



(12) **DEMANDE DE BREVET CANADIEN**
CANADIAN PATENT APPLICATION
(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2018/03/28	(51) Cl.Int./Int.Cl. <i>A61K 39/395</i> (2006.01), <i>A61K 49/00</i> (2006.01), <i>A61K 51/08</i> (2006.01), <i>C07K 1/36</i> (2006.01), <i>C07K 16/18</i> (2006.01), <i>C07K 16/28</i> (2006.01), <i>C12P 21/08</i> (2006.01)
(87) Date publication PCT/PCT Publication Date: 2018/10/04	(71) Demandeur/Applicant: CELGENE CORPORATION, US
(85) Entrée phase nationale/National Entry: 2019/09/09	(72) Inventeurs/Inventors: DAI, XIAO-PING, US; BANKS, DOUGLAS, US; FOSS, WILLARD R., US
(86) N° demande PCT/PCT Application No.: US 2018/024787	(74) Agent: SMART & BIGGAR
(87) N° publication PCT/PCT Publication No.: 2018/183459	
(30) Priorité/Priority: 2017/03/29 (US62/478,524)	

(54) Titre : FORMULATIONS COMPRENANT DES PROTEINES SE LIANT A PD-1 ET LEURS PROCEDES DE PREPARATION
(54) Title: FORMULATIONS COMPRISING PD-1 BINDING PROTEINS AND METHODS OF MAKING THEREOF

