCED™ database), and Germline Epitope ('GE' - human germline peptide sequence with high MHC Class II binding affinity). Germline Epitope 9mer peptides are unlikely to have immunogenic potential due to T cell tolerance, as validated by

previous studies with a wide range of germline peptides. Importantly, such germline v-domain epitopes (aided further by similar sequences that are found in the human antibody constant regions) also compete for MHC Class II occupancy at the membrane of antigen presenting cells, reducing the risk of foreign peptide presentation being sufficient to
5 achieve the 'activation threshold' required for T cell stimulation. High GE content is therefore a beneficial quality in clinical development of an antibody therapeutic.

As shown in Figure 7 and Table 5, key lead v-domains exhibited significant beneficial changes in peptide epitope content in comparison to Hu317. As the v-domain engineering
10 process undertaken here had successfully selected for antibodies that maintained anti-PD1 potency while humanizing a significant number of the murine residues included in the CDRs of Hu317 (Table 2), multiple HAF and LAF epitopes found in the v-domains of Hu317 (Fig. 7A) were absent in library-derived and designer leads (Table 5). Unexpectedly, GE epitope content was found to be significantly increased (from 5 to ≥ 14 in all leads),
15 particularly in the VH regions of lead clones (Fig. 7B-H), and TCED+ epitopes were reduced in all leads (Table 5). The marked improvements in immunogenicity risk in the VH domain were mediated specifically by adapting the CDRs of Hu317 to fit the IGHV3-7 germline, which we have now shown (for the first time) contains more GE epitopes in its frameworks than are found in the IGHV4-4 VH grafted Hu317 frameworks. For example,
20 the germlining of the last 7 residues of the HCDR2 sequence to match IGHV3-7 (YVDSVKG (SEQ ID NO:80) in all lead clones, Table 4) allowed a GE to be restored that spans the c-terminal HCDR2 and n-terminal framework 3 regions (VKGRFTISR (SEQ ID NO:81)). In addition, mutation of the HCDR1 sequence from 'GFSLTSYGVH' (SEQ ID NO:82) to the sequence 'GFTFSSYGMH' (SEQ ID NO:57) (found in clones 09C06, 17A12, 17D08, 17G08 and 15D07) not only ablated the LAF sequence 'LTSYGVHWI' (SEQ ID
25 NO:83) which spans the HCDR1 and framework 2 regions of Hu317, but also rendered this CDR fully germline identity to the human v-genes IGHV3-33 and IGHV3-30-5. The HCDR1 sequence 'GFTFSSYGMS' (SEQ ID NO:33) (found in clones 20C07 and all designer clones MH1-MH18, Table 4) also ablated the LAF sequence 'LTSYGVHWI' (SEQ ID
30 NO:83). Both humanized CDR1 sequences encoded a GE peptide sequence 'YGM(H/S)WVRQA' (SEQ ID NO:84) that was not found in either Hu317 or the library-derived clone 11C08, due to the presence of the residue valine in their HCDR1s at position 9 (e.g. GFSLTSYGVH (SEQ ID NO:82)).

35 Importantly, multiple foreign epitopes were also eliminated by germlining mutations found in the other CDRs of lead clones. For example, a TCED+ and LAF peptide 'YWYIDVWQG' (SEQ ID NO:85) which spans the HCDR3 and framework 4 of Hu317 was eliminated in the

majority of lead clones by the mutation V>R at position 6 (Table 4). Similarly, in clones MH1-MH18 and 09C06, the HAF peptide 'LEWIGVIYA' (SEQ ID NO:86) and LAF peptide 'IGVIYADGS' (SEQ ID NO:87) which are both found in Hu317 were simultaneously ablated by mutation of the residues 'IGV' to 'VAN' (Table 4, Table 5). A HAF peptide
5 'LEWVGVIWQ' (SEQ ID NO:88) was found in the VH domain of clone 11C08, which overlaps with the 'LEWIGVIYA' (SEQ ID NO:86) HAF from Hu317, while the LAF peptide 'IGVIYADGS' (SEQ ID NO:87) was ablated. In clone 17A12, the 'LEWIGVIYA' (SEQ ID NO:86) HAF from Hu317 was partially ablated, by mutation to the LAF peptide 'LEWLANIWQ'.

10

In the VL region of Hu317 and all leads, the total balance of GE versus foreign epitopes was not increased (FIG. 7, TABLE 5), despite the introduction of the mutations outlined above that ablated the oxidation risk in the LCDR2 by mutating the F at position 3 of the LCDR2 (YAE_HRFT (SEQ ID NO:31)). In total, the immunogenicity findings outlined above
15 demonstrated that through extensive, yet unpredictable germlining of multiple CDR positions in the VH domain (specifically into the IGHV3-7 framework), the lead antibodies achieved the removal of several significant high-risk human t cell epitope peptide sequences and acquired several GEs with the potential to reduce immunogenicity, greatly improving the ratio of GE to foreign epitopes.

20

Lead IgG potency in MLR assay

The aim of this study was to characterise the potency of lead PD-1 targeted antibodies in a human allogeneic MLR, by measurement of IFN- γ in the culture supernatants. In control conditions (Fig. 8A) the cytokine levels demonstrated that a Nivolumab analog significantly
25 increased IFN- γ levels compared to isotype control human IgG4. Isotype showed no difference compared to cells only, and the single cell conditions showed little to no measurable cytokine.

As all controls had demonstrated the expected signals, clones 09C06, MH4, MH8 and MH12
30 were examined for activity in the assay. The four test antibodies were used at three concentrations (0.1, 1 and 10 μ g/mL) and compared to the appropriate isotype control, human-IgG1. All four test antibodies significantly increased IFN- γ production within the cell culture supernatants in a dose- dependent manner (Fig. 8B). The data shows that all four test antibodies provided could enhance IFN- γ production in an allogeneic MLR when
35 compared to hIgG1. Finally, clones Hu317, MH4 and MH8 were tested in the assay across a wide concentration range (Fig. 8C). This analysis demonstrated that both clones MH4 and

MH8 retained fully overlapping concentration-dependent activity with Hu317 in a relevant human *ex-vivo* potency assay.

Charge variant Analyses

5 Charge heterogeneity analysis is used widely in the characterisation of monoclonal antibodies because it provides important information about product quality and uniformity. Heterogeneity can be caused by enzymatic post-translational modifications such as glycosylation, lysine truncation, oxidation or deamidation. Heterogeneity in IgGs is a manufacturing risk and can cause increased complexity in bioprocessing protocols.

10

The Protein Charge Variant Assay allows identification of basic and acidic protein variants relative to the dominant product peak. The microfluidics chip technology resolves protein charge variants after fluorescent labelling. The charge variant profiles for 09C06, MH4, MH8 MH12 and hu317 IgGs are depicted in Figure 9. All of mAbs 09C06, MH4, MH8 and MH12 display a highly homogeneous profile, with the main isoform comprising 77.4-82.8% of the total protein (Table 6). In contrast, however, Hu317 showed an unexpectedly more complex profile with 4 distinct peaks, a higher percentage of basic isoforms (23.1%) and with the main isoform representing < 69% of total. These significant improvements in charge homogeneity for clones 09C06, MH4, MH8 and MH12 over Hu317 were not immediately explained by the removal of potential post-translational modification sites in the CDRs of the lead IgGs, as any potential o-link glycosylation, deamidation or isomerisation sites in the CDRs were maintained and no n-link glycosylation sites had been introduced (Tables 2 and 4). As such improved homogeneity could also be caused by improvements in thermal stability, or improved resistance to oxidation, we investigated those characteristics.

25

Thermal Stability Evaluation Using DSC

A protein's DSC profile provides information about its total structural stability, via its thermal stability, but can also represent a structural 'fingerprint' for assessing structural modifications. The thermogram of an intact antibody could present two or three peaks, with the largest peak containing the contribution from the Fab fragment. Usually the first transition covers the unfolding of the CH2 domain, while the last one would include the unfolding of the CH3 domain. The Fab unfolding could occur at a distinct temperature compared to the unfolding of CH2 and CH3 domains, but it is also possible that the Fab fragment unfolding 'buries' the unfolding of either CH2 or CH3 domains, resulting in peak overlap. As the constant domains are virtually identical for antibodies of the same subclass, the CH2 and CH3 domains should have comparable T_m , while the Fab's T_m will vary from antibody to antibody.

35

All five IgGs tested (09C06, MH4, MH8, MH12 and Hu317) were fully compatible with DSC analysis and gave good resolution data (Fig. 10), presenting comparable sample homogeneity and cooperativity. In Figure 10A (09C06 IgG), the first transition represents CH2 domain unfolding, the second transition represents the unfolding of the Fab fragment and the third transition represents CH3 domain unfolding. For clones MH4, MH8 and MH12, the major Fab transition is lower, overlapping with the CH2 domain (Fig. 10B-D). For clone Hu317, the Fab domain transition is actually higher and overlapping with the CH3 (Fig. 10E). Overall, the Fab unfolding T_m values demonstrated that the v-domains of lead clones 09C06, MH4, MH8 and MH12, while still relatively stable, were actually reduced in overall stability in comparison to those of Hu317 (Table 7).

Forced Oxidation Analyses

Oxidation of exposed amino acid residues, such as tryptophan and methionine is a common degradation pathway for mAbs, altering their structural integrity with potential impact on their biological activity and heterogeneity. In this study, forced oxidation using 0.5% H₂O₂ for 2 hours at room temperature was applied to IgGs 09C06, MH4, MH8, MH12 and Hu317. As oxidation can alter overall hydrophobicity of an antibody, either by increasing the polarity of the oxidised form or through conformational changes, potential changes induced by forced oxidation were analysed by Size Exclusion (SEC), Reverse Phase (RP) and Hydrophobic Interaction (HIC) Chromatographies.

SEC analysis - No significant changes in SEC profile, induced by forced oxidation, were observed for any of the five IgGs, with higher molecular weight isoforms remaining below 0.6% of total protein (Table 8).

RP analysis - No significant changes in the retention time of intact mAbs (non-reduced and reduced) were observed upon H₂O₂ treatment, implying minimal oxidation of exposed amino acids (Table 8).

HIC analysis - H₂O₂ treatment induced only a minor (0.4-0.6) minutes decrease in the retention on HIC for all 5 test articles, implying limited oxidation of exposed amino acids (Table 8).

Together, these data confirmed that the lead IgGs 09C06, MH4, MH8 and MH12 did not exhibit improved stability or reduced oxidative degradation potential in comparison to Hu317 and that neither stability changes nor changes in post-translational CDR modification motifs were responsible for the observed improvements in charge homogeneity.

Antibody binding specificity analyses

To examine the proteomic selectivity of Hu317 and clones MH4, MH8 and MH12, *in vitro* technologies (Retrogenix, Ltd.), which are based on using high-density arrays of cells expressing 5528 unique human membrane receptors and tethered secreted proteins, were used to screen for off-target binding specificities in purified IgG form. This receptor array binding screen identified that Hu317 exhibited strong binding to membrane-expressed PD1 exclusively, with no measurable binding to any other proteins (Table 12). In contrast, clones MH4, MH8 and MH12 also exhibited very limited signals, with strongest signal for PD1, but also had 2 potential new binding specificities: BNT2A1 (accession number NM_007049) and LSAMP (BC033803). MH12 was the only clone to show any binding signal to BNT2A1. To examine these findings with an orthogonal, high-sensitivity assay, the plasmids encoding for CD20, PD1, BTN2A1, LSAMP, and ZS green only (negative control) were used to perform transient transfection of the human cell line HEK293. Transfected cells were then stained using Hu317, MH4, MH8, MH12 and Rituximab IgGs. In staining of PD1-transfected cells at 2 µg/ml, all tested antibodies other than the Rituximab and secondary only controls showed the expected strong, specific staining of PD1-transfected cells but not ZS green-transfected (Fig. 11). Hu317 IgG showed no binding to any cells other than PD1-transfected cells, confirming the findings of the chip analyses, where this IgG was fully PD1 selective. Rituximab positive control exhibited strong, specific staining of CD20-transfected cells and the negative control (secondary labelled antibody only) exhibited no binding to any cells (Fig. 11). In contrast, only clones MH8 and MH12 exhibited clear binding signal on both PD1 and LSAMP, but no binding of BTN2A1, both in histogram analysis (Fig. 11) and in median fold-change of mean fluorescence measurements over ZSgreen-only transfected cells (Table 13). This unexpected, newly-acquired, reactivity to a single new protein in the human receptor proteome for clones MH8 and MH12 may be of potential therapeutic benefit, as LSAMP is a cell surface receptor whose expression has been shown to be upregulated in specific tumour types such as Acute Myeloid Leukaemia (Coccaro, N. *et al.* Cancer Genetics 2015, 208(10):517-522) and may therefore be of value in co-targeting along with PD1.

Although the present invention has been described with reference to preferred or exemplary embodiments, those skilled in the art will recognize that various modifications and variations to the same can be accomplished without departing from the spirit and scope of the present invention and that such modifications are clearly contemplated herein. No limitation with respect to the specific embodiments disclosed herein and set forth in the appended claims is intended nor should any be inferred.

All documents, or portions of documents, cited herein, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose. In the event that one or more of the incorporated documents or portions of documents define a term that contradicts that term's definition in
5 the application, the definition that appears in this application controls. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as an acknowledgment, or any form of suggestion, that they constitute valid prior art or form part of the common general knowledge in any country in the world.

Table 1. Amino acid sequences murine anti-PD1 CDRs as defined here (“Unified” scheme) in comparison to alternative definitions.

<u>Scheme</u>	<u>HCDR1</u>	<u>HCDR2</u>	<u>HCDR3</u>	<u>LCDR1</u>	<u>LCDR2</u>	<u>LCDR3</u>
Unified	GFSLTSYGVH (SEQ ID NO:89)	LGVWAGGSTNYSALMS (SEQ ID NO:94)	AYGNYWYIDV (SEQ ID NO:101)	KASQSVSNDVA (SEQ ID NO:105)	YAFHRFT (SEQ ID NO:109)	HQAYSSPYT (SEQ ID NO:111)
Kabat	SYGVH (SEQ ID NO:90)	VIWAGGSTNYSALMS (SEQ ID NO:95)	AYGNYWYIDV (SEQ ID NO:101)	KASQSVSNDVA (SEQ ID NO:105)	YAFHRFT (SEQ ID NO:109)	HQAYSSPYT (SEQ ID NO:111)
Chotia	GFSLTSY (SEQ ID NO:91)	WAGGST (SEQ ID NO:96)	AYGNYWYIDV (SEQ ID NO:101)	KASQSVSNDVA (SEQ ID NO:105)	YAFHRFT (SEQ ID NO:109)	HQAYSSPYT (SEQ ID NO:111)
IMGT	GFSLTSYG (SEQ ID NO:92)	IWAGGSTN (SEQ ID NO:97)	ARAYGNYWYIDV (SEQ ID NO:102)	QSVSND (SEQ ID NO:106)	YAF (SEQ ID NO:111)	HQAYSSPYT (SEQ ID NO:111)
AHO	GFSLTSYGVH (SEQ ID NO:89)	IWAGGSTNYSALMS (SEQ ID NO:98)	AYGNYWYID (SEQ ID NO:103)	ASQSVSND (SEQ ID NO:107)	YAFHRFT (SEQ ID NO:109)	AYSSPY (SEQ ID NO:112)
AbM	GFSLTSYGVH (SEQ ID NO:89)	VIWAGGSTNY (SEQ ID NO:99)	AYGNYWYIDV (SEQ ID NO:101)	KASQSVSNDVA (SEQ ID NO:105)	YAFHRFT (SEQ ID NO:109)	HQAYSSPYT (SEQ ID NO:111)
Contact	TSYGVH (SEQ ID NO:93)	LGVWAGGSTNY (SEQ ID NO:100)	ARAYGNYWYID (SEQ ID NO:104)	SNDVAMY (SEQ ID NO:108)	LLIYYAFHRF (SEQ ID NO:110)	HQAYSSPY (SEQ ID NO:113)

Table 2. Amino acid sequence of MU317 murine anti-PD1 v-domains (mVH/mVL) and human germline CDR grafts (VH1/VL1).

V DOMAIN	Human germline¹	Amino acid sequence²
Mu317 VH	n/a	QVQLKESGPGILVAPSKNLSITCTVS GFSLTISYGVH WIRQPPGKGLLEW LGVIWAGGS TNYSALMSRLSISKDNRSSQVFLRMNSLQTDITAMYICAR AYGNIWYIDV WGAGTTVTVSS (SEQ ID NO:114)
Hu317 VH	IGHV4-4	QVQLQESGPGILVQPKSETLSTCTVS GFSLTISYGVH WIRQPPGKGLLEW IGVIYADGS TNINP SLKSR VTIISKDTSKNQVSLKLSSTAAADTAVYYICAR AYGNIWYIDV WGQGTITVTVSS (SEQ ID NO:115)
VH GRAFT	IGHV3-7 ³	EVQLVESGGGLVQPGGSLRSLSCAAS GFSLTISYGVH WVRQAPGKGLLEW LGVIWAGGS TNIN DSVKG RFTISRDNAKNSLYLQMNLSLRAEDTAVYYICAR AYGNIWYIDV WGQGTITVTVSS (SEQ ID NO:116)
Mu317 VL	n/a	DIVMTQTPKELLVSAQDRVTIT KAASQSVSNDVA WYQQKPGQSPKLLIN YAFHREF TGVPDRFTGSGYGTDFIFTITVQAEEDLAVYFC HQAYS SPYTFGGGTKLEMK (SEQ ID NO:117)
Hu317 VL	IGKV4-1	DIVMTQSPDLSIAVSLGERATIN CKSESVSNDVA WYQQKPGQPPLKLLIN YAFHREF TGVPDRFSGSGYGTDFLTITSSIQAEEDVAVYYC HQAYS SPYTFGGGTKLEIK (SEQ ID NO:118)
VL GRAFT	IGKV4-1 ³	DIVMTQSPDLSIAVSLGERATIN CKSSQSVSNDVA WYQQKPGQPPLKLLIN YAFHREF TGVPDRFSGSGYGTDFLTITSSIQAEEDVAVYYC HQAYS SPYTFGGGTKLEIK (SEQ ID NO:119)

¹Human germline definitions used for grafting, based on IMGT system. ²CDR residues are in bold and underlined. As noted above, the “Unified” CDR definitions used in this manuscript are an expanded definition in comparison to the classical Kabat definition. Each sequence above shows the framework regions (FRs) and the CDRs in the following order: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. ³Grafts used for library construction.

Table 3. Unique CDRs from Fab clones shown to bind human and cyno PD1 proteins.