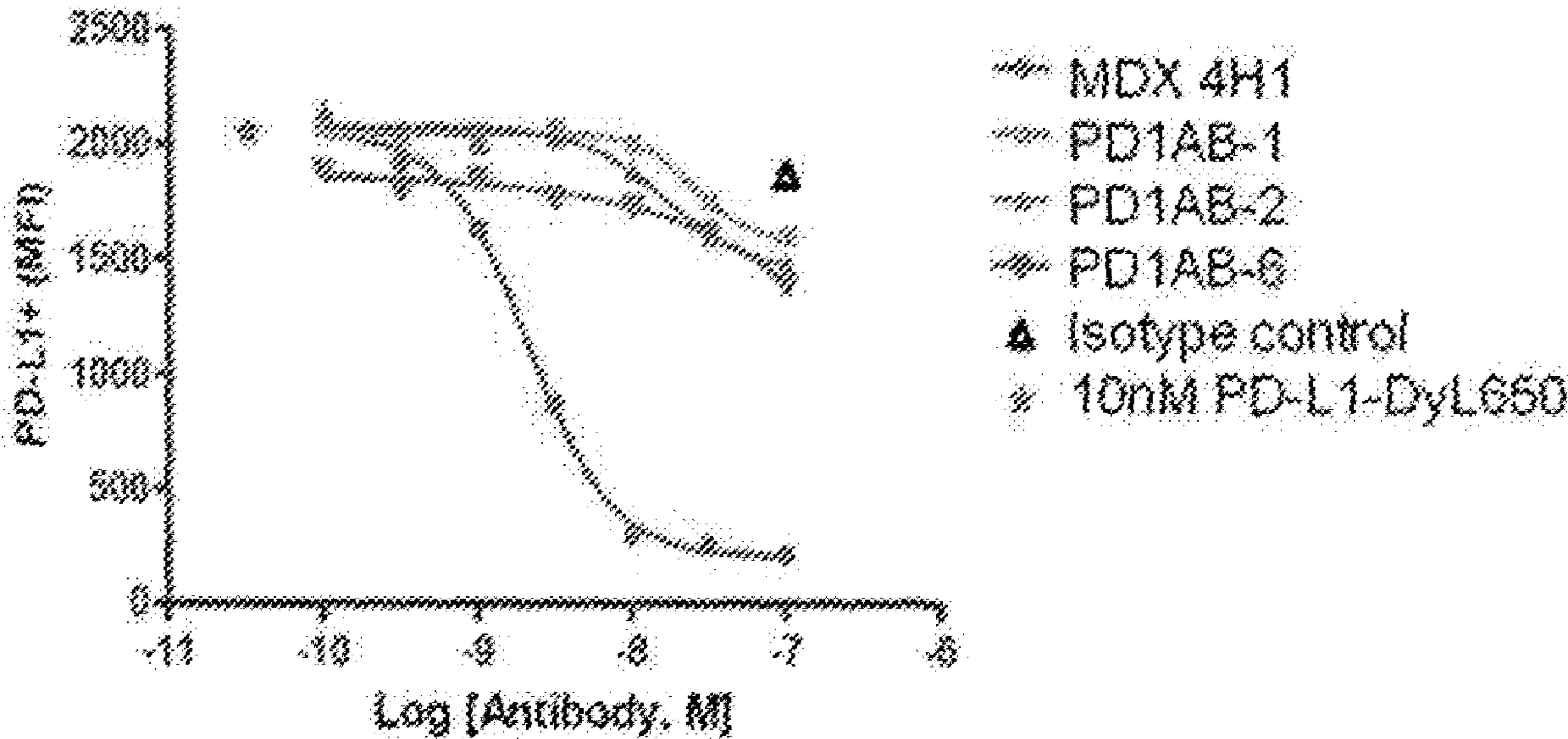


FIG. 1A

(57) **Abrégé/Abstract:**
Provided herein are formulations comprising antibodies that specifically bind to Programmed Death- 1 (PD-1) and methods of making such formulations.

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

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
04 October 2018 (04.10.2018)



(10) International Publication Number
WO 2018/183459 A1

(51) International Patent Classification:

C07K 16/18 (2006.01) A61K 39/395 (2006.01)
C07K 16/28 (2006.01)

(21) International Application Number:

PCT/US2018/024787

(22) International Filing Date:

28 March 2018 (28.03.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/478,524 29 March 2017 (29.03.2017) US

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

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

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: FORMULATIONS COMPRISING PD-1 BINDING PROTEINS AND METHODS OF MAKING THEREOF

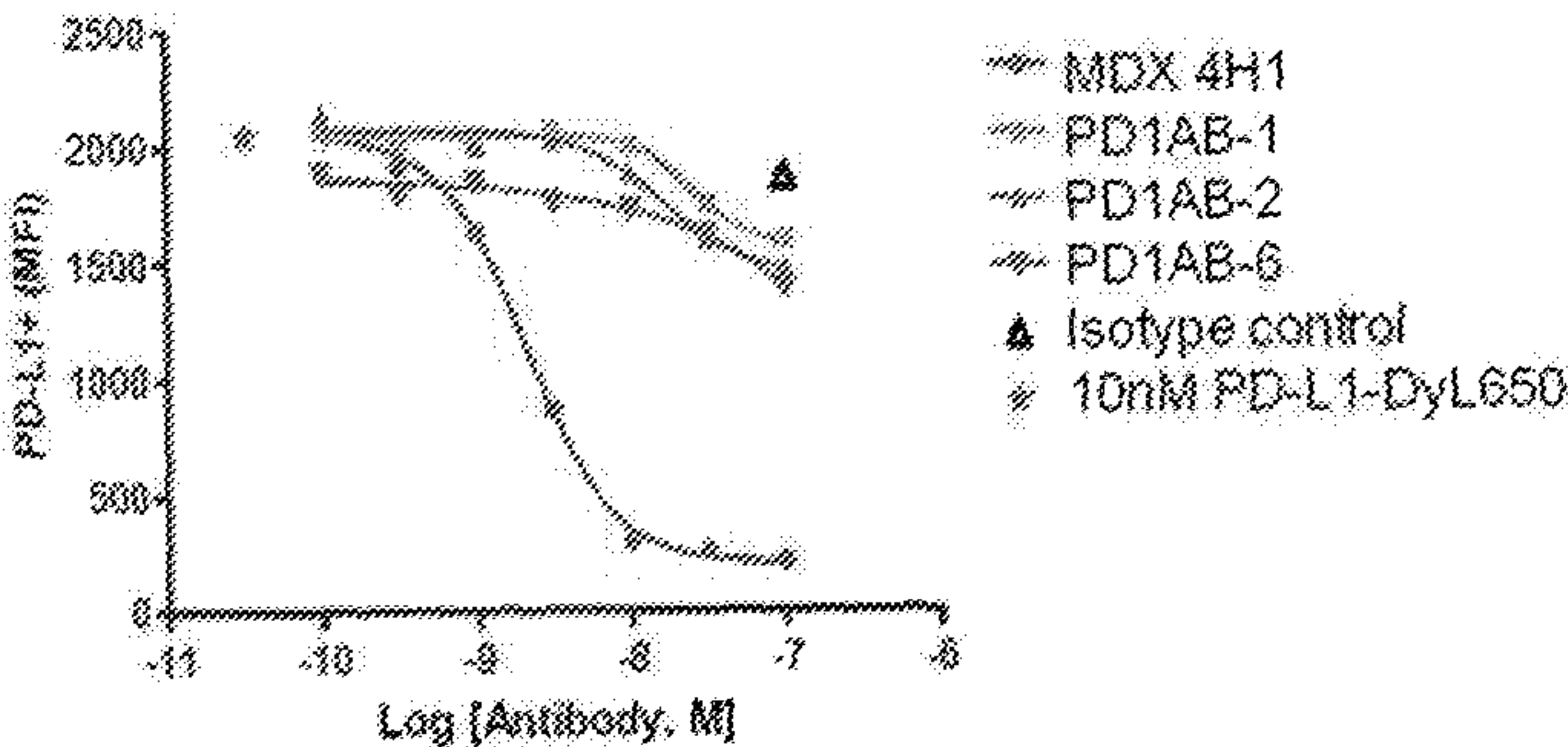


FIG. 1A

(57) Abstract: Provided herein are formulations comprising antibodies that specifically bind to Programmed Death- 1 (PD-1) and methods of making such formulations.

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FORMULATIONS COMPRISING PD-1 BINDING PROTEINS AND METHODS OF MAKING THEREOF

1. CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Serial No. 62/478,524 filed March 29, 2017, the content of which is incorporated by reference in its entirety.

2. FIELD

[0002] Provided herein are formulations comprising antibodies that specifically bind to human Programmed Death-1 (PD-1) and methods of making the formulations.

3. SUMMARY

[0003] Drug substances are usually administered as part of a formulation in combination with one or more other agents that serve varied and specialized pharmaceutical functions. Dosage forms of various types may be made through selective use of pharmaceutical excipients. As pharmaceutical excipients have various functions and contribute to the pharmaceutical formulations in many different ways, *e.g.*, solubilization, dilution, thickening, stabilization, preservation, coloring, flavoring, *etc.* The properties that are commonly considered when formulating an active drug substance include bioavailability, ease of manufacture, ease of administration, and stability of the dosage form. Due to the varying properties of active drug substances being formulated, dosage forms typically require pharmaceutical excipients that are uniquely tailored to the active drug substance in order to achieve advantageous physical and pharmaceutical properties.

[0004] The present disclosure provides formulations comprising proteins that bind to PD-1 (*e.g.*, human PD-1, SEQ ID NO:43), including binding proteins such as antibodies that bind to PD-1. Such binding proteins, including antibodies, can bind to a PD-1 polypeptide, a PD-1 fragment, and/or a PD-1 epitope. Such binding proteins, including antibodies, can be agonists (*e.g.*, induce PD-1 ligand-like signaling). In some embodiments, the binding proteins do not compete with PD-1 ligand (*e.g.*, PD-L1 and PD-L2) for the interaction with PD-1 (*e.g.*, a non-blocking antibody).

[0005] The present disclosure also provides, in certain embodiments, formulations comprising binding proteins, including antibodies or fragments thereof, that (i) bind to human

PD-1, (ii) induce PD-1 ligand-like signaling, and (iii) do not compete with PD-L1 and/or PD-L2 for the interaction with PD-1.

[0006] Also provided herein are methods of making the formulations comprising proteins that bind to PD-1 (*e.g.*, human PD-1, SEQ ID NO:43), including binding proteins such as antibodies that bind to PD-1.