<u>HCDR1</u>	<u>HCDR2</u>	<u>HCDR2 contd</u>	<u>HCDR2 contd</u>	<u>HCDR2 contd</u>	<u>HCDR3</u>	<u>ICDR1</u>	<u>ICDR2</u>	<u>ICDR3</u>
GFNFSSYGMH (SEQ ID NO:120)	LANIKADGSEKYVDSVKG (SEQ ID NO:147)	LGNIKQGGSENYVDSVKG (SEQ ID NO:210)	VANIWQDGSINYVDSVKG (SEQ ID NO:233)	AFGNWYIDV (SEQ ID NO:337)	KSSQSVGNDLA (SEQ ID NO:397)	YAFHRES (SEQ ID NO:400)	HQAYSNPYT (SEQ ID NO:407)	
GFNFSSYGMH (SEQ ID NO:42)	LANIKADGSENYVDSVKG (SEQ ID NO:148)	LGNIKQGGSTKYVDSVKG (SEQ ID NO:211)	VANIWQGGSEKYVDSVKG (SEQ ID NO:275)	AWGNWYIDV (SEQ ID NO:338)	KSSQSVGNDLA (SEQ ID NO:398)	YAFHRET (SEQ ID NO:401)	HQAYSPT (SEQ ID NO:46)	
GFNFSSYGMS (SEQ ID NO:121)	LANIKADGSTKYVDSVKG (SEQ ID NO:149)	LGNIKQGGSTNYVDSVKG (SEQ ID NO:212)	VANIWQGGSTKYVDSVKG (SEQ ID NO:276)	AYGAYWYIDV (SEQ ID NO:339)	KSSQSVSNDLA (SEQ ID NO:399)	YAFHRFA (SEQ ID NO:402)	QQAYSPPYT (SEQ ID NO:75)	
GFNFSSYGVH (SEQ ID NO:122)	LANIKADGSTNYVDSVKG (SEQ ID NO:150)	LGNIWADGSEKYVDSVKG (SEQ ID NO:213)	VAVIKADGSTNYVDSVKG (SEQ ID NO:277)	AYGEIWIYIDV (SEQ ID NO:340)	KSSQSVGNDLA (SEQ ID NO:77)	YAFHRFS (SEQ ID NO:403)	QQAYSPT (SEQ ID NO:52)	
GFNFSSYGVH (SEQ ID NO:123)	LANIKAGGSEKYVDSVKG (SEQ ID NO:151)	LGNIWADGSEKYVDSVKG (SEQ ID NO:214)	VAVIKQDGSINYVDSVKG (SEQ ID NO:278)	AYGFYWIYIDV (SEQ ID NO:341)	KSSQSVGNDLA (SEQ ID NO:74)	YAFPRFT (SEQ ID NO:404)	QQYSPT (SEQ ID NO:408)	
GFNFSSYWMH (SEQ ID NO:124)	LANIKAGGSEKYVDSVKG (SEQ ID NO:152)	LGNIWADGSENYVDSVKG (SEQ ID NO:215)	VAVIKQDGSINYVDSVKG (SEQ ID NO:279)	AYGAYWYIDV (SEQ ID NO:342)	KSSQSVSNDLA (SEQ ID NO:51)	YAFTRFS (SEQ ID NO:405)		
GFNFSSYGMH (SEQ ID NO:59)	LANIKAGSENYVDSVKG (SEQ ID NO:153)	LGNIWADGSENYVDSVKG (SEQ ID NO:216)	VAVIKQDGSINYVDSVKG (SEQ ID NO:280)	AYGHIWIYIDV (SEQ ID NO:343)	KSSQSVSNDLA (SEQ ID NO:44)	YAFTRPT (SEQ ID NO:406)		
GFNFSSYGMS (SEQ ID NO:47)	LANIKQDGSSEKYVDSVKG (SEQ ID NO:154)	LGNIWADGSTKYVDSVKG (SEQ ID NO:217)	VAVIKQDGSINYVDSVKG (SEQ ID NO:281)	AYGIYWIYIDV (SEQ ID NO:344)	KSSQSVTNDVA (SEQ ID NO:36)	YASHRFS (SEQ ID NO:79)		
GFNFSSYGVH (SEQ ID NO:125)	LANIKQDGSSENYVDSVKG (SEQ ID NO:155)	LGNIWADGSTKYVDSVKG (SEQ ID NO:218)	VAVIWDGSEKYVDSVKG (SEQ ID NO:282)	AYGNVWIYIDV (SEQ ID NO:396)		YASHRFT (SEQ ID NO:45)		
GFNFSSYGVH (SEQ ID NO:126)	LANIKQDGSSTKYVDSVKG (SEQ ID NO:156)	LGNIWADGSTNYVDSVKG (SEQ ID NO:219)	VAVIWDGSENYVDSVKG (SEQ ID NO:283)	AYGNWYIYIDV (SEQ ID NO:345)		YAYHRET (SEQ ID NO:37)		
GFNFSSYWMH (SEQ ID NO:127)	LANIKQDGSSTKYVDSVKG (SEQ ID NO:157)	LGNIWADGSTNYVDSVKG (SEQ ID NO:220)	VAVIWDGSTKYVDSVKG (SEQ ID NO:284)	AYGNYFYIDV (SEQ ID NO:346)		YAYHRFS (SEQ ID NO:78)		
GFNFSSYGIS (SEQ ID NO:128)	LANIWDGSEKYVDSVKG (SEQ ID NO:158)	LGNIWADGSENYVDSVKG (SEQ ID NO:221)	VAVIWDGSTKYVDSVKG (SEQ ID NO:285)	AYGNYFYIDW (SEQ ID NO:347)				
GFNFSSYGMH (SEQ ID NO:129)	LANIWDGSEKYVDSVKG (SEQ ID NO:159)	LGNIWQDGSSEKYVDSVKG (SEQ ID NO:222)	VAVIWDGSTNYVDSVKG (SEQ ID NO:286)	AYGNHYIYIDV (SEQ ID NO:348)				

GFSLSSYGMS (SEQ ID NO:130)	LANIWADGSENNDVSVKG (SEQ ID NO:160)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:223)	VAVIWDQSGSEKYNDVSVKG (SEQ ID NO:287)	AYGNYMYIDV (SEQ ID NO:356)		
GFSLSSYGVH (SEQ ID NO:131)	LANIWADGSENNDVSVKG (SEQ ID NO:161)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:224)	VAVIWDQSGSENNDVSVKG (SEQ ID NO:288)	AYGNYFYIDV (SEQ ID NO:349)		
GFSLSSYGVH (SEQ ID NO:132)	LANIWADGSENNDVSVKG (SEQ ID NO:162)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:225)	VAVIWDQSGSENNDVSVKG (SEQ ID NO:289)	AYGNYQYIDV (SEQ ID NO:350)		
GFSLSSYGMH (SEQ ID NO:133)	LANIWADGSENNDVSVKG (SEQ ID NO:163)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:226)	VAVIWDQSGTKYNDVSVKG (SEQ ID NO:290)	AYGNYSYIDV (SEQ ID NO:351)		
GFSLSSYGMH (SEQ ID NO:134)	LANIWADGSENNDVSVKG (SEQ ID NO:164)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:227)	VAVIWDQSGTKYVDVSVKG (SEQ ID NO:291)	AYGNYVYIDV (SEQ ID NO:352)		
GFSLSSYGMH (SEQ ID NO:135)	LANIWADGSENNDVSVKG (SEQ ID NO:165)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:228)	VAVIWDQSGSTNYNDVSVKG (SEQ ID NO:292)	AYGNYWYADV (SEQ ID NO:353)		
GFSLSSYGMH (SEQ ID NO:136)	LANIWADGSENNDVSVKG (SEQ ID NO:166)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:229)	VAVIWDQSGSTNYVDVSVKG (SEQ ID NO:293)	AYGNYWYADV (SEQ ID NO:354)		
GFSLSSYGMH (SEQ ID NO:137)	LANIWADGSENNDVSVKG (SEQ ID NO:167)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:230)	VAVIWDQSGSTNYVDVSVKG (SEQ ID NO:294)	AYGNYWYADV (SEQ ID NO:355)		
GFSLSSYGMH (SEQ ID NO:138)	LANIWADGSENNDVSVKG (SEQ ID NO:168)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:231)	VAVIWDQSGSTNYVDVSVKG (SEQ ID NO:295)	AYGNYWYADV (SEQ ID NO:356)		
GFSLSSYGMH (SEQ ID NO:139)	LANIWADGSENNDVSVKG (SEQ ID NO:169)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:232)	VAVIWDQSGSTNYVDVSVKG (SEQ ID NO:296)	AYGNYWYADV (SEQ ID NO:357)		
GFSLSSYGMH (SEQ ID NO:140)	LANIWADGSENNDVSVKG (SEQ ID NO:170)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:233)	VAVIWDQSGSTNYVDVSVKG (SEQ ID NO:297)	AYGNYWYADV (SEQ ID NO:358)		
GFSLSSYGMH (SEQ ID NO:141)	LANIWADGSENNDVSVKG (SEQ ID NO:171)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:234)	VAVIWDQSGSTNYVDVSVKG (SEQ ID NO:298)	AYGNYWYADV (SEQ ID NO:359)		
GFSLSSYGMH (SEQ ID NO:142)	LANIWADGSENNDVSVKG (SEQ ID NO:172)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:235)	VAVIWDQSGSTNYVDVSVKG (SEQ ID NO:299)	AYGNYWYADV (SEQ ID NO:360)		
GFSLSSYGMH (SEQ ID NO:143)	LANIWADGSENNDVSVKG (SEQ ID NO:173)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:236)	VAVIWDQSGSTNYVDVSVKG (SEQ ID NO:300)	AYGNYWYADV (SEQ ID NO:361)		
GFSLSSYGMH (SEQ ID NO:144)	LANIWADGSENNDVSVKG (SEQ ID NO:174)	LGNIWQDGSSEKYVDVSVKG (SEQ ID NO:237)	VAVIWDQSGSTNYVDVSVKG (SEQ ID NO:301)	AYGNYWYADV (SEQ ID NO:362)		

GFTLSSYGVH (SEQ ID NO:140)	LAVIKADGSEKYNDSVKG (SEQ ID NO:173)	LGVIKQGGSENYNDSVKG (SEQ ID NO:239)	VGNIKQDGGSTNYNDSVKG (SEQ ID NO:301)	AYGNIWYIDM (SEQ ID NO:363)		
GFTLSSYGVH (SEQ ID NO:141)	LAVIKADGSEKYNDSVKG (SEQ ID NO:174)	LGVIKADGSEKYNDSVKG (SEQ ID NO:240)	VGNIKQDGGSTNYNDSVKG (SEQ ID NO:302)	AYGNIWYIDR (SEQ ID NO:364)		
GFTLSSYGMH (SEQ ID NO:142)	LAVIKADGSEKYNDSVKG (SEQ ID NO:175)	LGVIKADGSEKYNDSVKG (SEQ ID NO:241)	VGNIKQGGSTKYNDSVKG (SEQ ID NO:303)	AYGNIWYIDS (SEQ ID NO:365)		
GFTLSSYGMH (SEQ ID NO:143)	LAVIKADGSTKYNDSVKG (SEQ ID NO:176)	LGVIKADGSTKYNDSVKG (SEQ ID NO:242)	VGNIWADGSENYNDSVKG (SEQ ID NO:304)	AYGNIWYIDT (SEQ ID NO:366)		
GFTLSSYGMH (SEQ ID NO:144)	LAVIKADGSTNYNDSVKG (SEQ ID NO:177)	LGVIKADGSTNYNDSVKG (SEQ ID NO:243)	VGNIWADGSEKYNDSVKG (SEQ ID NO:305)	AYGNIWYIDW (SEQ ID NO:367)		
GFTLSSYGVH (SEQ ID NO:145)	LAVIKADGSTNYNDSVKG (SEQ ID NO:178)	LGVIKADGSTNYNDSVKG (SEQ ID NO:244)	VGNIWADGSEKYNDSVKG (SEQ ID NO:306)	AYGNIWYIDY (SEQ ID NO:368)		
GFTLSSYGVH (SEQ ID NO:146)	LAVIKADGSEKYNDSVKG (SEQ ID NO:179)	LGVIKADGSEKYNDSVKG (SEQ ID NO:245)	VGNIWADGSEKYNDSVKG (SEQ ID NO:307)	AYGNIWYIDV (SEQ ID NO:369)		
	LAVIKADGSEKYNDSVKG (SEQ ID NO:180)	LGVIKADGSEKYNDSVKG (SEQ ID NO:246)	VGNIWADGSEKYNDSVKG (SEQ ID NO:308)	AYGNIWYIDV (SEQ ID NO:370)		
	LAVIKADGSEKYNDSVKG (SEQ ID NO:181)	LGVIKADGSEKYNDSVKG (SEQ ID NO:247)	VGNIWADGSEKYNDSVKG (SEQ ID NO:309)	AYGNIWYIDV (SEQ ID NO:371)		
	LAVIKADGSEKYNDSVKG (SEQ ID NO:182)	LGVIKADGSEKYNDSVKG (SEQ ID NO:248)	VGNIWADGSEKYNDSVKG (SEQ ID NO:310)	AYGNIWYIDV (SEQ ID NO:372)		
	LAVIKADGSEKYNDSVKG (SEQ ID NO:183)	LGVIKADGSEKYNDSVKG (SEQ ID NO:249)	VGNIWADGSEKYNDSVKG (SEQ ID NO:311)	AYGNIWYIDV (SEQ ID NO:373)		
	LAVIKADGSEKYNDSVKG (SEQ ID NO:184)	LGVIKADGSEKYNDSVKG (SEQ ID NO:250)	VGNIWADGSEKYNDSVKG (SEQ ID NO:312)	AYGNIWYIDV (SEQ ID NO:374)		
	LAVIKADGSEKYNDSVKG (SEQ ID NO:185)	LGVIKADGSEKYNDSVKG (SEQ ID NO:251)	VGNIWADGSEKYNDSVKG (SEQ ID NO:313)	AYGNIWYIDV (SEQ ID NO:375)		
	LAVIKADGSEKYNDSVKG (SEQ ID NO:186)	LGVIKADGSEKYNDSVKG (SEQ ID NO:252)	VGNIWADGSEKYNDSVKG (SEQ ID NO:314)	AYGNIWYIDV (SEQ ID NO:376)		
	LAVIKADGSEKYNDSVKG (SEQ ID NO:187)	LGVIKADGSEKYNDSVKG (SEQ ID NO:253)	VGNIWADGSEKYNDSVKG (SEQ ID NO:315)	AYGNIWYIDV (SEQ ID NO:376)		

LAVIWADGSTNYVDSVKG (SEQ ID NO: 55)	LGVWQDGGSTKYVDSVKG (SEQ ID NO: 254)	VGVIKADGGSTKYVDSVKG (SEQ ID NO: 316)	AYGSYWIYIDV (SEQ ID NO: 377)
LAVIWAGGSEKYVDSVKG (SEQ ID NO: 188)	LGVWQDGGSTNYVDSVKG (SEQ ID NO: 255)	VGVIKADGGSTNYVDSVKG (SEQ ID NO: 317)	AYGTIWIYIDV (SEQ ID NO: 378)
LAVIWAGGSENYVDSVKG (SEQ ID NO: 189)	LGVWQDGGSTNYVDSVKG (SEQ ID NO: 256)	VGVIKADGGSTNYVDSVKG (SEQ ID NO: 318)	AYGYWIYIDR (SEQ ID NO: 379)
LAVIWAGGSTKYVDSVKG (SEQ ID NO: 190)	LGVWQDGGSTKYVDSVKG (SEQ ID NO: 257)	VGVIKQDGGSENYVDSVKG (SEQ ID NO: 319)	AYGYWIYIDV (SEQ ID NO: 380)
LAVIWQDGGSEKYVDSVKG (SEQ ID NO: 191)	LGVWQDGGSTNYVDSVKG (SEQ ID NO: 258)	VGVIKQDGGSTKYVDSVKG (SEQ ID NO: 320)	AYGWYWIYIDV (SEQ ID NO: 381)
LAVIWQDGGSEKYVDSVKG (SEQ ID NO: 192)	VANIKADGGSEKYVDSVKG (SEQ ID NO: 259)	VGVIKQDGGSTNYVDSVKG (SEQ ID NO: 321)	AYGYWIYIDV (SEQ ID NO: 382)
LAVIWQDGGSENYVDSVKG (SEQ ID NO: 193)	VANIKADGGSENYVDSVKG (SEQ ID NO: 260)	VGVIWADGGSEKYVDSVKG (SEQ ID NO: 322)	DYGNWIYIDV (SEQ ID NO: 383)
LAVIWQDGGSENYVDSVKG (SEQ ID NO: 194)	VANIKADGGSTKYVDSVKG (SEQ ID NO: 261)	VGVIWADGGSENYVDSVKG (SEQ ID NO: 323)	EYGNWIYIDR (SEQ ID NO: 384)
LAVIWQDGGSTKYVDSVKG (SEQ ID NO: 195)	VANIKQDGGSEKYVDSVKG (SEQ ID NO: 262)	VGVIWADGGSENYVDSVKG (SEQ ID NO: 324)	EYGNWIYIDV (SEQ ID NO: 385)
LAVIWQDGGSTKYVDSVKG (SEQ ID NO: 196)	VANIKQDGGSEKYVDSVKG (SEQ ID NO: 263)	VGVIWADGGSTKYVDSVKG (SEQ ID NO: 325)	GYGNWIYIDV (SEQ ID NO: 61)
LAVIWQDGGSTNYVDSVKG (SEQ ID NO: 197)	VANIKQDGGSTKYVDSVKG (SEQ ID NO: 264)	VGVIWADGGSTKYVDSVKG (SEQ ID NO: 326)	HYGNWIYIDV (SEQ ID NO: 386)
LAVIWQDGGSTNYVDSVKG (SEQ ID NO: 198)	VANIKQDGGSTNYVDSVKG (SEQ ID NO: 265)	VGVIWADGGSTNYVDSVKG (SEQ ID NO: 327)	IYGNWIYIDR (SEQ ID NO: 387)
LAVIWQDGGSEKYVDSVKG (SEQ ID NO: 199)	VANIWADGGSEKYVDSVKG (SEQ ID NO: 266)	VGVIWADGGSTNYVDSVKG (SEQ ID NO: 328)	IYGNWIYIDV (SEQ ID NO: 388)
LAVIWQDGGSENYVDSVKG (SEQ ID NO: 200)	VANIWADGGSTKYVDSVKG (SEQ ID NO: 267)	VGVIWQDGGSEKYVDSVKG (SEQ ID NO: 329)	LYGNWIYIDV (SEQ ID NO: 389)
LGNIKADGGSENYVDSVKG (SEQ ID NO: 201)	VANIWADGGSTNYVDSVKG (SEQ ID NO: 268)	VGVIWQDGGSEKYVDSVKG (SEQ ID NO: 330)	MYGNWIYIDV (SEQ ID NO: 390)

LGNIKADGSTKYND SVKG (SEQ ID NO: 202)	VANIWADGSTNYVDSVKG (SEQ ID NO: 269)	VGVIWQDGSSENYVDSVKG (SEQ ID NO: 331)	QYGNWYIDR (SEQ ID NO: 391)		
LGNIKADGSTKYVDSVKG (SEQ ID NO: 203)	VANIWAGGSEINYVDSVKG (SEQ ID NO: 270)	VGVIWQDGSSENYVDSVKG (SEQ ID NO: 50)	QYGNWYIDV (SEQ ID NO: 392)		
LGNIKADGSTNYVDSVKG (SEQ ID NO: 204)	VANIWQDGSSEKYND SVKG (SEQ ID NO: 271)	VGVIWQDGSSTKYND SVKG (SEQ ID NO: 332)	SYGNWYIDV (SEQ ID NO: 393)		
LGNIKAGGSTNYVDSVKG (SEQ ID NO: 205)	VANIWQDGSSEKYVDSVKG (SEQ ID NO: 41)	VGVIWQDGSSTKYVDSVKG (SEQ ID NO: 333)	VYGNWYIDV (SEQ ID NO: 394)		
LGNIKAGGSTNYVDSVKG (SEQ ID NO: 206)	VANIWQDGSSENYVDSVKG (SEQ ID NO: 272)	VGVIWQDGSSTNYVDSVKG (SEQ ID NO: 334)	WYGNWYIDV (SEQ ID NO: 395)		
LGNIKQDGSSENYVDSVKG (SEQ ID NO: 207)	VANIWQDGSSENYVDSVKG (SEQ ID NO: 273)	VGVIWQDGSSTNYVDSVKG (SEQ ID NO: 60)			
LGNIKQDGSTKYND SVKG (SEQ ID NO: 208)	VANIWQDGSSTKYND SVKG (SEQ ID NO: 274)	VGVIWQDGSSEKYVDSVKG (SEQ ID NO: 335)			
LGNIKQDGSTNYVDSVKG (SEQ ID NO: 209)		VGVIWQDGSSTNYVDSVKG (SEQ ID NO: 336)			

Table 4. CDR sequences of unique, library-derived and designer, PD1 antagonistic IgGs.