[0007] In some embodiments of various formulations provided herein, a binding protein (*e.g.*, an anti-PD-1 antibody) comprises six complementarity determining regions (CDRs) or fewer than six CDRs. In other embodiments, a binding protein (*e.g.*, an anti-PD-1 antibody) comprises one, two, three, four, five, or six CDRs selected from heavy chain variable region (VH) CDR1, VH CDR2, VH CDR3, light chain variable region (VL) CDR1, VL CDR2, and/or VL CDR3. In certain embodiments, a binding protein (*e.g.*, an anti-PD-1 antibody) comprises one, two, three, four, five, or six CDRs selected from VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of a monoclonal antibody designated as PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as described herein, or a humanized variant thereof. In some embodiments, a binding protein (*e.g.*, an anti-PD-1 antibody) further comprises a scaffold region or framework region (FR), including a VH FR1, VH FR2, VH FR3, VH FR4, VL FR1, VL FR2, VL FR3, and/or VL FR4 of a human immunoglobulin amino acid sequence or a variant thereof.

[0008] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that binds to an epitope of human PD-1 recognized by an antibody comprising a light chain variable region having an amino acid sequence of SEQ ID NO:8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO:13.

[0009] In other embodiments, the formulation comprises an antibody or antibody fragment thereof that competes for the binding to human PD-1 with an antibody comprising a light chain variable region having an amino acid sequence of SEQ ID NO:8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO:13.

[0010] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a VL comprising VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in **Table 1**.

[0011] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a VH comprising VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in **Table 2**.

[0012] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises:

- (a) a VL comprising VL FR1, VL FR2, VL FR3, and VL FR4 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in **Table 3**; and
- (b) a VH comprising VH FR1, VH FR2, VH FR3, and VH FR4 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in **Table 4**.

[0013] In certain embodiments, the VL CDR1, VL CDR2, and VL CDR3 of the antibody or antigen-binding fragment thereof of the formulation comprise amino acid sequences of SEQ ID NOS:1, 2, and 3, respectively, and the VH CDR1, VH CDR2, and VH CDR3 of the antibody or antigen-binding fragment thereof of the formulation comprise amino acid sequences of SEQ ID NOS:4, 5, and 6, respectively.

[0014] In yet another embodiment, the VL CDR1, VL CDR2, and VL CDR3 of the antibody or antigen-binding fragment thereof of the formulation comprise amino acid sequences of SEQ ID NOS:7, 2, and 3, respectively, and the VH CDR1, VH CDR2, and VH CDR3 of the antibody or antigen-binding fragment thereof of the formulation comprise amino acid sequences of SEQ ID NOS:4, 5, and 6, respectively.

[0015] In another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a VL comprising an amino acid sequence of SEQ ID NO:8. In some embodiments, the amino acid sequence comprises one or more conservative modifications thereof.

[0016] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a VL comprising an amino acid sequence of SEQ ID NO:9. In some embodiments, the amino acid sequence comprises one or more conservative modifications thereof.

[0017] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a VL comprising an amino acid sequence of SEQ ID NO:10. In some embodiments, the amino acid sequence comprises one or more conservative modifications thereof.

[0018] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a VH comprising an amino acid sequence of SEQ ID NO:11. In some embodiments, the amino acid sequence comprises one or more conservative modifications thereof.

[0019] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a VH comprising an amino acid sequence of SEQ ID NO:12. In some embodiments, the amino acid sequence comprises one or more conservative modifications thereof.

[0020] In another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a VH comprising an amino acid sequence of SEQ ID NO:13. In some embodiments, the amino acid sequence comprises one or more conservative modifications thereof.

[0021] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a VL comprising an amino acid sequence of SEQ ID NO:8; and (b) a VH comprising an amino acid sequence of SEQ ID NO:11.

[0022] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a VL comprising an amino acid sequence of SEQ ID NO:9; and (b) a VH comprising an amino acid sequence of SEQ ID NO:11.

[0023] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a VL comprising an amino acid sequence of SEQ ID NO:10; and (b) a VH comprising an amino acid sequence of SEQ ID NO:11.

[0024] In one embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a VL comprising an amino acid sequence of SEQ ID NO:8; and (b) a VH comprising an amino acid sequence of SEQ ID NO:12.

[0025] In another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a VL comprising an amino acid sequence of SEQ ID NO:9; and (b) a VH comprising an amino acid sequence of SEQ ID NO:12.

[0026] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a VL comprising an amino acid sequence of SEQ ID NO:10; and (b) a VH comprising an amino acid sequence of SEQ ID NO:12.

[0027] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a VL comprising an amino acid sequence of SEQ ID NO:8; and (b) a VH comprising an amino acid sequence of SEQ ID NO:13.

[0028] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a VL comprising an amino acid sequence of SEQ ID NO:9; and (b) a VH comprising an amino acid sequence of SEQ ID NO:13.

[0029] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a VL comprising an amino acid sequence of SEQ ID NO:10; and (b) a VH comprising an amino acid sequence of SEQ ID NO:13.

[0030] In some embodiments, the amino acid sequence of the VL comprises one or more conservative modifications thereof. In some embodiments, the amino acid sequence of the VH comprises one or more conservative modifications thereof. In some embodiments, the amino acid sequence of the VL and the VH comprises one or more conservative modifications thereof.

[0031] In some embodiments, the formulation comprises an antibody that comprises a human IgG1 Fc region. In other embodiments, the formulation comprises an antibody that comprises a variant human IgG1 Fc region.

[0032] In one embodiment, the formulation comprises an antibody that comprises a human IgG1-K322A Fc region.

[0033] In some embodiments, the formulation comprises an antibody that comprises a human IgG4 Fc region. In other embodiments, the formulation comprises an antibody that comprises a variant human IgG4 Fc region.

[0034] In another embodiment, the formulation comprises an antibody that comprises a human IgG4P Fc region.

[0035] In still another embodiment, the formulation comprises an antibody that comprises a human IgG4PE Fc region.

[0036] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that further comprises a light chain constant region comprising an amino acid sequence of SEQ ID NO:41.

[0037] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that further comprises a heavy chain Fc region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:36-40.

[0038] In yet another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that further comprises a light chain constant region comprising an amino acid sequence of SEQ ID NO:41; and a heavy chain Fc region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:36-40.

[0039] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a light chain comprising an amino acid sequence of SEQ ID NO:31.

[0040] In another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:32.

[0041] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a light chain comprising an amino acid sequence of SEQ ID NO:31; and (b) a heavy chain comprising an amino acid sequence of SEQ ID NO:32.

[0042] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:33.

[0043] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a light chain comprising an amino acid sequence of SEQ ID NO:31; and (b) a heavy chain comprising an amino acid sequence of SEQ ID NO:33.

[0044] In one embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:34.

[0045] In yet another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a light chain comprising an amino acid sequence of SEQ ID NO:31; and (b) a heavy chain comprising an amino acid sequence of SEQ ID NO:34.

[0046] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:35.

[0047] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that comprises: (a) a light chain comprising an amino acid sequence of SEQ ID NO:31; and (b) a heavy chain comprising an amino acid sequence of SEQ ID NO:35.

[0048] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to at least one of residues 100-109 within an amino acid sequence of SEQ ID NO:42.

[0049] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to at least one of residues 100-105 within an amino acid sequence of SEQ ID NO:42.

[0050] In particular embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to at least one residue selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0051] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to two or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0052] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to three or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0053] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to four or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0054] In one embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to five or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0055] In another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to six or more residues selected from the group

consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0056] In yet another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to seven or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0057] In still another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to eight or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0058] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to nine or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0059] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to all ten residues from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0060] In one embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to N33 within an amino acid sequence of SEQ ID NO:42.

[0061] In another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to T51 within an amino acid sequence of SEQ ID NO:42.

[0062] In a particular embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to S57 within an amino acid sequence of SEQ ID NO:42.

[0063] In one specific embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to L100 within an amino acid sequence of SEQ ID NO:42.

[0064] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to N102 within an amino acid sequence of SEQ ID NO:42.

[0065] In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to G103 within an amino acid sequence of SEQ ID NO:42.

[0066] In another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to R104 within an amino acid sequence of SEQ ID NO:42.

[0067] In yet another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to G103 and R104 within an amino acid sequence of SEQ ID NO:42.

[0068] In still another embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to D105 within an amino acid sequence of SEQ ID NO:42.

[0069] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to H107 within an amino acid sequence of SEQ ID NO:42.

[0070] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that, when bound to PD-1, binds to S109 within an amino acid sequence of SEQ ID NO:42.

[0071] In one embodiment, the epitope of human PD-1 is distinct from the PD-L1 binding site. In another embodiment, the epitope of human PD-1 is distinct from the PD-L2 binding site. In a specific embodiment, the epitope of human PD-1 is distinct from both the PD-L1 binding site and the PD-L2 binding site.