<u>Clone name</u>	<u>LCDR1</u>	<u>LCDR2</u>	<u>LCDR3</u>	<u>HCDR1</u>	<u>HCDR2</u>	<u>HCDR3</u>
20C07	KSSQSVSNDVA (SEQ ID NO:44)	YASHRFT (SEQ ID NO:45)	HQAYSTPYT (SEQ ID NO:46)	GFSFTSYGMS (SEQ ID NO:47)	LANIWQDGSINYVDSVKG (SEQ ID NO:48)	AYGNYWYIDR (SEQ ID NO:35)
11C08	KSSQSVSNDLA (SEQ ID NO:51)	YASHRFT (SEQ ID NO:45)	QQAYSTPYT (SEQ ID NO:52)	GFTFSSYGMH (SEQ ID NO:49)	VGVIWQDGSINYVDSVKG (SEQ ID NO:50)	AYGNYWYIDR (SEQ ID NO:35)
09C06	KSSQSVSNDVA (SEQ ID NO:44)	YASHRFT (SEQ ID NO:45)	HQAYSTPYT (SEQ ID NO:46)	GFSFSSYGMH (SEQ ID NO:42)	VANIWQDGSINYVDSVKG (SEQ ID NO:43)	AYGNYWYIDR (SEQ ID NO:35)
17A12	KSSQSVSNDVA (SEQ ID NO:44)	YASHRFT (SEQ ID NO:45)	QQAYSTPYT (SEQ ID NO:52)	GFSFSSYGMH (SEQ ID NO:42)	LANIWQDGSINYVDSVKG (SEQ ID NO:53)	AYGNYWYIDR (SEQ ID NO:35)
17D08	KSSQSVSNDVA (SEQ ID NO:44)	YASHRFT (SEQ ID NO:45)	HQAYSTPYT (SEQ ID NO:46)	GFTLSSYGMH (SEQ ID NO:54)	LAVIWDGGSINYVDSVKG (SEQ ID NO:55)	AYGNYMYIDV (SEQ ID NO:56)
17G08	KSSQSVSNDVA (SEQ ID NO:44)	YASHRFT (SEQ ID NO:45)	HQAYSTPYT (SEQ ID NO:46)	GFTFSSYGMH (SEQ ID NO:57)	VGVIKQDGSINYVDSVKG (SEQ ID NO:58)	AYGNYWYIDR (SEQ ID NO:35)
15D07	KSSQSVSNDLA (SEQ ID NO:51)	YASHRFT (SEQ ID NO:45)	QQAYSTPYT (SEQ ID NO:52)	GFSFTSYGMH (SEQ ID NO:59)	VGVIWQDGSINYVDSVKG (SEQ ID NO:60)	GYGNYWYIDV (SEQ ID NO:61)
MH1	KSSQSVGNDVA (SEQ ID NO:74)	YASHRFT (SEQ ID NO:45)	QQAYSSPYT (SEQ ID NO:75)	GFSLSSYGMS (SEQ ID NO:39)	VAVIWDGGSINYVDSVKG (SEQ ID NO:40)	AYGNYWYIDR (SEQ ID NO:35)
MH2	KSSQSVTNDLA (SEQ ID NO:76)	YASHRFT (SEQ ID NO:45)	QQAYSTPYT (SEQ ID NO:52)	GFSLSSYGMS (SEQ ID NO:39)	VAVIWDGGSINYVDSVKG (SEQ ID NO:40)	AYGNYWYIDR (SEQ ID NO:35)
MH3	KSSQSVGNDLA (SEQ ID NO:77)	YAYHRFS (SEQ ID NO:78)	QQAYSTPYT (SEQ ID NO:52)	GFSLSSYGMS (SEQ ID NO:39)	VAVIWDGGSINYVDSVKG (SEQ ID NO:40)	AYGNYWYIDR (SEQ ID NO:35)
MH4	KSSQSVTNDVA (SEQ ID NO:36)	YAYHRFT (SEQ ID NO:37)	HQAYSTPYT (SEQ ID NO:46)	GFSLSSYGMS (SEQ ID NO:39)	VAVIWDGGSINYVDSVKG (SEQ ID NO:40)	AYGNYWYIDR (SEQ ID NO:35)
MH5	KSSQSVGNDVA (SEQ ID NO:74)	YASHRFT (SEQ ID NO:45)	QQAYSSPYT (SEQ ID NO:75)	GFTFSSYGMS (SEQ ID NO:33)	VANIWQDGSITKYVDSVKG (SEQ ID NO:34)	AYGNYWYIDR (SEQ ID NO:35)
MH6	KSSQSVTNDLA (SEQ ID NO:76)	YASHRFT (SEQ ID NO:45)	QQAYSTPYT (SEQ ID NO:52)	GFTFSSYGMS (SEQ ID NO:33)	VANIWQDGSITKYVDSVKG (SEQ ID NO:34)	AYGNYWYIDR (SEQ ID NO:35)
MH7	KSSQSVGNDLA (SEQ ID NO:77)	YAYHRFS (SEQ ID NO:78)	QQAYSTPYT (SEQ ID NO:52)	GFTFSSYGMS (SEQ ID NO:33)	VANIWQDGSITKYVDSVKG (SEQ ID NO:34)	AYGNYWYIDR (SEQ ID NO:35)
MH8	KSSQSVTNDVA (SEQ ID NO:36)	YAYHRFT (SEQ ID NO:37)	HQAYSTPYT (SEQ ID NO:46)	GFTFSSYGMS (SEQ ID NO:33)	VANIWQDGSITKYVDSVKG (SEQ ID NO:34)	AYGNYWYIDR (SEQ ID NO:35)
MH9	KSSQSVGNDVA (SEQ ID NO:74)	YASHRFT (SEQ ID NO:45)	QQAYSSPYT (SEQ ID NO:75)	GFTFSSYGMS (SEQ ID NO:33)	VANIWQDGSITKYVDSVKG (SEQ ID NO:41)	AYGNYWYIDR (SEQ ID NO:35)
MH10	KSSQSVTNDLA (SEQ ID NO:76)	YASHRFT (SEQ ID NO:45)	QQAYSTPYT (SEQ ID NO:52)	GFTFSSYGMS (SEQ ID NO:33)	VANIWQDGSITKYVDSVKG (SEQ ID NO:41)	AYGNYWYIDR (SEQ ID NO:35)
MH11	KSSQSVGNDLA (SEQ ID NO:77)	YAYHRFS (SEQ ID NO:78)	QQAYSTPYT (SEQ ID NO:52)	GFTFSSYGMS (SEQ ID NO:33)	VANIWQDGSITKYVDSVKG (SEQ ID NO:41)	AYGNYWYIDR (SEQ ID NO:35)

MH12	KSSQSVTNDVA (SEQ ID NO: 36)	YAYHRFT (SEQ ID NO: 37)	HQAYSTPYT (SEQ ID NO: 46)	GFTFSSYGMS (SEQ ID NO: 33)	VANIWQDGGSEKYVDSVKG (SEQ ID NO: 41)	AYGNYWYIDR (SEQ ID NO: 35)
MH13	KSSQSVTNDLA (SEQ ID NO: 76)	YAYHRFT (SEQ ID NO: 37)	HQAYSTPYT (SEQ ID NO: 46)	GFTFSSYGMS (SEQ ID NO: 33)	VANIWQDGGSTKYVDSVKG (SEQ ID NO: 34)	AYGNYWYIDR (SEQ ID NO: 35)
MH14	KSSQSVTNDLA (SEQ ID NO: 76)	YAYHRFS (SEQ ID NO: 78)	HQAYSTPYT (SEQ ID NO: 46)	GFTFSSYGMS (SEQ ID NO: 33)	VANIWQDGGSTKYVDSVKG (SEQ ID NO: 34)	AYGNYWYIDR (SEQ ID NO: 35)
MH15	KSSQSVTNDLA (SEQ ID NO: 76)	YASHRFS (SEQ ID NO: 79)	HQAYSTPYT (SEQ ID NO: 46)	GFTFSSYGMS (SEQ ID NO: 33)	VANIWQDGGSTKYVDSVKG (SEQ ID NO: 34)	AYGNYWYIDR (SEQ ID NO: 35)
MH16	KSSQSVTNDLA (SEQ ID NO: 76)	YAYHRFT (SEQ ID NO: 37)	HQAYSTPYT (SEQ ID NO: 46)	GFTFSSYGMS (SEQ ID NO: 33)	VANIWQDGGSEKYVDSVKG (SEQ ID NO: 41)	AYGNYWYIDR (SEQ ID NO: 35)
MH17	KSSQSVTNDLA (SEQ ID NO: 76)	YAYHRFS (SEQ ID NO: 78)	HQAYSTPYT (SEQ ID NO: 46)	GFTFSSYGMS (SEQ ID NO: 33)	VANIWQDGGSEKYVDSVKG (SEQ ID NO: 41)	AYGNYWYIDR (SEQ ID NO: 35)
MH18	KSSQSVTNDLA (SEQ ID NO: 76)	YASHRFS (SEQ ID NO: 79)	HQAYSTPYT (SEQ ID NO: 46)	GFTFSSYGMS (SEQ ID NO: 33)	VANIWQDGGSEKYVDSVKG (SEQ ID NO: 41)	AYGNYWYIDR (SEQ ID NO: 35)

Table 5. Predicted t cell epitope content scores for Hu317 and example lead clones.

<u>Clone Name</u>	<u>GE</u>	<u>HAF</u>	<u>LAF</u>	<u>TCED+</u>
Hu317	9	4	7	2
09C06	15	4	2	1
20C07	15	4	3	1
11C08	14	4	5	1
17A12	15	4	3	1
MH4	15	4	3	1
MH8	15	3	3	1
MH12	15	3	3	1

5

Table 6. Charge isoform distributions for Hu317 and example lead clones.

<u>Clone Name</u>	<u>% Basic Isoforms</u>	<u>% Main Peak</u>	<u>% Acidic Isoforms</u>
Hu317	23.1	68.9	8
09C06	3.5	82.8	13.7
MH4	7	81.6	11.4
MH8	6	77.4	16.6
MH12	7.4	80.4	12.2

10 **Table 7.** Thermal transition midpoints for Hu317 and example lead clones.

<u>Clone</u>	<u>Tm1 °C</u>	<u>Tm2 °C</u>	<u>Tm3 °C</u>
Hu317	72.3	79.4*	86.1
09C06		76.6*	86.5
MH4		75.3*	86.2
MH8		74.2*	86.2
MH12	71.9		86.5*

* Fab Tm

Table 8. IgGs show high integrity before and after forced oxidation with 0.5% H₂O₂, measured by Size Exclusion (SEC), Reverse Phase (RP) and Hydrophobic Interaction (HIC) Chromatographies

Clone	<u>% HMW by SEC</u>		<u>Retention RP (mins)</u>		<u>RP Heavy (mins)</u>		<u>RP Light (mins)</u>		<u>Retention HIC (mins)</u>	
	<u>0 mins</u>	<u>120 min</u>	<u>0 mins</u>	<u>120 min</u>	<u>0 mins</u>	<u>120 min</u>	<u>0 mins</u>	<u>120 min</u>	<u>0 mins</u>	<u>120 min</u>
	<u>H2O2</u>	<u>H2O2</u>	<u>H2O2</u>	<u>H2O2</u>	<u>H2O2</u>	<u>H2O2</u>	<u>H2O2</u>	<u>H2O2</u>	<u>H2O2</u>	<u>H2O2</u>
Hu317	0.13	0.17	8.3	8.2	7.7	7.7	6.5	6.5	7.2	6.9
09C06	0.27	0.27	12.8	12.7	11.7	11.6	8.6	8.6	6.3	5.7
MH4	0.28	0.41	13.7	13.7	12.8	12.5	8.9	8.8	7.2	6.8
MH8	0.3	0.25	13.2	13.1	12	11.9	8.8	8.8	6.9	6.5
MH12	0.52	0.31	13.2	13.2	12	12	8.9	8.8	7	6.9

Table 9. Examples of antibody variable region amino acid sequences.

	Antibody MH8 heavy chain variable (VH) region
5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVANIWQDGSTK YVDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARAYGNYWYIDRWGQGTTVTVS S (SEQ ID NO: 1)
	Antibody MH8 light chain variable (VL) region
10	DIVMTQSPDSLAVSLGERATINCKSSQSVTNDVAWYQQKPGQPPLKLLINYYHRFTGVPD RFGSGYGTDFTLTISSLQAEDVAVYYCHQAYSTPYTFGGQGTKLEIK (SEQ ID NO: 2)
	Antibody MH4 heavy chain variable (VH) region
15	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVAVIWQDGSTN YVDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARAYGNYWYIDRWGQGTTVTVS S (SEQ ID NO: 3)
	Antibody MH4 light chain variable (VL) region
20	DIVMTQSPDSLAVSLGERATINCKSSQSVTNDVAWYQQKPGQPPLKLLINYYHRFTGVPD RFGSGYGTDFTLTISSLQAEDVAVYYCHQAYSTPYTFGGQGTKLEIK (SEQ ID NO: 4)
	Antibody MH12 heavy chain variable (VH) region
25	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVANIWQDGSE KYVDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARAYGNYWYIDRWGQGTTVTV SS (SEQ ID NO: 5)
	Antibody MH12 light chain variable (VL) region
30	DIVMTQSPDSLAVSLGERATINCKSSQSVTNDVAWYQQKPGQPPLKLLINYYHRFTGVPD RFGSGYGTDFTLTISSLQAEDVAVYYCHQAYSTPYTFGGQGTKLEIK (SEQ ID NO: 6)
	Antibody 09C06 heavy chain variable (VH) region
35	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVANIWQDGST NYVDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARAYGNYWYIDRWGQGTTVTV SS (SEQ ID NO: 7)
	Antibody 09C06 light chain variable (VL) region
40	DIVMTQSPDSLAVSLGERATINCKSSQSVSNDVAWYQQKPGQPPLKLLINYYASHRFTGVPD RFGSGYGTDFTLTISSLQAEDVAVYYCHQAYSTPYTFGGQGTKLEIK (SEQ ID NO: 8)

Table 10. Examples of antibody Fc region amino acid sequences.

	Human IgG4 wild type
45	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSDQED PEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFIYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLGLK (SEQ ID NO: 9)
50	Human IgG4(S228P)
	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSDQED PEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMT

KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFLYSRLTVDKSRWQ
EGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 10)

Human IgG1 wild type
5 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
10 TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 11)

Human IgG1-3M
15 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPEAAGA
PSVFLFPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 12)

20 Human IgG2 wild type
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTKVERKCCVECPAPPVAGPSV
FLFPPKPKDITLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF
25 RVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 13)

Human IgG1 wild type "REEM" allotype
30 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFLYSKLTVDKSR
35 WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 14)

Human IgG1-3M "REEM" allotype
40 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPEAAGA
PSVFLFPPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 15)

45 **Table 11.** Examples of target protein amino acid sequences.

Human PD1 sequence
MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPTTFSPALLVTEGDNATFTCSFSN
TSESVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCFRFRVTQLPNGRDFHMSVVRARRN
50 DSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLVVGVGG
LLGSLVLLVWVLAVICSRAARGTIGARRTGQPLKEDPSAVPVFSDYGELDFQWREKTP
PPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL (SEQ ID
NO: 16)

55

Cynomolgus monkey PD1 sequence

MQIPQAPWPVVWAVLQLGWRPGWFLESPDRPWNAPTFSPALLLVTEGDNATFTCSFSN
 ASESFVLNWYRMSPSNQTDKLAAPEDRSQPGQDCRFVTRLPNGRDFHMSVVRARRN
 DSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQALVVGVVGG
 5 LLGSLVLLVWVLAVICSRAAQGTIEARRTGQPLKEDPSAVPVFVSVDYGELDFQWREKTPE
 PPAPCVPEQTEYATIVFPSGLGTSSPARRGSADGPRSPRPLRPEDGHCSWPL (SEQ ID
 NO: 17)

Human LSAMP sequence

10 MVRRVQPDRKQLPLVLLRLLCPLLPTGLPVRSVDFNRGTDNITVRQGDTAILRCVVEDKNSK
 VAWLNRSGIIFAGHDKWSLDPRVELEKRHSLEYSRLRIQKVDVYDEGSYTCVQTQHEPKT
 SQVYLIVQVPPKISNISSDVTVNEGSNVTLCMANGRPEPVITWRHLTPTGREFEGEEEEYL
 EILGITREQSGKYECKAANEVSSADVQVKVTVNYPPTITESKSNEATTGRQASLKCEASA
 VPAPDFEWYRDDTRINSANGLEIKSTEGQSSLTVTNVTEEHYGNYTCVAANKLGVNASL
 15 VLFRRPGSVRGINGSISLAVPLWLLAASLLCLLSKC (SEQ ID NO: 415)

Human BTN2A1 sequence

MESAAALHFSRPA\$LLLLLLSLCALVSAQFIVVGPTDPILATVGENTTLRCHLSPEKNAEDM
 EVRWFRSQFSPA\$VFVYKGGREERTEEQMEEYRGR\$TTFVSKDISRGSVALVIHNITAEQNGT
 20 YRCYFQEGRSYDEAILHLVAVAGLGSKPLISMRGHEDGGIRLECISRGWYPKPLTVWRDPY
 GGVAPALKEVSM\$PADGLFMVTTAVIIRDKSVRNMSCSINNTLLGQKESVIFIPESFMPSV
 SPCAV\$LP\$VILMIP\$VAVCIYWINKLQKEKKILS\$EKEFERETREIALKELEKERVQKEEELQ
 VKEKLQEELRWRR\$FLHAVDVVLD\$PDTAHPDLFL\$EDRRSVRRC\$PFRHLGESVPD\$NPER
 FDSQPCVLGRESFASGKH\$YWEVEVENVIEWTVGVCRDSVERKGEVLLIPQNGFWTLEMH
 25 KGQYRAVSSPDRILPLKESLCRVGVFLDYEAGDV\$FYNMRDRSHIYTCPRSAF\$V\$PVRPF
 FRLGCEDSPIFICPALTGANGVTVPEEGLTLHRV\$GTHQSL (SEQ ID NO: 416)

Table 12. Target proteins identified via IgG screening of proteome arrays

IgG clone	Number of hits in chip screen	PD1 (PDCD1)	BTN2A1	LSAMP
MH4 (2µg/ml)	2	strong	NM_007049	BC033803
MH8 (2µg/ml)	2	strong		weak
MH12 (2µg/ml)	3	strong	weak/med	weak
Ilu317 (2µg/ml)	1	strong		
Anti-fluorescein (4-4-20e) Human IgG4 kappa. Ab00102-13.0	0			
negative control (2µg/ml)				
PBS (secondary only)	0			

Table 13. Fold fluorescence changes in IgG binding on non-target protein-transfected cells versus mock (ZSgreen only) cells

<u>IgG clone</u>	<u>BTN2A1</u>	<u>LSAMP</u>	<u>CD20</u>
Hu317	1.2	1.5	1.4
MH4	1.2	1.9	1.1
MH8	1.1	7.1	0.9
MH12	1.3	4.1	1.1
Secondary only	1.1	1.5	0.9

5

CLAIMS

1. An anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein
- 5 (a) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID NO:33), HCDR2 of VANIWQDGSTKYVDSVKG (SEQ ID NO:34), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);
- 10 (b) the VH region amino acid sequence comprises HCDR1 of GFSLSSYGMS (SEQ ID NO:39), HCDR2 of VAVIWQDGSTNYVDSVKG (SEQ ID NO:40), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);
- 15 (c) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID NO:33), HCDR2 of VANIWQDGSEKYVDSVKG (SEQ ID NO:41), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);
- 20 (d) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
- 25 (e) the VH region amino acid sequence comprises HCDR1 of GFSFTSYGMS (SEQ ID NO:47), HCDR2 of LANIWQDGSTNYVDSVKG (SEQ ID NO:48), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
- 30 (f) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGVH (SEQ ID NO:49), HCDR2 of VGVIWQDGSENYVDSVKG (SEQ ID NO:50), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52);
- 35 (g) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1

of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);

(h) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of LANIWQDGSSENYVDSVKG (SEQ ID NO:53), and HCDR3 of
5 AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52);

(i) the VH region amino acid sequence comprises HCDR1 of GFTLSSYGMH (SEQ ID NO: 54), HCDR2 of LAVIWADGSTNYVDSVKG (SEQ ID NO:55), and HCDR3 of AYGNYMYIDV
10 (SEQ ID NO:56); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);

(j) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMH (SEQ ID NO:57), HCDR2 of VGVIKQDGSSENYVDSVKG (SEQ ID NO:58), and HCDR3 of
15 AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46); or

(k) the VH region amino acid sequence comprises HCDR1 of GFSFTSYGMH (SEQ ID NO:59), HCDR2 of VGVIWQDGSTNYVDSVKG (SEQ ID NO:60), and HCDR3 of
20 GYGNYWYIDV (SEQ ID NO:61); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52).

2. The antibody or antigen-binding portion of claim 1, wherein

25 (a) the VH region amino acid sequence comprises SEQ ID NO:1 and the VL region amino acid sequence comprises SEQ ID NO:2;

(b) the VH region amino acid sequence comprises SEQ ID NO:3 and the VL region amino acid sequence comprises SEQ ID NO:4;

(c) the VH region amino acid sequence comprises SEQ ID NO:5 and the VL region
30 amino acid sequence comprises SEQ ID NO:6; or

(d) the VH region amino acid sequence comprises SEQ ID NO:7 and the VL region amino acid sequence comprises SEQ ID NO:8.

3. An anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody
35 comprises a heavy chain variable (VH) region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable (VL) region comprising LCDR1, LCDR2, and LCDR3, wherein

(a) the HCDR1 comprises the amino acid sequence G-F-X₁-X₂-X₃-S-Y-X₄-X₅-X₆, wherein X₁ is T or a conservative substitution of T, X₂ is F or a conservative substitution of F, X₃ is S or a conservative substitution of S, X₄ is G or any other amino acid, X₅ is M or a conservative substitution of M, and X₆ is S or any other amino acid (SEQ ID NO:20);

5 (b) the HCDR2 comprises the amino acid sequence X₁-X₂-X₃-I-X₄-X₅-X₆-G-S-X₇-X₈-Y-X₉-D-S-V-K-G, wherein X₁ is V or a conservative substitution of V, X₂ is A or a conservative substitution of A, X₃ is V or N, X₄ is W or K, X₅ is Q or A, X₆ is D or G, X₇ is T or E, X₈ is N, K, or S, and X₉ is N or V (SEQ ID NO:21);

10 (c) the HCDR3 comprises the amino acid sequence X₁-X₂-G-X₃-X₄-X₅-Y-X₆-X₇-X₈, wherein X₁ is A or any other amino acid, X₂ is Y or a conservative substitution of Y, X₃ is N or any other amino acid, X₄ is Y or a conservative substitution of Y, X₅ is W or any other amino acid, X₆ is I or any other amino acid, X₇ is D or a conservative substitution of D, and X₈ is V or any other amino acid (SEQ ID NO:22);

15 (d) the LCDR1 comprises the amino acid sequence K-S-S-X₁-S-V-X₂-N-D-X₃-A, wherein X₁ is Q or E, X₂ is S or a conservative substitution of S, and X₃ is L or a conservative substitution of L (SEQ ID NO:26);

(e) the LCDR2 comprises the amino acid sequence Y-A-X₁-X₂-R-F-X₃, wherein X₁ is F or any other amino acid, X₂ is H or any other amino acid, and X₃ is S or a conservative substitution of S (SEQ ID NO:27); and

20 (f) the LCDR3 comprises the amino acid sequence X₁-Q-X₂-Y-S-X₃-P-X₄-T, wherein X₁ is Q or any other amino acid, X₂ is A or any other amino acid, X₃ is T or any other amino acid, and X₄ is Y or any other amino acid (SEQ ID NO:28).

4. An anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody or
25 antigen-binding portion cross-competes for binding to PD1 with the antibody or antigen-binding portion of any one of claims 1-3; and

(a) comprises fully germline human framework amino acid sequences; and/or

(b) binds specifically to human PD1 and cynomolgus PD1; and/or

(c) does not comprise an oxidation site in the LCDR2; and/or

30 (d) comprises a human germline peptide sequence with high MHC class II binding affinity in the HCDR2/framework 3 region of the VH domain; and/or

(e) does not comprise a human T cell epitope sequence in the HCDR1/framework 2 region of the VH domain; and/or

(f) does not comprise a human T cell epitope sequence in the HCDR3/framework 4
35 region of the VH domain; and/or

(g) exhibits reduced charge species heterogeneity compared to antibody Hu317, when in IgG1 effector null antibody format.

5. The antibody or antigen-binding portion of any one of claims 1-4, wherein the antibody is human, humanized or chimeric.
- 5 6. The antibody or antigen-binding portion of any one of claims 1-5, wherein the VH region, the VL region, or both the VH and the VL region comprise one or more human framework region amino acid sequences.
7. The antibody or antigen-binding portion of any one of claims 1-6, wherein the VH
10 region, the VL region, or both the VH and the VL region comprise a human variable region framework scaffold amino acid sequence into which the CDRs have been inserted.
8. The antibody or antigen-binding portion of claim 1 or 3, wherein the VH region
15 comprises an IGHV3-7 human germline scaffold amino acid sequence into which the HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted.
9. The antibody or antigen-binding portion of any one of claims 1, 3 and 8, wherein the
VL region comprises an IGKV4-1 human germline scaffold amino acid sequence into which
the LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted.
- 20 10. The antibody or antigen-binding portion of any one of claims 1-9, wherein the antibody comprises an immunoglobulin constant region.
11. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin
25 constant region is IgG, IgE, IgM, IgD, IgA or IgY.
12. The antibody or antigen-binding portion of claim 11, wherein the immunoglobulin
constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.
- 30 13. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin
constant region is immunologically inert.
14. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin
constant region is a wild-type human IgG4 constant region, a human IgG4 constant region
35 comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a
human IgG1 constant region comprising the amino acid substitutions L234A, L235A and
G237A or a wild-type human IgG2 constant region.

15. The antibody or antigen-binding portion of claim 13, wherein the immunoglobulin constant region comprises any one of SEQ ID NOS:9-15.
- 5 16. The antigen-binding portion of any one of claims 1-15, wherein the antibody or antigen-binding portion is an Fab, an Fab', an F(ab')₂, an Fd, an Fv, an scFv, a single domain antibody (dAb), a maxibody, a minibody, an intrabody, a diabody, a triabody, a tetrabody, a v-NAR or a bis-scFv.
- 10 17. The antibody or antigen-binding portion of any one of claims 1-16, wherein the antibody is monoclonal.
18. The antibody or antigen-binding portion of any one of claims 1-17, wherein the antibody is a tetrameric antibody, a tetravalent antibody or a multispecific antibody.
- 15 19. The antibody or antigen-binding portion of any one of claims 1-18, wherein the antibody is a bispecific antibody that binds specifically to a first antigen and a second antigen, wherein the first antigen is PD1 and the second antigen is not PD1.
- 20 20. The antibody or antigen-binding portion of any one of claims 1-19, wherein the antibody or antigen-binding portion binds specifically to (a) human PD1 or (b) human PD1 and cynomolgus PD1.
- 25 21. An immunoconjugate comprising the antibody or antigen-binding portion of any one of claims 1-20 linked to a therapeutic agent.
- 30 22. The immunoconjugate of claim 21, wherein the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, an anti-angiogenic agent, an antiproliferative agent, a pro-apoptotic agent, a cytostatic enzyme, a cytolytic enzymes, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.
- 35 23. A pharmaceutical composition comprising the antibody or antigen-binding portion of any one of claims 1-20 or the immunoconjugate of claim 21 or 22, and a pharmaceutically acceptable carrier, diluent or excipient.
24. An nucleic acid molecule encoding

- (a) the VH region amino acid sequence;
- (b) the VL region amino acid sequence; or
- (c) both the VH and the VL region amino acid sequences

of the antibody or antigen-binding portion of any one of claims 1-20.

5

25. An expression vector comprising the nucleic acid molecule of claim 24.

26. A recombinant host cell comprising the nucleic acid molecule of claim 24 or the expression vector of claim 25.

10

27. A method of producing an anti-PD1 antibody or an antigen-binding portion thereof, the method comprising:

culturing a recombinant host cell comprising the expression vector of claim 25 under conditions whereby the nucleic acid molecule is expressed, thereby producing the antibody or antigen-binding portion; and

15

isolating the antibody or antigen-binding portion from the host cell or culture.

28. A method for enhancing an immune response in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23.

20

29. A method of treating or preventing cancer, an infectious disease, or an immune disease in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23.

25

30. The method of claim 29, wherein the cancer is pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

35

31. The method of claim 29, wherein the infectious disease is viral, bacterial, fungal, or parasitic.

32. The method of claim 29, the infectious disease is human immunodeficiency virus (HIV) infection.

5 33. The antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23 for use in the treatment of cancer, an infectious disease, or an immune disease.

10 34. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 33, wherein the cancer is pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer,
15 testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

20 35. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 33, wherein the infectious disease is viral, bacterial, fungal, or parasitic.

25 36. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 33, wherein the infectious disease is human immunodeficiency virus (HIV) infection.

30 37. The antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23, for use as a medicament.