[0072] In an embodiment, the formulation comprises an antibody or antigen-binding fragment thereof that specifically binds to human PD-1 and/or monkey PD-1 (for example, cynomolgus monkey), but not rodent PD-1.

[0073] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that has attenuated antibody dependent cellular cytotoxicity (ADCC) activity. In other embodiments, the formulation comprises an antibody or antigen-binding fragment

thereof that has attenuated complement dependent cytotoxicity (CDC) activity. In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that has attenuated ADCC and/or attenuated CDC activity.

[0074] In one aspect, provided herein is a formulation comprising an antibody or antigen-binding fragment thereof that binds to an epitope of human PD-1, wherein the antibody or antigen-binding fragment thereof: (a) attenuates T cell activity; and/or (b) downregulates PD-1 expression on the surface of T cells.

[0075] In one embodiment, the formulation comprises an antibody that attenuates T cell activity. In another embodiment, the formulation comprises an antibody that downregulates PD-1 expression on the surface of T cells.

[0076] In some embodiments, the attenuation of T cell activity is measured by a T cell effector function.

[0077] In certain embodiments, the attenuation of T cell activity by the antibody or antigen-binding fragment thereof occurs in human PBMC or whole blood samples.

[0078] In some embodiments, the attenuation of T cell activity is measured by inhibition of cytokine production.

[0079] In other embodiments, the cytokine that is inhibited by the antibody or antigen-binding fragment thereof comprises IL-2, IL-17, and/or IFN- γ . In certain embodiments, the cytokine is selected from the group consisting of IL-1, IL-2, IL-6, IL-12, IL-17, IL-22, IL-23, GM-CSF, IFN- γ , and TNF- α . In certain embodiments, the cytokine is IL-1. In some embodiments, the cytokine is IL-2. In other embodiments, the cytokine is IL-6. In another embodiment, the cytokine is IL-12. In some other embodiments, the cytokine is IL-17. In yet other embodiments, the cytokine is IL-22. In still other embodiments, the cytokine is IL-23. In some embodiments, the cytokine is GM-CSF. In other embodiments, the cytokine is IFN- γ . In yet other embodiments, the cytokine is TNF- α . In certain embodiments, the cytokine is IL-2 and IL-17. In some embodiments, the cytokine is IL-2 and IFN- γ . In yet other embodiments, the cytokine is IL-17 and IFN- γ . In still other embodiments, the cytokine is IL-2, IL-17, and IFN- γ . Other combinations of two, three or more of the above-mentioned cytokines are also contemplated.

[0080] In certain embodiments, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the contact with the antibody or antigen-binding fragment

thereof of the formulation. In another embodiment, the downregulation occurs as early as 6 hours after the contact. In yet another embodiment, the downregulation occurs as early as 8 hours after the contact. In still another embodiment, the downregulation occurs as early as 10 hours after the contact. In one embodiment, the downregulation occurs as early as 12 hours after the contact. In another embodiment, the downregulation occurs as early as 14 hours after the contact. In yet another embodiment, the downregulation occurs as early as 16 hours after the contact. In still another embodiment, the downregulation occurs as early as 18 hours after the contact. In one embodiment, the downregulation occurs as early as 20 hours after the contact. In another embodiment, the downregulation occurs as early as 22 hours after the contact. In yet another embodiment, the downregulation occurs as early as 24 hours after the contact. In some embodiments, the contact is with the antibody of the formulation. In other embodiments, the contact is with an antigen-binding fragment thereof of the formulation.

[0081] In some embodiments, the downregulation of PD-1 expression on the surface of T cells precedes cytokine inhibition. In one embodiment, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In another embodiment, the downregulation occurs as early as 6 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 8 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In still another embodiment, the downregulation occurs as early as 10 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In one embodiment, the downregulation occurs as early as 12 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In another embodiment, the downregulation occurs as early as 14 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 16 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In still another embodiment, the downregulation occurs as early as 18 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In one embodiment, the

downregulation occurs as early as 20 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In another embodiment, the downregulation occurs as early as 22 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 24 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and precedes cytokine inhibition.