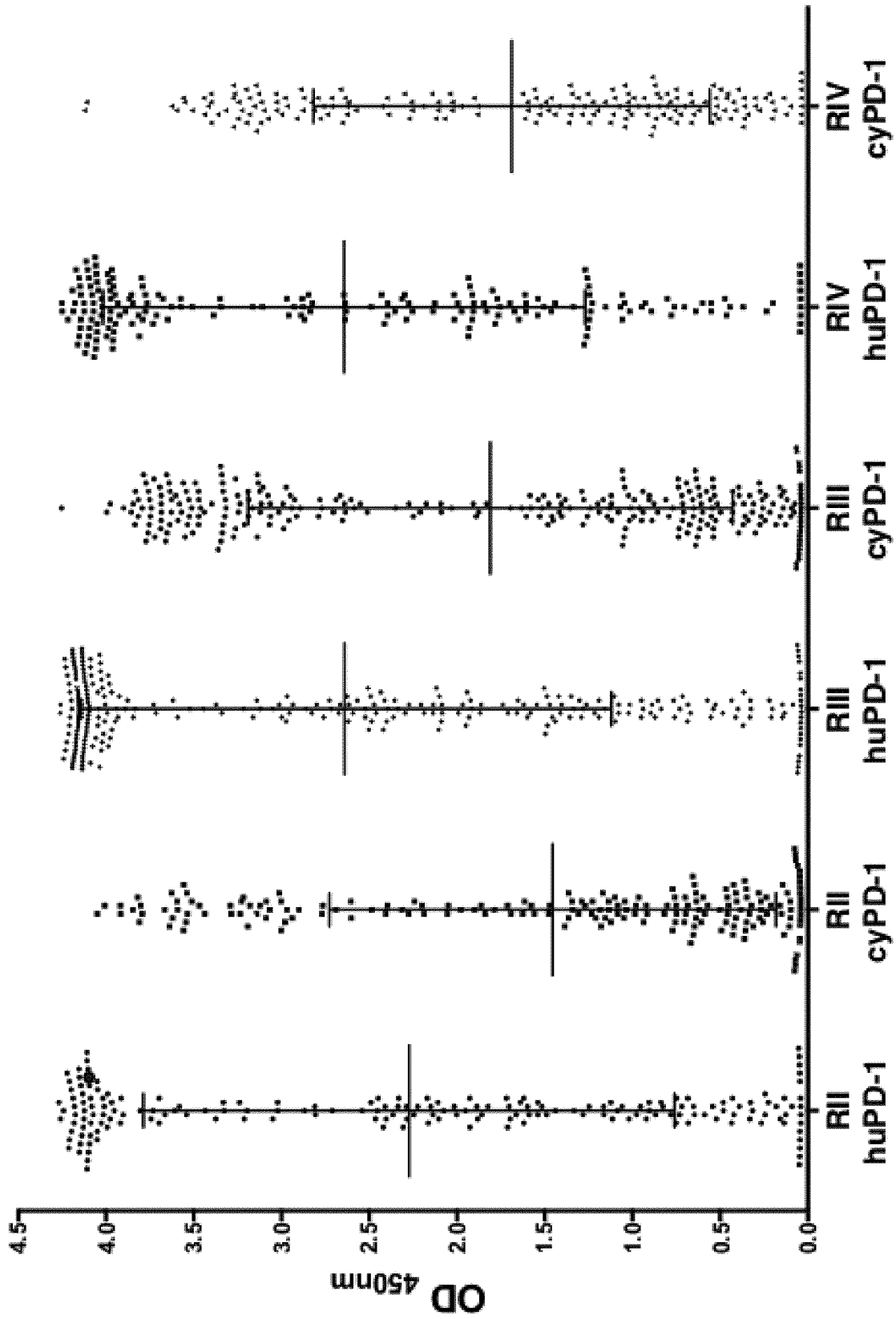


FIG. 1A

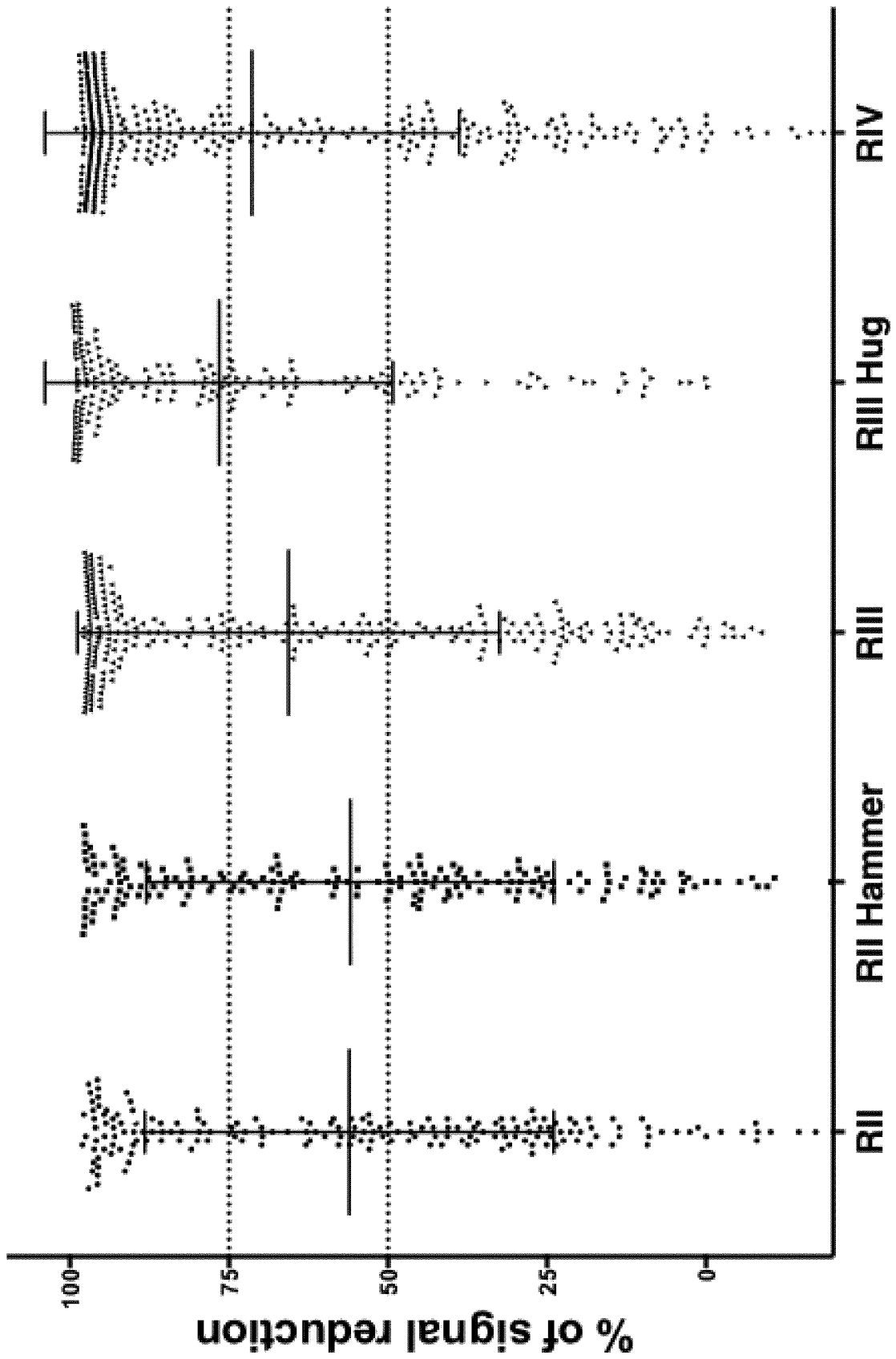


FIG. 1B

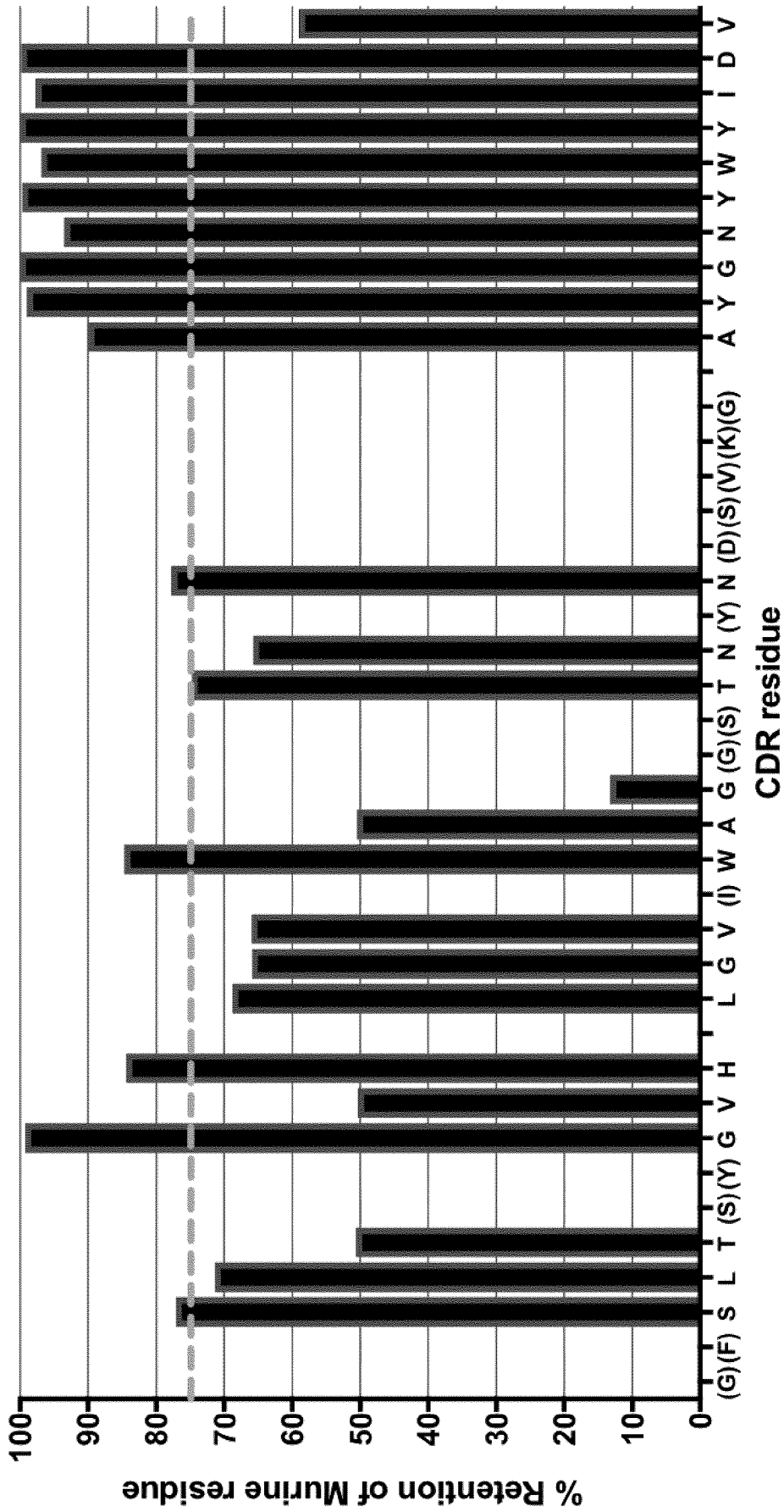


FIG. 2B

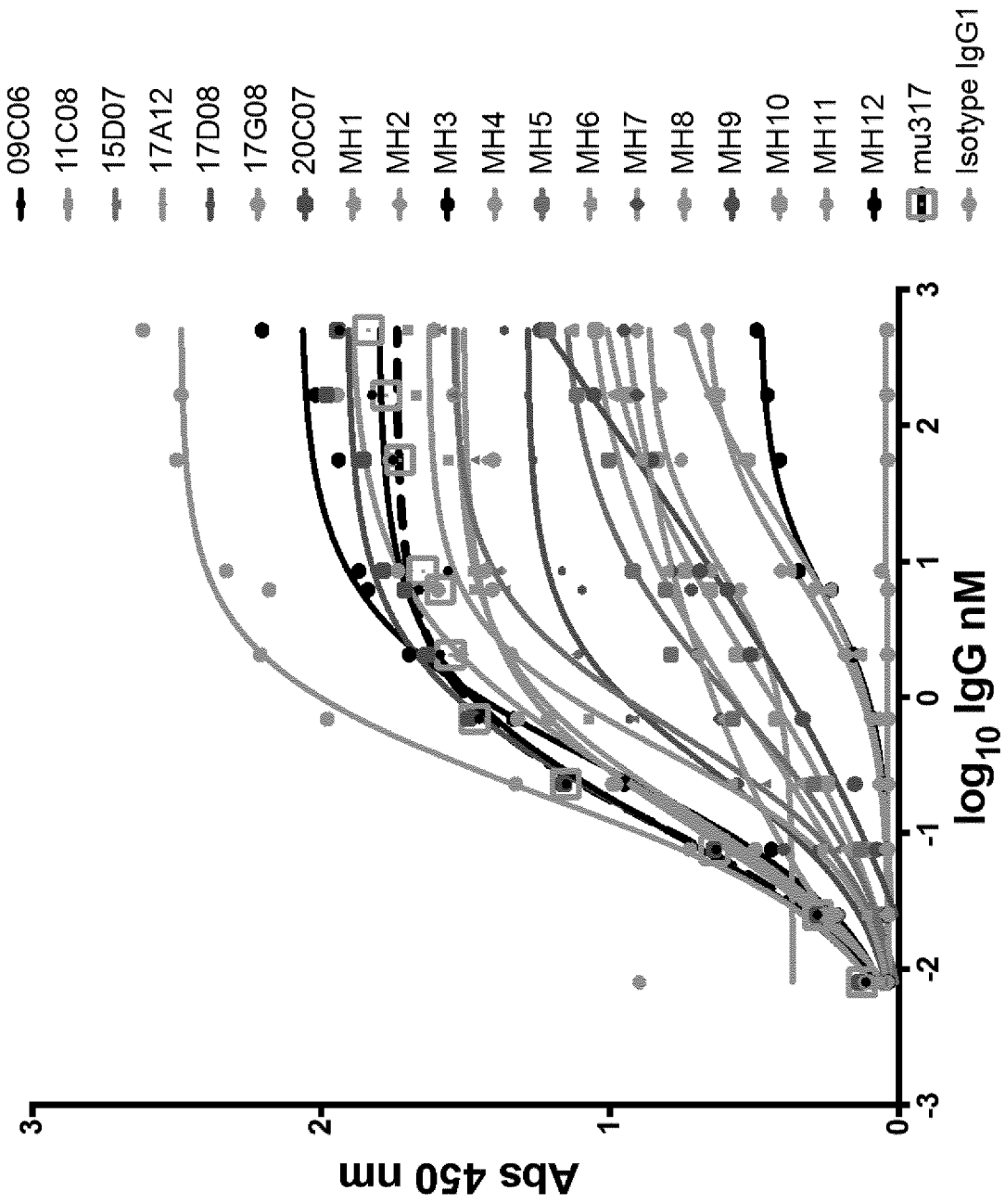


FIG. 3A

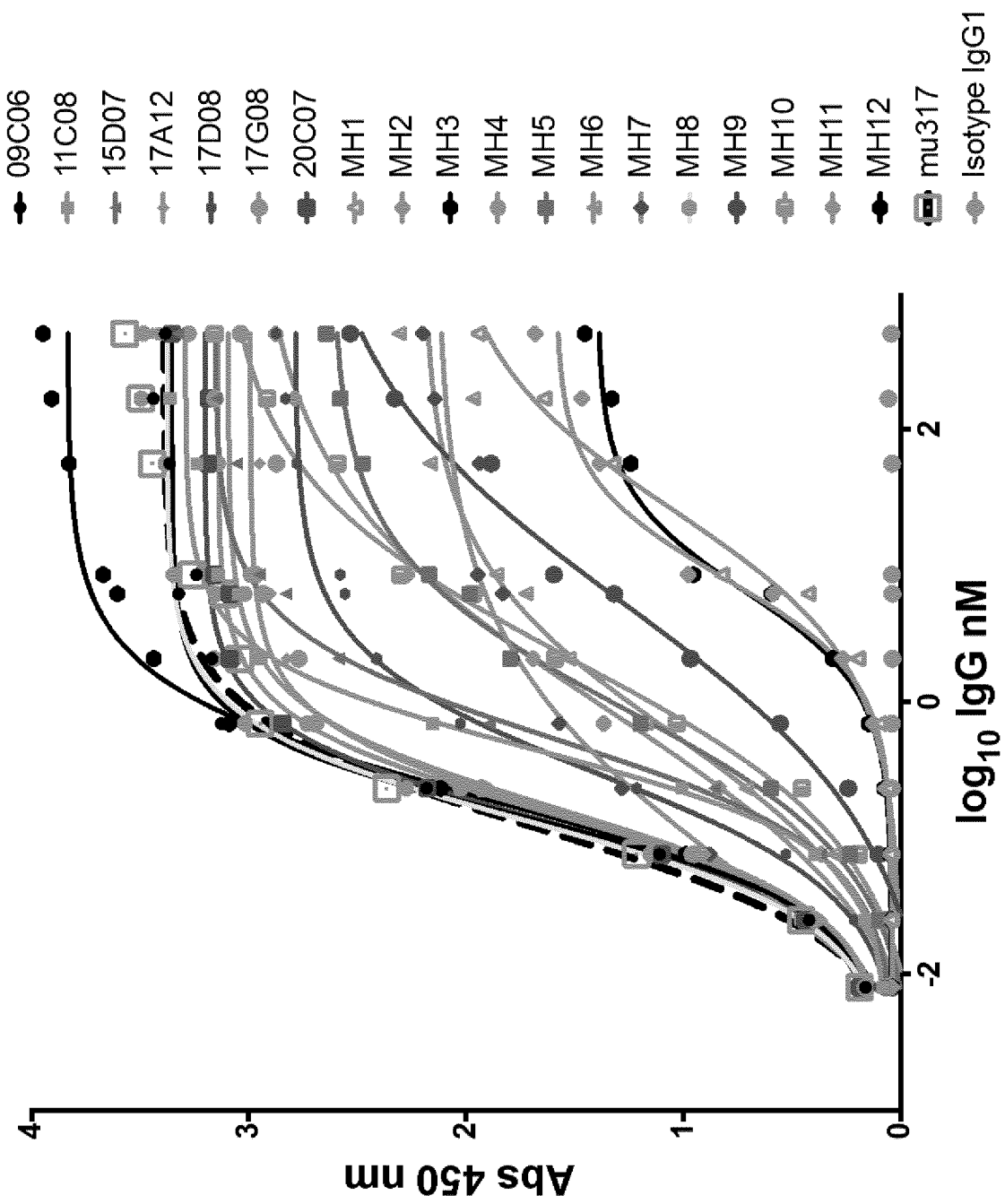


FIG. 3B

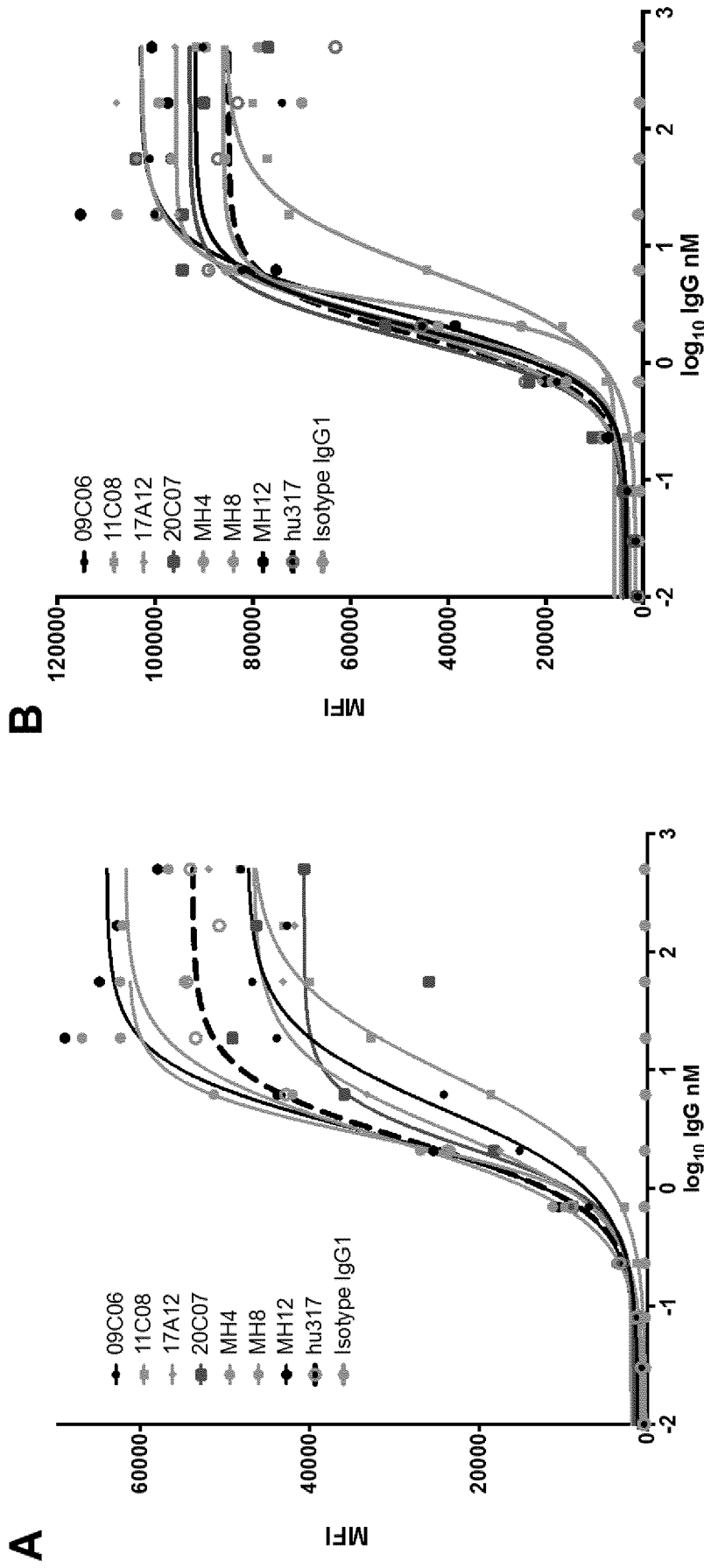


FIG. 4

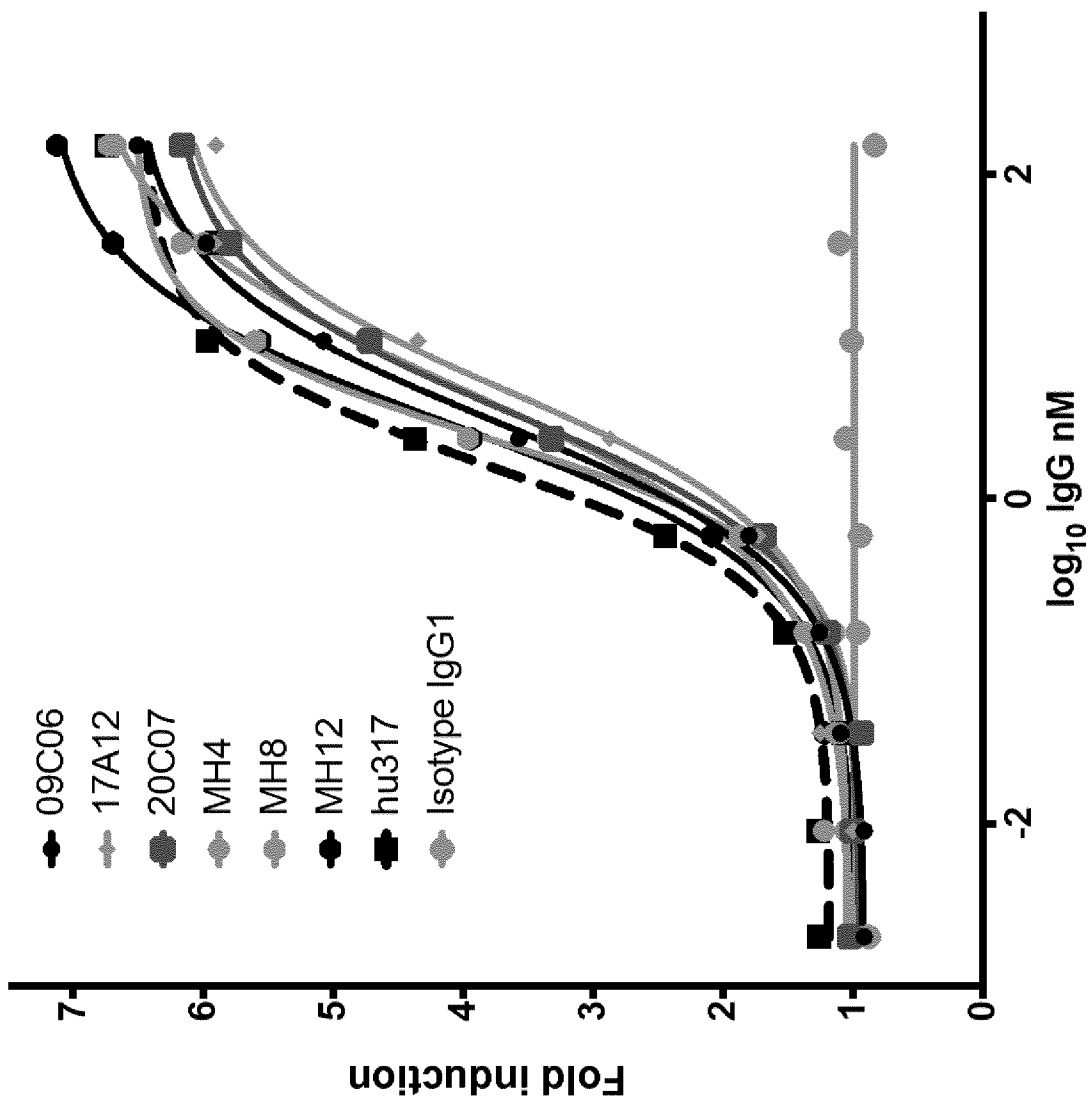


FIG. 5

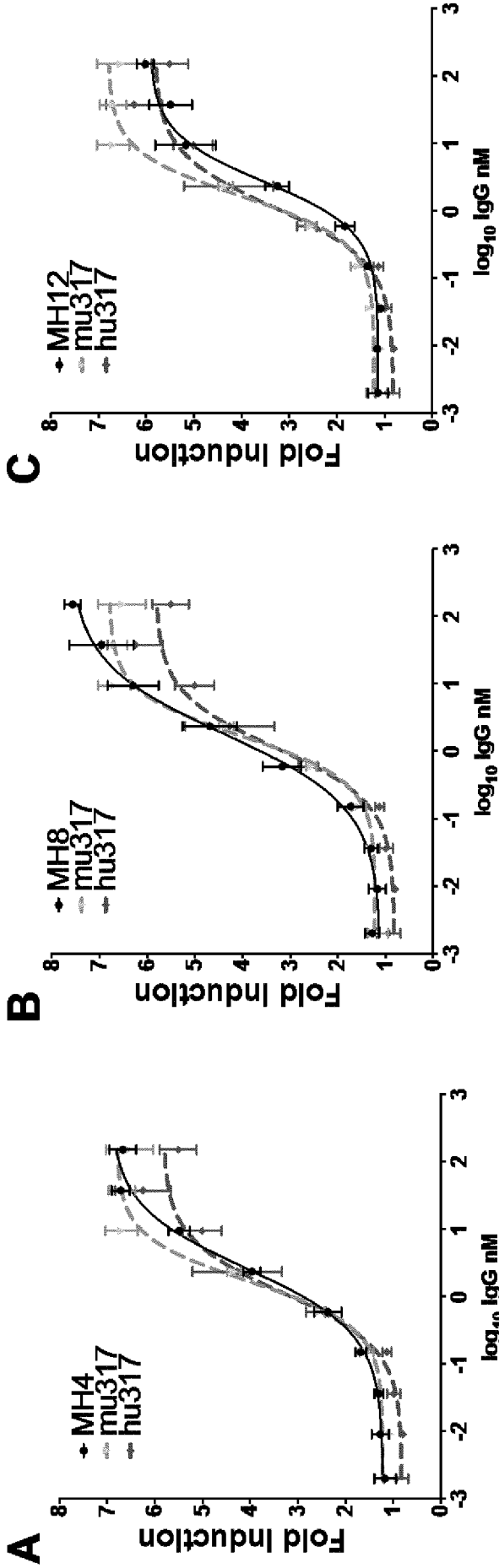


FIG. 6

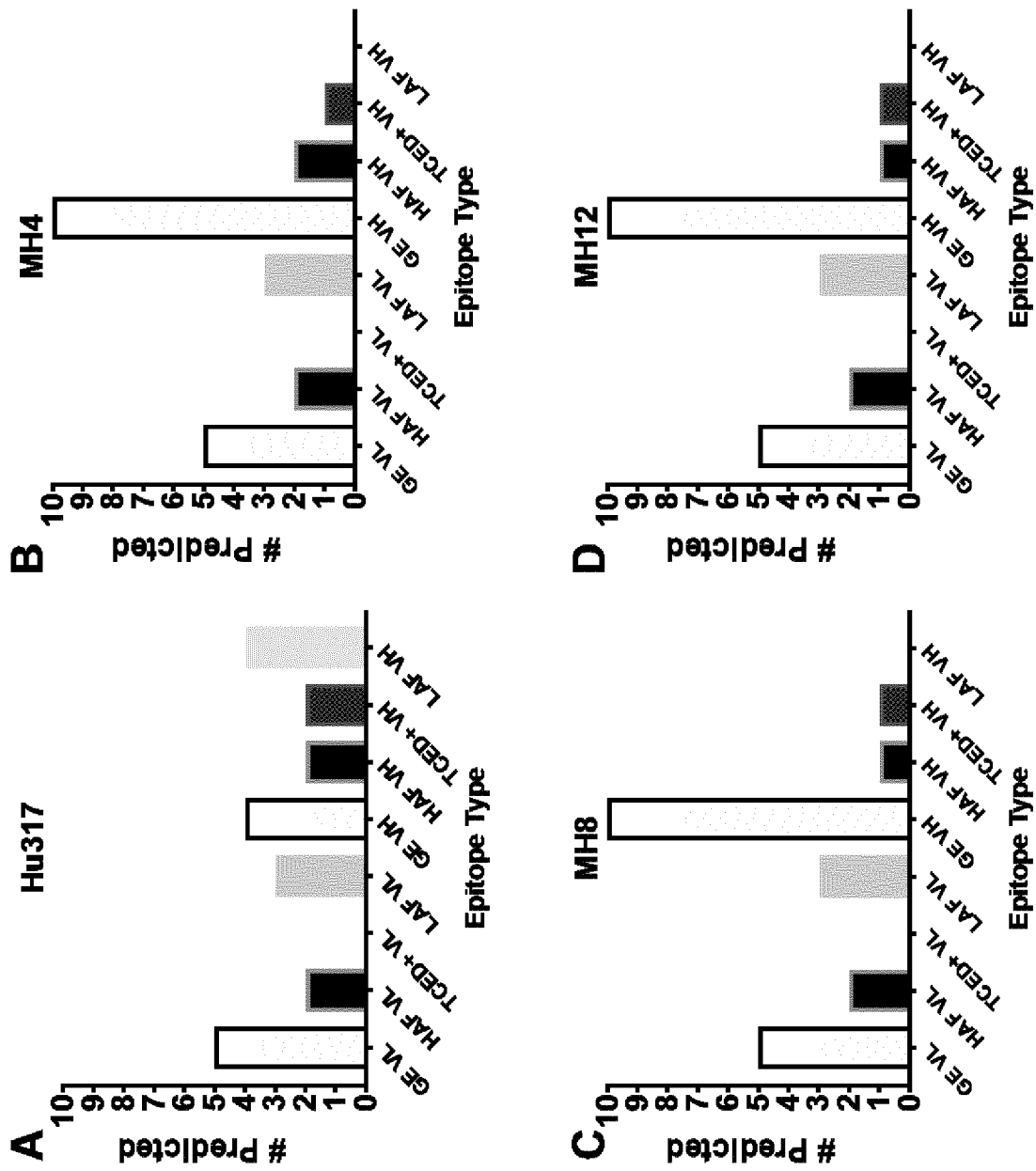


FIG. 7A-7D

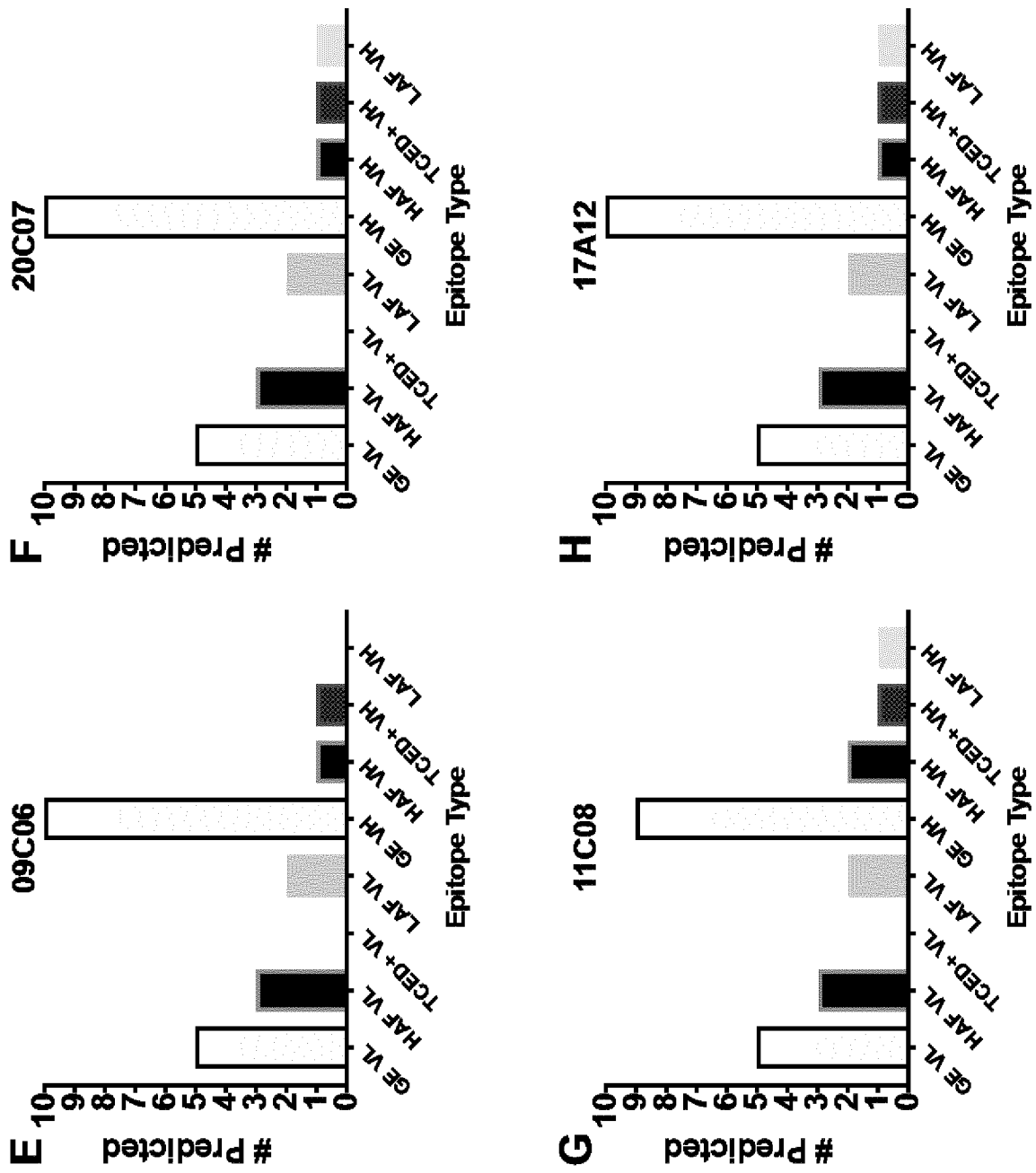


FIG. 7E-7H

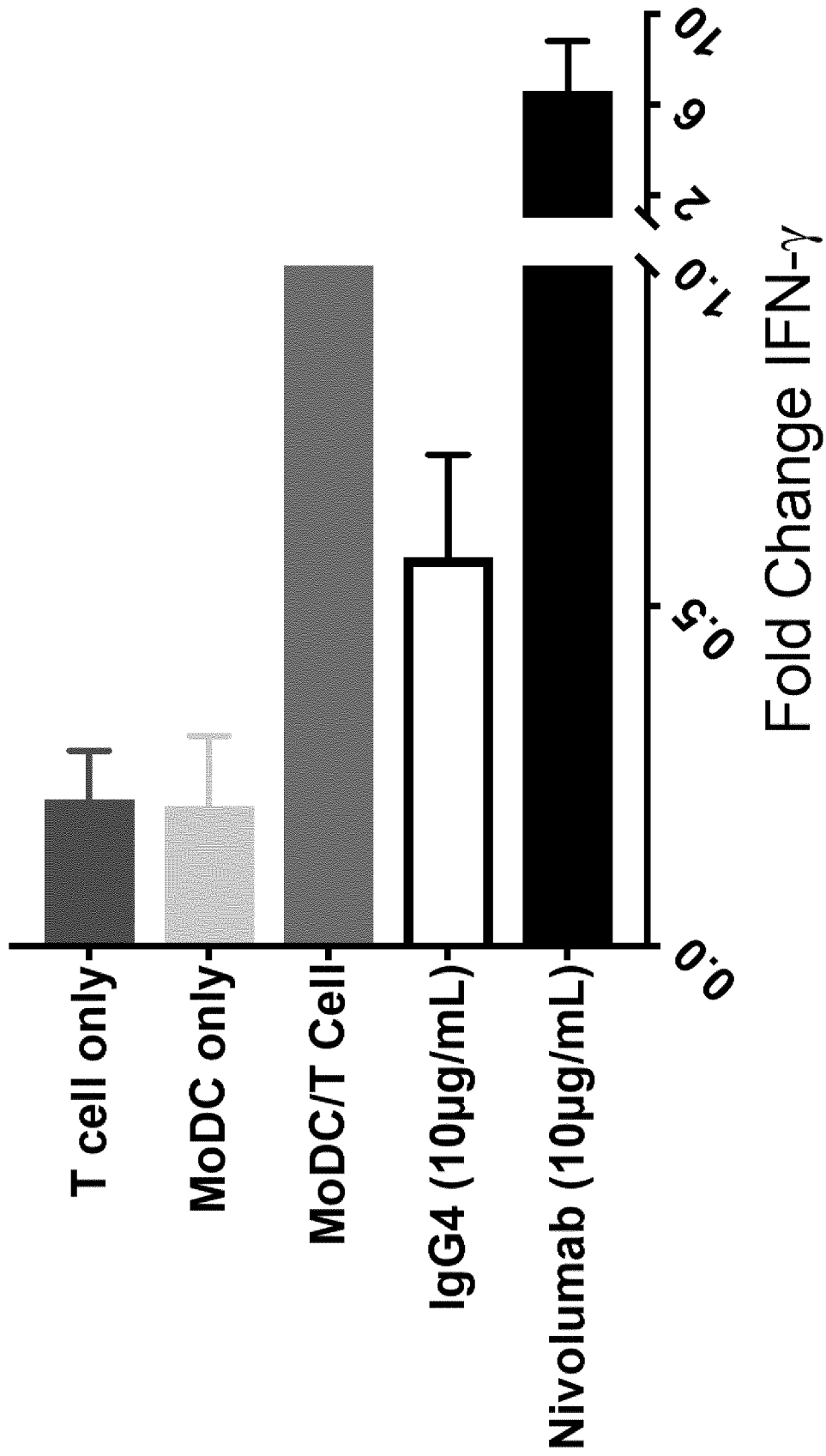


FIG. 8A

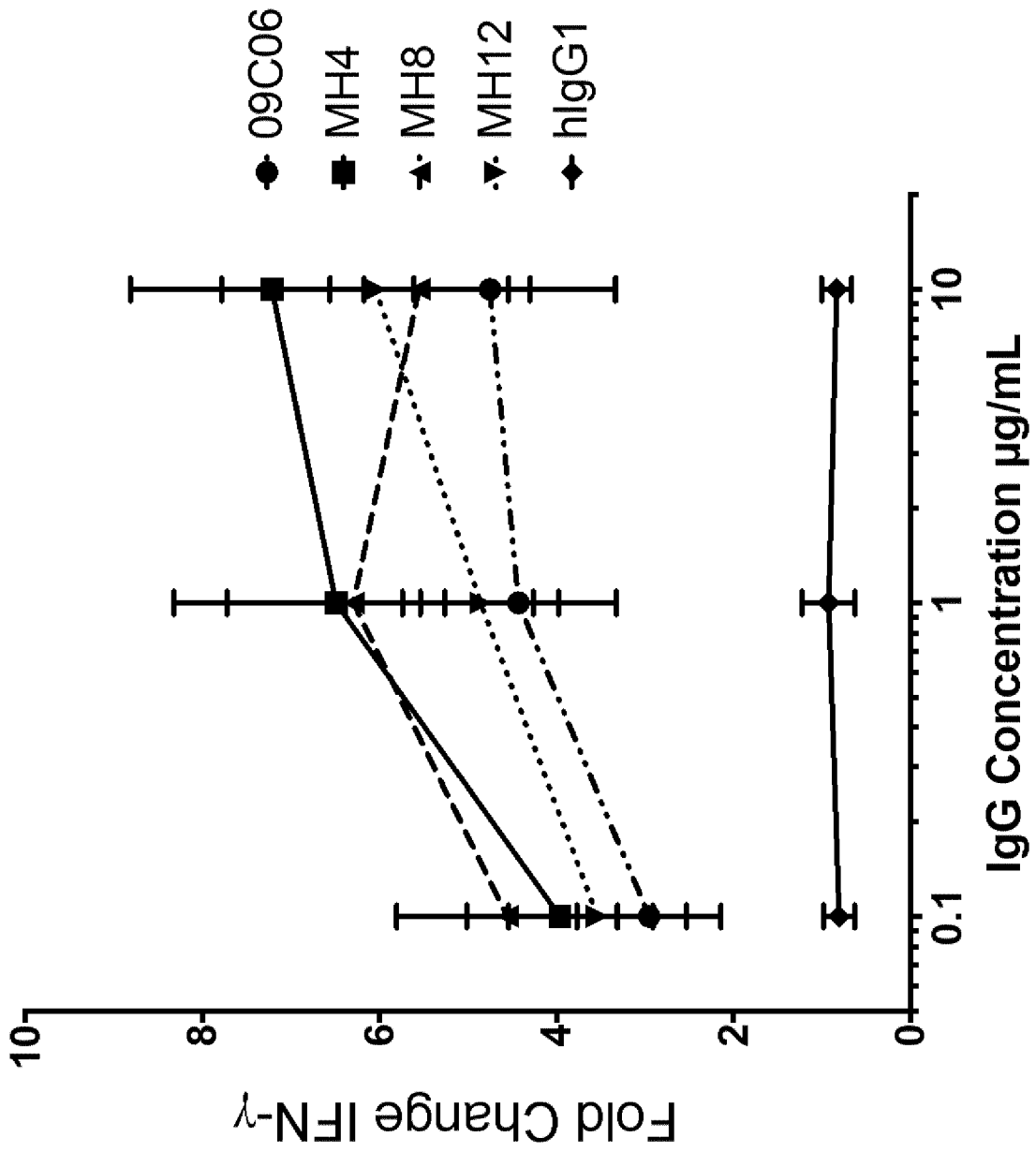


FIG. 8B

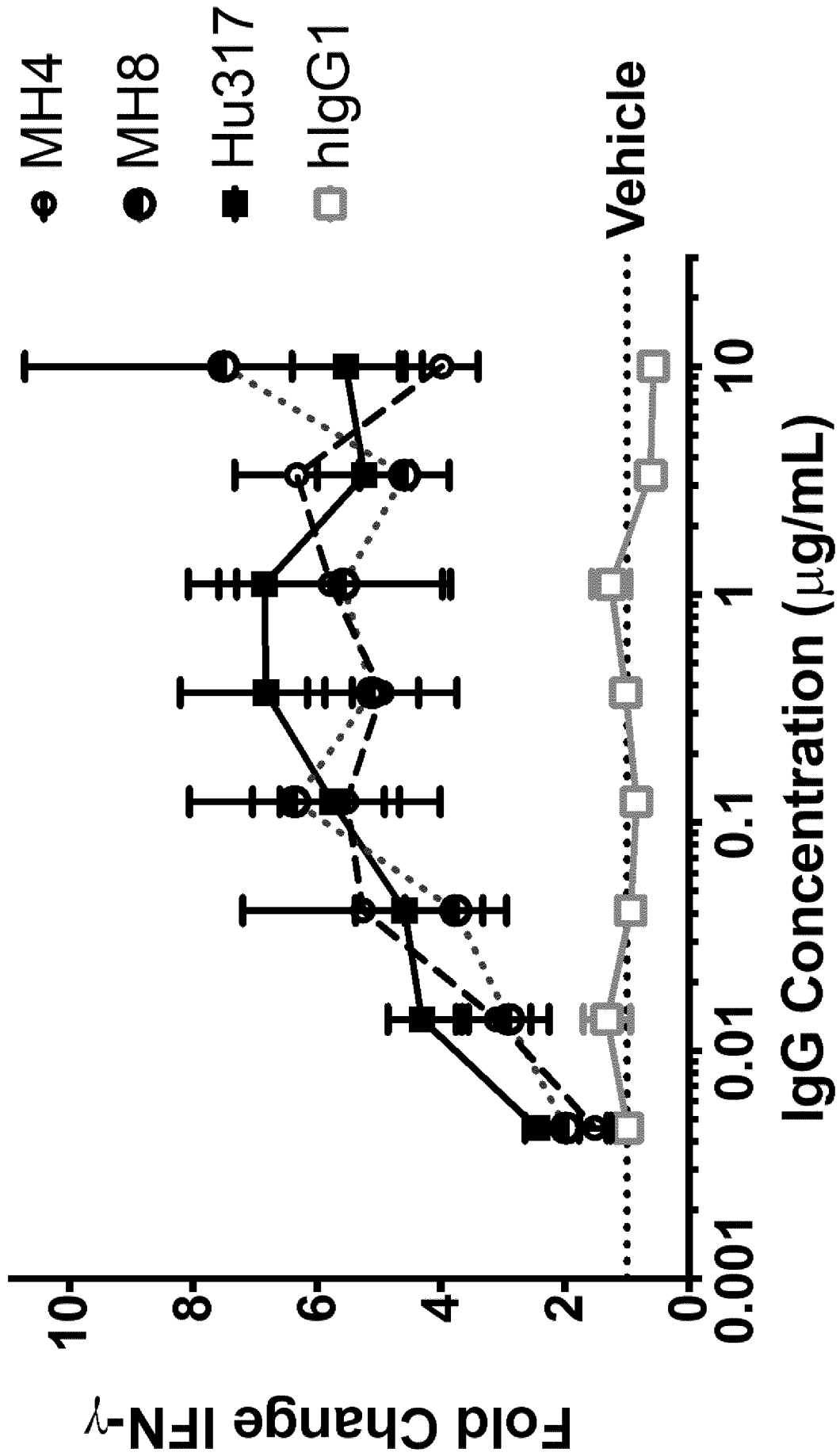
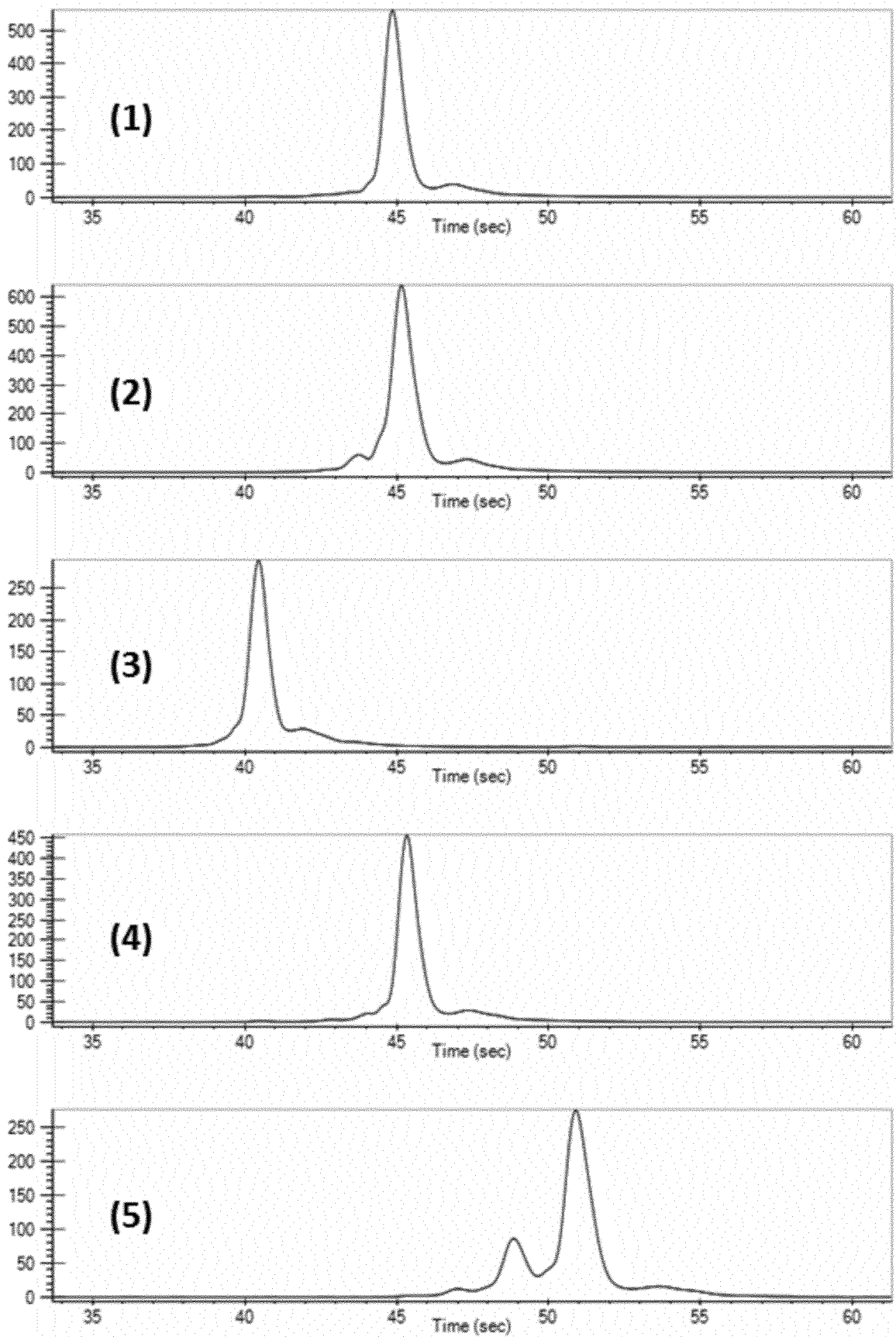