[0082] In other embodiments, the downregulation of PD-1 expression on the surface of T cells is concurrent with cytokine inhibition. In one embodiment, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In another embodiment, the downregulation occurs as early as 6 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 8 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In still another embodiment, the downregulation occurs as early as 10 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In one embodiment, the downregulation occurs as early as 12 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In another embodiment, the downregulation occurs as early as 14 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 16 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In still another embodiment, the downregulation occurs as early as 18 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In one embodiment, the downregulation occurs as early as 20 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In another embodiment, the downregulation occurs as early as 22 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition. In yet another embodiment, the downregulation occurs as

early as 24 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is concurrent with cytokine inhibition.

[0083] In yet other embodiments, the downregulation of PD-1 expression on the surface of T cells is after cytokine inhibition. In one embodiment, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In another embodiment, the downregulation occurs as early as 6 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 8 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In still another embodiment, the downregulation occurs as early as 10 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In one embodiment, the downregulation occurs as early as 12 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In another embodiment, the downregulation occurs as early as 14 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 16 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In still another embodiment, the downregulation occurs as early as 18 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In one embodiment, the downregulation occurs as early as 20 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In another embodiment, the downregulation occurs as early as 22 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 24 hours after the contact with the antibody or antigen-binding fragment thereof of the formulation, and is after cytokine inhibition.

[0084] In one embodiment, the K_D of the antibody or antigen-binding fragment thereof of the formulation for binding to purified human PD-1 is from about 1 nM to about 100 nM. In another embodiment, the K_D of the antibody or antigen-binding fragment thereof of the formulation for binding to human PD-1 expressed on a cell surface is from about 100 pM to about 10 nM. In

another embodiment, the K_D of the antibody or antigen-binding fragment thereof of the formulation for binding to monkey PD-1 expressed on a cell surface is from about 100 pM to about 10 nM.

[0085] In some embodiments, the EC_{50} of the antibody or antigen-binding fragment thereof of the formulation for attenuating T cell activity is from about 1 pM to about 10 pM, from about 10 pM to about 100 pM, from about 100 pM to about 1 nM, from about 1 nM to about 10 nM, or from about 10 nM to about 100 nM.

[0086] In other embodiments, the maximal percent attenuation of T cell activity by the antibody or antigen-binding fragment thereof of the formulation is at least about 10%, 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

[0087] In another embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof of the formulation is at least about 10%, 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

[0088] In certain embodiments, the formulation comprises an antibody that is a monoclonal antibody. In some embodiments, the formulation comprises an antibody that is a humanized, human, or chimeric antibody. In another embodiment, the formulation comprises a humanized antibody that is a deimmunized antibody or a composite human antibody. In certain embodiments, the formulation comprises an antibody that is a humanized antibody. In specific embodiments, the formulation comprises an antibody that is a humanized antibody that specifically binds human PD-1. In some embodiments, the antibody is a humanized monoclonal antibody.

[0089] In certain embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that is a Fab, a Fab', a $F(ab')_2$, a Fv, a scFv, a dsFv, a diabody, a triabody, or a tetrabody. In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that is a multispecific antibody formed from antibody fragments. In other embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that is a bispecific antibody. In certain embodiments, the antibody is not an antibody fragment.

[0090] In some embodiments, the formulation comprises an antibody or antigen-binding fragment thereof that is conjugated to an agent. In one embodiment, the agent is a radioisotope, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound, or a chemiluminescent compound.

[0091] In certain embodiments, the pharmaceutical formulation comprises a buffer. In some embodiments, the buffer is an acetate buffer, succinate buffer, histidine buffer, or citrate buffer. In one embodiment, the buffer is an acetate buffer. In another embodiment, the buffer is a succinate buffer. In yet another embodiment, the buffer is a histidine buffer. In still another embodiment, the buffer is a citrate buffer.

[0092] In some embodiments, the concentration of the buffer is from 0.1 mM to 1 M. In other embodiments, the concentration of the buffer is from 1 mM to 100 mM. In other embodiments, the concentration of the buffer is 10 mM.