FIG. 8C



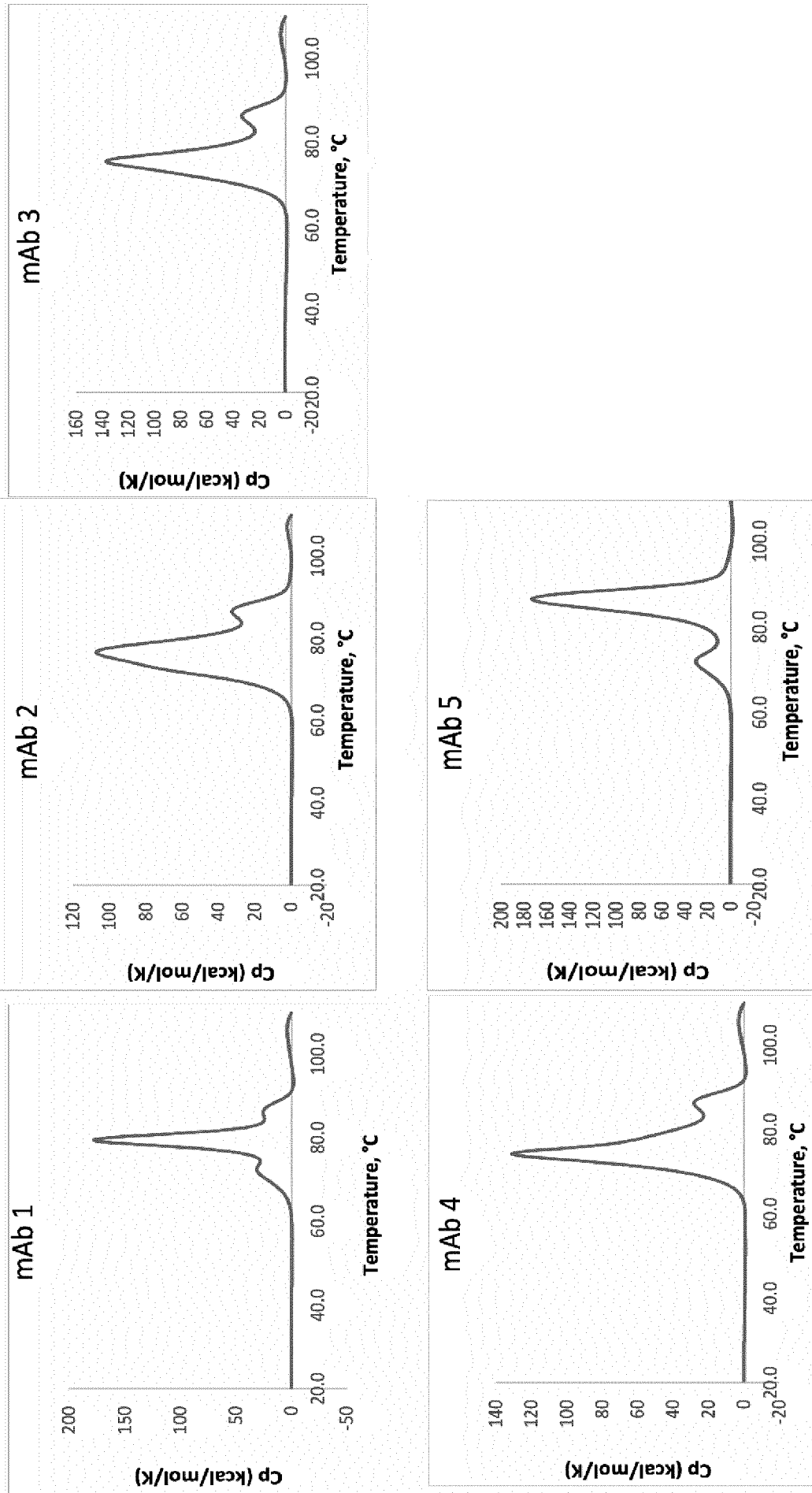


FIG. 10

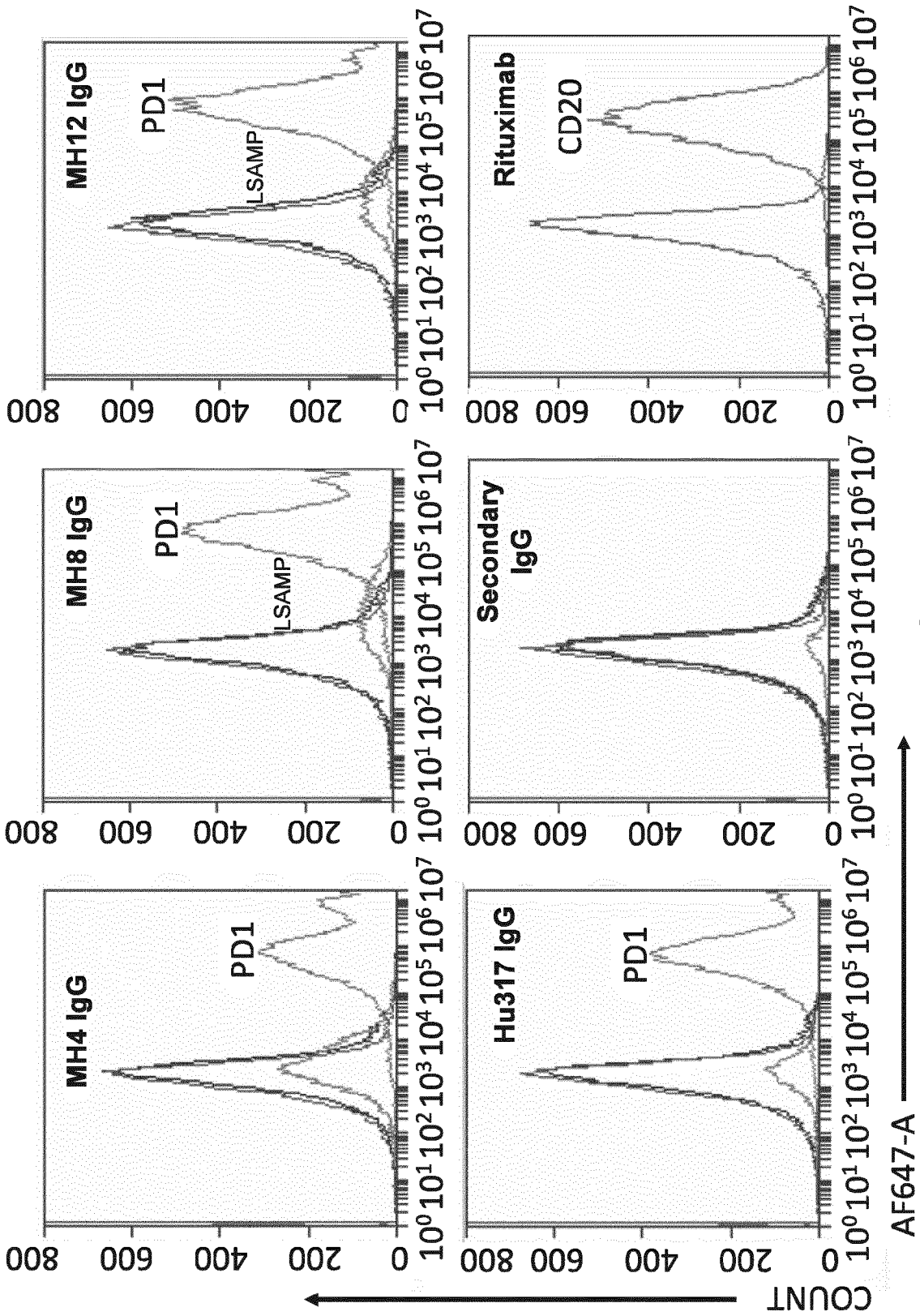


FIG. 11

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<120> PD1 BINDING AGENTS

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<170> PatentIn version 3.5

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20 25 30

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35 40 45

Ala Asn Ile Trp Gln Asp Gly Ser Thr Lys Tyr Val Asp Ser Val Lys
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eolf-seql (46).txt

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20 25 30

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35 40 45

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

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
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20 25 30

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35 40 45

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

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

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

Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Arg Trp Gly Gln Gly Thr
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Thr Val Thr Val Ser Ser
115

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 20 25 30

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 35 40 45

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

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
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20 25 30

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50 55 60

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

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
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115

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20 25 30

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35 40 45

eolf-seql (46).txt

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50 55 60

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20 25 30

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35 40 45

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

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

eolf-seq1 (46).txt

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Thr Val Thr Val Ser Ser
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20 25 30

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35 40 45

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

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

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85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
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eolf-seql (46).txt

<210> 9

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<212> PRT

<213> Homo sapiens

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20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

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

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

eolf-seql (46).txt

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

<210> 10
<211> 327
<212> PRT

eolf-seql (46).txt

<213> Homo sapiens

<400> 10

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

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

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

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

eolf-seq1 (46).txt

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

- <210> 11
- <211> 330
- <212> PRT
- <213> Homo sapiens

<400> 11

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys

eolf-seql (46).txt

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

eolf-seql (46).txt

195

200

205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 325 330

<210> 12
 <211> 330
 <212> PRT
 <213> Homo sapiens

<400> 12

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

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

eolf-seql (46).txt

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

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

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

eolf-seql (46).txt

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 13
<211> 326
<212> PRT
<213> Homo sapiens

<400> 13

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

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

eolf-seql (46).txt

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

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

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

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
 100 105 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 130 135 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
 145 150 155 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
 165 170 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
 180 185 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
 195 200 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
 210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
 225 230 235 240

eolf-seql (46).txt

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
245 250 255

Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
260 265 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
290 295 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305 310 315 320

Ser Leu Ser Pro Gly Lys
325

<210> 14
<211> 330
<212> PRT
<213> Homo sapiens

<400> 14

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

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

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

eolf-seq1 (46).txt

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

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

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

eolf-seql (46).txt

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 15
<211> 329
<212> PRT
<213> Homo sapiens

<400> 15

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

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys

eolf-seq1 (46).txt

85

90

95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 245 250 255

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 260 265 270

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu

eolf-seq1 (46).txt

275

280

285

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 290 295 300

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 305 310 315 320

Lys Ser Leu Ser Leu Ser Pro Gly Lys
 325

<210> 16
 <211> 288
 <212> PRT
 <213> Homo sapiens

<400> 16

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
 1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
 20 25 30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
 35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
 50 55 60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
 65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
 85 90 95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
 100 105 110

eolf-seql (46).txt

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
115 120 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
130 135 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145 150 155 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
165 170 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
180 185 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
195 200 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
210 215 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225 230 235 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
245 250 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
260 265 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
275 280 285

<210> 17
<211> 288

eolf-seql (46).txt

<212> PRT

<213> *Macaca fascicularis*

<400> 17

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
 1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Glu Ser Pro Asp Arg Pro Trp
 20 25 30

Asn Ala Pro Thr Phe Ser Pro Ala Leu Leu Leu Val Thr Glu Gly Asp
 35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Ala Ser Glu Ser Phe Val
 50 55 60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
 65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
 85 90 95

Val Thr Arg Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
 100 105 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
 115 120 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
 130 135 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
 145 150 155 160

Arg Pro Ala Gly Gln Phe Gln Ala Leu Val Val Gly Val Val Gly Gly
 165 170 175

eolf-seql (46).txt

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
180 185 190

Ser Arg Ala Ala Gln Gly Thr Ile Glu Ala Arg Arg Thr Gly Gln Pro
195 200 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
210 215 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Ala Pro
225 230 235 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
245 250 255

Leu Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
260 265 270

Ser Pro Arg Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
275 280 285

<210> 18
<211> 5
<212> PRT
<213> Homo sapiens

<400> 18

Arg Asp Glu Leu Thr
1 5

<210> 19
<211> 4
<212> PRT
<213> Homo sapiens

<400> 19

Arg Glu Glu Met

1

<210> 20
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa is Thr or a conservative substitution of Thr

<220>
<221> misc_feature
<222> (4)..(4)
<223> Xaa is Phe or a conservative substitution of Phe

<220>
<221> misc_feature
<222> (5)..(5)
<223> Xaa is Ser or a conservative substitution of Ser

<220>
<221> misc_feature
<222> (8)..(8)
<223> Xaa is Gly or any other amino acid

<220>
<221> misc_feature
<222> (9)..(9)
<223> Xaa is Met or a conservative substitution of Met

<220>
<221> misc_feature
<222> (10)..(10)
<223> Xaa is Ser or any other amino acid

<400> 20

Gly Phe Xaa Xaa Xaa Ser Tyr Xaa Xaa Xaa
1 5 10

eolf-seq1 (46).txt

<210> 21
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa is Val or a conservative substitution of Val

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa is Ala or a conservative substitution of Ala

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa is Val or Asn

<220>
<221> misc_feature
<222> (5)..(5)
<223> Xaa is Trp or Lys

<220>
<221> misc_feature
<222> (6)..(6)
<223> Xaa is Gln or Ala

<220>
<221> misc_feature
<222> (7)..(7)
<223> Xaa is Asp or Gly

<220>
<221> misc_feature
<222> (10)..(10)
<223> Xaa is Thr or Glu

<220>
<221> misc_feature
<222> (11)..(11)
<223> Xaa is Asn, Lys, or Ser

eolf-seq1 (46).txt

<220>
<221> misc_feature
<222> (13)..(13)
<223> Xaa is Asn or Val

<400> 21

Xaa Xaa Xaa Ile Xaa Xaa Xaa Gly Ser Xaa Xaa Tyr Xaa Asp Ser Val
1 5 10 15

Lys Gly

<210> 22
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR3

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa is Ala or any other amino acid

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa is Tyr or a conservative substitution of Tyr

<220>
<221> misc_feature
<222> (4)..(4)
<223> Xaa is Asn or any other amino acid

<220>
<221> misc_feature
<222> (5)..(5)
<223> Xaa is Tyr or a conservative substitution of Tyr

<220>
<221> misc_feature
<222> (6)..(6)

<223> Xaa is Trp or any other amino acid

<220>

<221> misc_feature

<222> (8)..(8)

<223> Xaa is Ile or any other amino acid

<220>

<221> misc_feature

<222> (9)..(9)

<223> Xaa is Asp or a conservative substitution of Asp

<220>

<221> misc_feature

<222> (10)..(10)

<223> Xaa is Val or any other amino acid

<400> 22

Xaa Xaa Gly Xaa Xaa Xaa Tyr Xaa Xaa Xaa
1 5 10

<210> 23

<211> 10

<212> PRT

<213> Mus musculus

<400> 23

Gly Phe Ser Leu Thr Ser Tyr Gly Val His
1 5 10

<210> 24

<211> 16

<212> PRT

<213> Mus musculus

<400> 24

Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met Ser
1 5 10 15

<210> 25

<211> 10

<212> PRT

eolf-seq1 (46).txt

<213> Mus musculus

<400> 25

Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val
1 5 10

<210> 26

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR1

<220>

<221> misc_feature

<222> (4)..(4)

<223> Xaa is Gln or Glu

<220>

<221> misc_feature

<222> (7)..(7)

<223> Xaa is Ser or a conservative substitution of Ser

<220>

<221> misc_feature

<222> (10)..(10)

<223> Xaa is Leu or a conservative substitution of Leu

<400> 26

Lys Ser Ser Xaa Ser Val Xaa Asn Asp Xaa Ala
1 5 10

<210> 27

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<220>

eolf-seq1 (46).txt

<221> misc_feature
<222> (3)..(3)
<223> Xaa is Phe or any other amino acid

<220>
<221> misc_feature
<222> (4)..(4)
<223> Xaa is His or any other amino acid

<220>
<221> misc_feature
<222> (7)..(7)
<223> Xaa is Ser or a conservative substitution of Ser

<400> 27

Tyr Ala Xaa Xaa Arg Phe Xaa
1 5

<210> 28
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion LCDR3

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa is Gln or any other amino acid

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa is Ala or any other amino acid

<220>
<221> misc_feature
<222> (6)..(6)
<223> Xaa is Thr or any other amino acid

<220>
<221> misc_feature
<222> (8)..(8)
<223> Xaa is Tyr or any other amino acid

eolf-seq1 (46).txt

<400> 28

Xaa Gln Xaa Tyr Ser Xaa Pro Xaa Thr
1 5

<210> 29

<211> 11

<212> PRT

<213> Mus musculus

<400> 29

Lys Ala Ser Gln Ser Val Ser Asn Asp Val Ala
1 5 10

<210> 30

<211> 11

<212> PRT

<213> Mus musculus

<400> 30

Lys Ser Ser Gln Glu Val Ser Asn Asp Val Ala
1 5 10

<210> 31

<211> 7

<212> PRT

<213> Mus musculus

<400> 31

Tyr Ala Phe His Arg Phe Thr
1 5

<210> 32

<211> 9

<212> PRT

<213> Mus musculus

<400> 32

His Gln Ala Tyr Ser Ser Pro Tyr Thr

eolf-seql (46).txt

1 5

<210> 33
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<400> 33

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1 5 10

<210> 34
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 34

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

Lys Gly

<210> 35
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR3

<400> 35

Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Arg
1 5 10

eolf-seq1 (46).txt

<210> 36
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion LCDR1

<400> 36

Lys Ser Ser Gln Ser Val Thr Asn Asp Val Ala
1 5 10

<210> 37
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 37

Tyr Ala Tyr His Arg Phe Thr
1 5

<210> 38
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion LCDR3

<400> 38

His Gln Ala Tyr Ser Ser Pro Tyr Thr
1 5

<210> 39
<211> 10
<212> PRT
<213> Artificial Sequence

eolf-seq1 (46).txt

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<400> 39

Gly Phe Ser Leu Ser Ser Tyr Gly Met Ser
1 5 10

<210> 40

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 40

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

Lys Gly

<210> 41

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 41

Val Ala Asn Ile Trp Gln Asp Gly Ser Glu Lys Tyr Val Asp Ser Val
1 5 10 15

Lys Gly

<210> 42

<211> 10

<212> PRT

eolf-seql (46).txt

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<400> 42

Gly Phe Ser Phe Ser Ser Tyr Gly Met His
1 5 10

<210> 43

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 43

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

Lys Gly

<210> 44

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR1

<400> 44

Lys Ser Ser Gln Ser Val Ser Asn Asp Val Ala
1 5 10

<210> 45

<211> 7

<212> PRT

<213> Artificial Sequence

eolf-seq1 (46).txt

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 45

Tyr Ala Ser His Arg Phe Thr
1 5

<210> 46

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR3

<400> 46

His Gln Ala Tyr Ser Thr Pro Tyr Thr
1 5

<210> 47

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<400> 47

Gly Phe Ser Phe Thr Ser Tyr Gly Met Ser
1 5 10

<210> 48

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 48

Leu Ala Asn Ile Trp Gln Asp Gly Ser Thr Asn Tyr Val Asp Ser Val

1 5 10 15

Lys Gly

<210> 49
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 49

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

<210> 50
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 50

Val Gly Val Ile Trp Gln Asp Gly Ser Glu Asn Tyr Val Asp Ser Val
 1 5 10 15

Lys Gly

<210> 51
 <211> 11
 <212> PRT
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<220>
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<400> 51

eolf-seql (46).txt

Lys Ser Ser Gln Ser Val Ser Asn Asp Leu Ala
1 5 10

<210> 52
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion LCDR3

<400> 52

Gln Gln Ala Tyr Ser Thr Pro Tyr Thr
1 5

<210> 53
<211> 18
<212> PRT
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<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 53

Leu Ala Asn Ile Trp Gln Asp Gly Ser Glu Asn Tyr Val Asp Ser Val
1 5 10 15

Lys Gly

<210> 54
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<400> 54

Gly Phe Thr Leu Ser Ser Tyr Gly Met His

eolf-seq1 (46).txt

1 5

10

<210> 55

<211> 18

<212> PRT

<213> Artificial Sequence

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<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 55

Leu Ala Val Ile Trp Ala Asp Gly Ser Thr Asn Tyr Val Asp Ser Val

1

5

10

15

Lys Gly

<210> 56

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR3

<400> 56

Ala Tyr Gly Asn Tyr Met Tyr Ile Asp Val

1

5

10

<210> 57

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<400> 57

Gly Phe Thr Phe Ser Ser Tyr Gly Met His

1

5

10

eolf-seq1 (46).txt

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<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 58

Val Gly Val Ile Lys Gln Asp Gly Ser Glu Asn Tyr Val Asp Ser Val
1 5 10 15

Lys Gly

<210> 59
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<400> 59

Gly Phe Ser Phe Thr Ser Tyr Gly Met His
1 5 10

<210> 60
<211> 18
<212> PRT
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<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<400> 60

Val Gly Val Ile Trp Gln Asp Gly Ser Thr Asn Tyr Val Asp Ser Val
1 5 10 15

Lys Gly

eolf-seql (46).txt

<210> 61
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<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR3

<400> 61

Gly Tyr Gly Asn Tyr Trp Tyr Ile Asp Val
1 5 10

<210> 62
<211> 10
<212> PRT
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<220>
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<223> Xaa is Met or Val

<220>
<221> misc_feature
<222> (10)..(10)
<223> Xaa is Ser or His

<400> 62

Gly Phe Thr Phe Ser Ser Tyr Gly Xaa Xaa
1 5 10

<210> 63
<211> 18
<212> PRT
<213> Artificial Sequence

<220>

eolf-seql (46).txt

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR2

<220>

<221> misc_feature

<222> (3)..(3)

<223> Xaa is Val or Asn

<220>

<221> misc_feature

<222> (5)..(5)

<223> Xaa is Trp or Lys

<220>

<221> misc_feature

<222> (10)..(10)

<223> Xaa is Glu or Thr

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa is Asn or Lys

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa is Val or Asn

<400> 63

Val Ala Xaa Ile Xaa Gln Asp Gly Ser Xaa Xaa Tyr Xaa Asp Ser Val
1 5 10 15

Lys Gly

<210> 64

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR3

<220>

eolf-seql (46).txt

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<223> Xaa is Ala, Asp, Glu, Gly, His, Ile, Lys, Leu, Gln,
Ser, Val or Trp

<220>
<221> misc_feature
<222> (2)..(2)
<223> Xaa is Tyr, Phe or Trp

<220>
<221> misc_feature
<222> (4)..(4)
<223> Xaa is Asn, Ala, Glu, Phe, Gly, His, Ile, Gln, Arg,
Ser, Thr, Val, Trp or Tyr

<220>
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<222> (5)..(5)
<223> Xaa is Tyr, Val or Trp

<220>
<221> misc_feature
<222> (6)..(6)
<223> Xaa is Trp, Phe, His, Met, Pro, Gln, Ser or Val

<220>
<221> misc_feature
<222> (8)..(8)
<223> Xaa is Ile, Leu, Met, Ser, Thr, Val or Tyr

<220>
<221> misc_feature
<222> (9)..(9)
<223> Xaa is Asp or Glu

<220>
<221> misc_feature
<222> (10)..(10)
<223> Xaa is Val, Ala, Glu, Phe, Gly, His, Ile, Gln, Arg,
Ser, Thr, Trp or Tyr

<400> 64

Xaa Xaa Gly Xaa Xaa Xaa Tyr Xaa Xaa Xaa
1 5 10

eolf-seq1 (46).txt

<210> 65
<211> 10
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<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<220>
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<400> 65

Gly Phe Thr Phe Ser Ser Tyr Gly Met Xaa
1 5 10

<210> 66
<211> 18
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<220>
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<223> Xaa is Glu or Thr

<220>
<221> misc_feature
<222> (11)..(11)
<223> Xaa is Asn or Lys

<400> 66

Val Ala Xaa Ile Trp Gln Asp Gly Ser Xaa Xaa Tyr Val Asp Ser Val

1 5 10 15

Lys Gly

<210> 67
 <211> 10
 <212> PRT
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<220>
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<220>
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 <222> (6)..(6)
 <223> Xaa is Trp or Met

<220>
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 <222> (10)..(10)
 <223> Xaa is Arg or Val

<400> 67

Xaa Tyr Gly Asn Tyr Xaa Tyr Ile Asp Xaa
 1 5 10

<210> 68
 <211> 11
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<221> misc_feature

<222> (7)..(7)

<223> Xaa is Ser, Gly or Thr

<220>

<221> misc_feature

<222> (10)..(10)

<223> Xaa is Leu or Val

<400> 68

Lys Ser Ser Xaa Ser Val Xaa Asn Asp Xaa Ala

1

5

10

<210> 69

<211> 7

<212> PRT

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<220>

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<220>

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<222> (3)..(3)

<223> Xaa is Phe, Ser or Tyr

<220>

<221> misc_feature

<222> (4)..(4)

<223> Xaa is His, Pro or Thr

<220>

<221> misc_feature

<222> (7)..(7)

<223> Xaa is Ser or Thr

<400> 69

Tyr Ala Xaa Xaa Arg Phe Xaa

1

5

eolf-seq1 (46).txt

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<220>
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<222> (3)..(3)
<223> Xaa is Ala or Ser

<220>
<221> misc_feature
<222> (6)..(6)
<223> Xaa is Thr, Asn or Ser

<400> 70

Xaa Gln Xaa Tyr Ser Xaa Pro Tyr Thr
1 5

<210> 71
<211> 11
<212> PRT
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<220>
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<223> Xaa is Ser, Gly or Thr

<220>
<221> misc_feature
<222> (10)..(10)

eolf-seql (46).txt

<223> Xaa is Leu or Val

<400> 71

Lys Ser Ser Gln Ser Val Xaa Asn Asp Xaa Ala
1 5 10

<210> 72

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<220>

<221> misc_feature

<222> (3)..(3)

<223> Xaa is Ser or Tyr

<220>

<221> misc_feature

<222> (7)..(7)

<223> Xaa is Ser or Thr

<400> 72

Tyr Ala Xaa His Arg Phe Xaa
1 5

<210> 73

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR3

<220>

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<223> Xaa is Gln or His

<220>

eolf-seql (46).txt

Lys Ser Ser Gln Ser Val Thr Asn Asp Leu Ala
1 5 10

<210> 77
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion LCDR1

<400> 77

Lys Ser Ser Gln Ser Val Gly Asn Asp Leu Ala
1 5 10

<210> 78
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 78

Tyr Ala Tyr His Arg Phe Ser
1 5

<210> 79
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 79

Tyr Ala Ser His Arg Phe Ser
1 5

<210> 80
<211> 7

eolf-seq1 (46).txt

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion partial HCDR2

<400> 80

Tyr Val Asp Ser Val Lys Gly
1 5

<210> 81

<211> 9

<212> PRT

<213> Homo sapiens

<400> 81

Val Lys Gly Arg Phe Thr Ile Ser Arg
1 5

<210> 82

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<400> 82

Gly Phe Ser Leu Thr Ser Tyr Gly Val His
1 5 10

<210> 83

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> LAF sequence

<400> 83

Leu Thr Ser Tyr Gly Val His Trp Ile

1 5

<210> 84
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> GE peptide

<220>
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<222> (4)..(4)
<223> Xaa is His or Ser

<400> 84

Tyr Gly Met Xaa Trp Val Arg Gln Ala
1 5

<210> 85
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> TCED+ and LAF peptide

<400> 85

Tyr Trp Tyr Ile Asp Val Trp Gly Gln
1 5

<210> 86
<211> 9
<212> PRT
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<220>
<223> HAF peptide

<400> 86

Leu Glu Trp Ile Gly Val Ile Tyr Ala

1 5

<210> 87
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> LAF peptide

<400> 87

Ile Gly Val Ile Tyr Ala Asp Gly Ser
1 5

<210> 88
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> HAF peptide

<400> 88

Leu Glu Trp Val Gly Val Ile Trp Gln
1 5

<210> 89
<211> 10
<212> PRT
<213> Mus musculus

<400> 89

Gly Phe Ser Leu Thr Ser Tyr Gly Val His
1 5 10

<210> 90
<211> 5
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<400> 90

eolf-seq1 (46).txt

Ser Tyr Gly Val His
1 5

<210> 91
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<400> 91

Gly Phe Ser Leu Thr Ser Tyr
1 5

<210> 92
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<212> PRT
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<400> 92

Gly Phe Ser Leu Thr Ser Tyr Gly
1 5

<210> 93
<211> 6
<212> PRT
<213> Mus musculus

<400> 93

Thr Ser Tyr Gly Val His
1 5

<210> 94
<211> 18
<212> PRT
<213> Mus musculus

<400> 94

Leu Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu
1 5 10 15

eolf-seq1 (46).txt

Met Ser

<210> 95
<211> 16
<212> PRT
<213> Mus musculus

<400> 95

Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met Ser
1 5 10 15

<210> 96
<211> 6
<212> PRT
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<400> 96

Trp Ala Gly Gly Ser Thr
1 5

<210> 97
<211> 8
<212> PRT
<213> Mus musculus

<400> 97

Ile Trp Ala Gly Gly Ser Thr Asn
1 5

<210> 98
<211> 15
<212> PRT
<213> Mus musculus

<400> 98

Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met Ser
1 5 10 15

eolf-seql (46).txt

<210> 99
<211> 10
<212> PRT
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<400> 99

Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr
1 5 10

<210> 100
<211> 12
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<400> 100

Leu Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr
1 5 10

<210> 101
<211> 10
<212> PRT
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<400> 101

Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val
1 5 10

<210> 102
<211> 12
<212> PRT
<213> Mus musculus

<400> 102

Ala Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val
1 5 10

<210> 103
<211> 9
<212> PRT

eolf-seq1 (46).txt

<213> Mus musculus

<400> 103

Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp
1 5

<210> 104

<211> 11

<212> PRT

<213> Mus musculus

<400> 104

Ala Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp
1 5 10

<210> 105

<211> 11

<212> PRT

<213> Mus musculus

<400> 105

Lys Ala Ser Gln Ser Val Ser Asn Asp Val Ala
1 5 10

<210> 106

<211> 6

<212> PRT

<213> Mus musculus

<400> 106

Gln Ser Val Ser Asn Asp
1 5

<210> 107

<211> 8

<212> PRT

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<400> 107

eolf-seql (46).txt

Ala Ser Gln Ser Val Ser Asn Asp
1 5

<210> 108
<211> 7
<212> PRT
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<400> 108

Ser Asn Asp Val Ala Trp Tyr
1 5

<210> 109
<211> 7
<212> PRT
<213> Mus musculus

<400> 109

Tyr Ala Phe His Arg Phe Thr
1 5

<210> 110
<211> 10
<212> PRT
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<400> 110

Leu Leu Ile Tyr Tyr Ala Phe His Arg Phe
1 5 10

<210> 111
<211> 9
<212> PRT
<213> Mus musculus

<400> 111

His Gln Ala Tyr Ser Ser Pro Tyr Thr
1 5

eolf-seql (46).txt

<210> 112
<211> 6
<212> PRT
<213> Mus musculus

<400> 112

Ala Tyr Ser Ser Pro Tyr
1 5

<210> 113
<211> 8
<212> PRT
<213> Mus musculus

<400> 113

His Gln Ala Tyr Ser Ser Pro Tyr
1 5

<210> 114
<211> 118
<212> PRT
<213> Mus musculus

<400> 114

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

Asn Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

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

Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Arg Ser Gln Val Phe Leu
65 70 75 80

eolf-seql (46).txt

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

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

Thr Val Thr Val Ser Ser
115

<210> 115

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Hu317 VH IGHV4-4

<400> 115

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

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

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

Ser Arg Val Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly Thr

100

105

110

Thr Val Thr Val Ser Ser
115

<210> 116

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> VH GRAFT IGHV3-7

<400> 116

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

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

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

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

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

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

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

Thr Val Thr Val Ser Ser
115

eolf-seql (46).txt

<210> 117
<211> 107
<212> PRT
<213> Mus musculus

<400> 117

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

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

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

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

Ser Gly Tyr Gly Thr Asp Phe Ile Phe Thr Ile Ser Thr Val Gln Ala
65 70 75 80

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Met Lys
100 105

<210> 118
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Hu317 VL IGKV4-1

<400> 118

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

eolf-seql (46).txt

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Glu Ser Val Ser Asn Asp
20 25 30

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

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

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

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

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

<210> 119
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> VL GRAFT IGKV4-1

<400> 119

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

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

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

eolf-seq1 (46).txt

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

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

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

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

<210> 120
<211> 10
<212> PRT
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<220>
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<400> 120

Gly Phe Asn Phe Ser Ser Tyr Gly Met His
1 5 10

<210> 121
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-PD1 antibody molecule or antigen-binding portion HCDR1

<400> 121

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eolf-seq1 (46).txt

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<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR3

<400> 391

Gln Tyr Gly Asn Tyr Trp Tyr Ile Asp Arg
1 5 10

<210> 392

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR3

<400> 392

Gln Tyr Gly Asn Tyr Trp Tyr Ile Asp Val
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<210> 393

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion HCDR3

<400> 393

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

<210> 394
<211> 10
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<220>
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<400> 394

Val Tyr Gly Asn Tyr Trp Tyr Ile Asp Val
1 5 10

<210> 395
<211> 10
<212> PRT
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<220>
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<400> 395

Trp Tyr Gly Asn Tyr Trp Tyr Ile Asp Val
1 5 10

<210> 396
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<220>
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<400> 396

Ala Tyr Gly Asn Val Trp Tyr Ile Asp Val
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<210> 397
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<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR1

<400> 397

Lys Ser Ser Glu Ser Val Gly Asn Asp Leu Ala
1 5 10

<210> 398

<211> 11

<212> PRT

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<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR1

<400> 398

Lys Ser Ser Glu Ser Val Gly Asn Asp Val Ala
1 5 10

<210> 399

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<212> PRT

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<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR1

<400> 399

Lys Ser Ser Glu Ser Val Ser Asn Asp Leu Ala
1 5 10

<210> 400

<211> 7

<212> PRT

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<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

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<210> 401

<211> 7

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<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 401

Tyr Ala Phe His Arg Glu Thr
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<210> 402

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 402

Tyr Ala Phe His Arg Phe Ala
1 5

<210> 403

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 403

Tyr Ala Phe His Arg Phe Ser
1 5

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<210> 404

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 404

Tyr Ala Phe Pro Arg Phe Thr

1 5

<210> 405

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 405

Tyr Ala Phe Thr Arg Phe Ser

1 5

<210> 406

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> anti-PD1 antibody molecule or antigen-binding portion LCDR2

<400> 406

Tyr Ala Phe Thr Arg Phe Thr

1 5

<210> 407

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> anti-PD1 antibody molecule or antigen-binding portion LCDR3

<400> 407

His Gln Ala Tyr Ser Asn Pro Tyr Thr

1 5

<210> 408

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion LCDR3

<400> 408

Gln Gln Ser Tyr Ser Thr Pro Tyr Thr

1 5

<210> 409

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion consensus LCDR1

<400> 409

Lys Ser Ser Gln Ser Val Ser Asn Asp Val Ala

1 5 10

<210> 410

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion consensus LCDR2

<400> 410

Tyr Ala Phe His Arg Phe Thr

1 5

eolf-seq1 (46).txt

<210> 411
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<220>
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<400> 411

His Gln Ala Tyr Ser Ser Pro Tyr Thr
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<210> 412
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<212> PRT
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<220>
<223> anti-PD1 antibody molecule or antigen-binding portion consensus HCDR1

<400> 412

Gly Phe Ser Leu Thr Ser Tyr Gly Val His
1 5 10

<210> 413
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<212> PRT
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<220>
<223> anti-PD1 antibody molecule or antigen-binding portion consensus HCDR2

<400> 413

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

Lys Gly

eolf-seql (46).txt

<210> 414

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> anti-PD1 antibody molecule or antigen-binding portion consensus HCDR3

<400> 414

Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val
1 5 10

<210> 415

<211> 338

<212> PRT

<213> Homo sapiens

<400> 415

Met Val Arg Arg Val Gln Pro Asp Arg Lys Gln Leu Pro Leu Val Leu
1 5 10 15

Leu Arg Leu Leu Cys Leu Leu Pro Thr Gly Leu Pro Val Arg Ser Val
20 25 30

Asp Phe Asn Arg Gly Thr Asp Asn Ile Thr Val Arg Gln Gly Asp Thr
35 40 45

Ala Ile Leu Arg Cys Val Val Glu Asp Lys Asn Ser Lys Val Ala Trp
50 55 60

Leu Asn Arg Ser Gly Ile Ile Phe Ala Gly His Asp Lys Trp Ser Leu
65 70 75 80

Asp Pro Arg Val Glu Leu Glu Lys Arg His Ser Leu Glu Tyr Ser Leu
85 90 95

Arg Ile Gln Lys Val Asp Val Tyr Asp Glu Gly Ser Tyr Thr Cys Ser
100 105 110

eolf-seql (46).txt

Val Gln Thr Gln His Glu Pro Lys Thr Ser Gln Val Tyr Leu Ile Val
 115 120 125

Gln Val Pro Pro Lys Ile Ser Asn Ile Ser Ser Asp Val Thr Val Asn
 130 135 140

Glu Gly Ser Asn Val Thr Leu Val Cys Met Ala Asn Gly Arg Pro Glu
 145 150 155 160

Pro Val Ile Thr Trp Arg His Leu Thr Pro Thr Gly Arg Glu Phe Glu
 165 170 175

Gly Glu Glu Glu Tyr Leu Glu Ile Leu Gly Ile Thr Arg Glu Gln Ser
 180 185 190

Gly Lys Tyr Glu Cys Lys Ala Ala Asn Glu Val Ser Ser Ala Asp Val
 195 200 205

Lys Gln Val Lys Val Thr Val Asn Tyr Pro Pro Thr Ile Thr Glu Ser
 210 215 220

Lys Ser Asn Glu Ala Thr Thr Gly Arg Gln Ala Ser Leu Lys Cys Glu
 225 230 235 240

Ala Ser Ala Val Pro Ala Pro Asp Phe Glu Trp Tyr Arg Asp Asp Thr
 245 250 255

Arg Ile Asn Ser Ala Asn Gly Leu Glu Ile Lys Ser Thr Glu Gly Gln
 260 265 270

Ser Ser Leu Thr Val Thr Asn Val Thr Glu Glu His Tyr Gly Asn Tyr
 275 280 285

Thr Cys Val Ala Ala Asn Lys Leu Gly Val Thr Asn Ala Ser Leu Val
 290 295 300

eolf-seql (46).txt

Leu Phe Arg Pro Gly Ser Val Arg Gly Ile Asn Gly Ser Ile Ser Leu
305 310 315 320

Ala Val Pro Leu Trp Leu Leu Ala Ala Ser Leu Leu Cys Leu Leu Ser
325 330 335

Lys Cys

<210> 416

<211> 527

<212> PRT

<213> Homo sapiens

<400> 416

Met Glu Ser Ala Ala Ala Leu His Phe Ser Arg Pro Ala Ser Leu Leu
1 5 10 15

Leu Leu Leu Leu Ser Leu Cys Ala Leu Val Ser Ala Gln Phe Ile Val
20 25 30

Val Gly Pro Thr Asp Pro Ile Leu Ala Thr Val Gly Glu Asn Thr Thr
35 40 45

Leu Arg Cys His Leu Ser Pro Glu Lys Asn Ala Glu Asp Met Glu Val
50 55 60

Arg Trp Phe Arg Ser Gln Phe Ser Pro Ala Val Phe Val Tyr Lys Gly
65 70 75 80

Gly Arg Glu Arg Thr Glu Glu Gln Met Glu Glu Tyr Arg Gly Arg Thr
85 90 95

Thr Phe Val Ser Lys Asp Ile Ser Arg Gly Ser Val Ala Leu Val Ile
100 105 110

eolf-seq1 (46).txt

His Asn Ile Thr Ala Gln Glu Asn Gly Thr Tyr Arg Cys Tyr Phe Gln
 115 120 125

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

Leu Gly Ser Lys Pro Leu Ile Ser Met Arg Gly His Glu Asp Gly Gly
 145 150 155 160

Ile Arg Leu Glu Cys Ile Ser Arg Gly Trp Tyr Pro Lys Pro Leu Thr
 165 170 175

Val Trp Arg Asp Pro Tyr Gly Gly Val Ala Pro Ala Leu Lys Glu Val
 180 185 190

Ser Met Pro Asp Ala Asp Gly Leu Phe Met Val Thr Thr Ala Val Ile
 195 200 205

Ile Arg Asp Lys Ser Val Arg Asn Met Ser Cys Ser Ile Asn Asn Thr
 210 215 220

Leu Leu Gly Gln Lys Lys Glu Ser Val Ile Phe Ile Pro Glu Ser Phe
 225 230 235 240

Met Pro Ser Val Ser Pro Cys Ala Val Ala Leu Pro Ile Ile Val Val
 245 250 255

Ile Leu Met Ile Pro Ile Ala Val Cys Ile Tyr Trp Ile Asn Lys Leu
 260 265 270

Gln Lys Glu Lys Lys Ile Leu Ser Gly Glu Lys Glu Phe Glu Arg Glu
 275 280 285

Thr Arg Glu Ile Ala Leu Lys Glu Leu Glu Lys Glu Arg Val Gln Lys
 290 295 300

eolf-seq1 (46).txt

Glu Glu Glu Leu Gln Val Lys Glu Lys Leu Gln Glu Glu Leu Arg Trp
 305 310 315 320

Arg Arg Thr Phe Leu His Ala Val Asp Val Val Leu Asp Pro Asp Thr
 325 330 335

Ala His Pro Asp Leu Phe Leu Ser Glu Asp Arg Arg Ser Val Arg Arg
 340 345 350

Cys Pro Phe Arg His Leu Gly Glu Ser Val Pro Asp Asn Pro Glu Arg
 355 360 365

Phe Asp Ser Gln Pro Cys Val Leu Gly Arg Glu Ser Phe Ala Ser Gly
 370 375 380

Lys His Tyr Trp Glu Val Glu Val Glu Asn Val Ile Glu Trp Thr Val
 385 390 395 400

Gly Val Cys Arg Asp Ser Val Glu Arg Lys Gly Glu Val Leu Leu Ile
 405 410 415

Pro Gln Asn Gly Phe Trp Thr Leu Glu Met His Lys Gly Gln Tyr Arg
 420 425 430

Ala Val Ser Ser Pro Asp Arg Ile Leu Pro Leu Lys Glu Ser Leu Cys
 435 440 445

Arg Val Gly Val Phe Leu Asp Tyr Glu Ala Gly Asp Val Ser Phe Tyr
 450 455 460

Asn Met Arg Asp Arg Ser His Ile Tyr Thr Cys Pro Arg Ser Ala Phe
 465 470 475 480

Ser Val Pro Val Arg Pro Phe Phe Arg Leu Gly Cys Glu Asp Ser Pro
 485 490 495

eolf-seq1 (46).txt

Ile Phe Ile Cys Pro Ala Leu Thr Gly Ala Asn Gly Val Thr Val Pro
500 505 510

Glu Glu Gly Leu Thr Leu His Arg Val Gly Thr His Gln Ser Leu
515 520 525