[0093] In one embodiment, the formulation comprises acetate buffer at a concentration of from 0.1 mM to 1 M. In another embodiment, the formulation comprises acetate buffer at a concentration of from 0.1 mM to 100 mM. In one embodiment, the formulation comprises acetate buffer at a concentration of from 0.1 mM to 10 mM. In one embodiment, the formulation comprises acetate buffer at a concentration of from 1 mM to 100 mM. In another embodiment, the formulation comprises acetate buffer at a concentration of from 1 mM to 10 mM. In one embodiment, the formulation comprises acetate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the formulation comprises acetate buffer at a concentration of 5 mM. In one embodiment, the formulation comprises acetate buffer at a concentration of 15 mM. In another embodiment, the formulation comprises acetate buffer at a concentration of 10 mM.

[0094] In one embodiment, the formulation comprises succinate buffer at a concentration of from 0.1 mM to 1 M. In another embodiment, the formulation comprises succinate buffer at a concentration of from 0.1 mM to 100 mM. In one embodiment, the formulation comprises succinate buffer at a concentration of from 0.1 mM to 10 mM. In one embodiment, the formulation comprises succinate buffer at a concentration of from 1 mM to 100 mM. In another embodiment, the formulation comprises succinate buffer at a concentration of from 1 mM to 10 mM. In one embodiment, the formulation comprises succinate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the formulation comprises succinate buffer at a concentration of 5 mM. In one embodiment, the formulation comprises succinate buffer at a concentration of 15 mM. In another embodiment, the formulation comprises succinate buffer at a concentration of 10 mM.

[0095] In one embodiment, the formulation comprises histidine buffer at a concentration of from 0.1 mM to 1M. In another embodiment, the formulation comprises histidine buffer at a

concentration of from 0.1 mM to 100 mM. In one embodiment, the formulation comprises histidine buffer at a concentration of from 0.1 mM to 10 mM. In one embodiment, the formulation comprises histidine buffer at a concentration of from 1 mM to 100 mM. In another embodiment, the formulation comprises histidine buffer at a concentration of from 1 mM to 10 mM. In one embodiment, the formulation comprises histidine buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the formulation comprises histidine buffer at a concentration of 5 mM. In one embodiment, the formulation comprises histidine buffer at a concentration of 15 mM. In another embodiment, the formulation comprises histidine buffer at a concentration of 10 mM.

[0096] In one embodiment, the formulation comprises citrate buffer at a concentration of from 0.1 mM to 1M. In another embodiment, the formulation comprises citrate buffer at a concentration of from 0.1 mM to 100 mM. In one embodiment, the formulation comprises citrate buffer at a concentration of from 0.1 mM to 10 mM. In one embodiment, the formulation comprises citrate buffer at a concentration of from 1 mM to 100 mM. In another embodiment, the formulation comprises citrate buffer at a concentration of from 1 mM to 10 mM. In one embodiment, the formulation comprises citrate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the formulation comprises citrate buffer at a concentration of 5 mM. In one embodiment, the formulation comprises citrate buffer at a concentration of 15 mM. In another embodiment, the formulation comprises citrate buffer at a concentration of 10 mM.

[0097] In certain embodiments, the pH of the buffer is within the range of pH 4 and 6.5. In some embodiments, the pH of the buffer is within the range of pH 4.7 and 5.7. In other embodiments, the pH of the buffer is about 5.2. In other embodiments, the pH of the buffer is 5.2. In one embodiment, the buffer is 10 mM acetate buffer and the pH is about 5.2. In another embodiment, the buffer is 10 mM succinate buffer and the pH is about 5.2. In yet another embodiment, the buffer is 10 mM histidine buffer and the pH is about 5.2. In still another embodiment, the buffer is 10 mM citrate buffer and the pH is about 5.2.

[0098] In certain embodiments, the pH of the formulation is within the range of pH 4 and 6.5. In some embodiments, the pH of the formulation is within the range of pH 4.7 and 5.7. In other embodiments, the pH of the formulation is about 5.2. In other embodiments, the pH of the formulation is 5.2.

[0099] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises acetate buffer. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises acetate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises acetate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises acetate buffer. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises acetate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises acetate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises acetate buffer. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises acetate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises acetate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises acetate buffer. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises acetate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises acetate buffer at a concentration of 10 mM. In one embodiment, a acetate buffer is the only buffer present in the formulation.

[00100] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises succinate buffer. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises succinate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises succinate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises succinate buffer. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises succinate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises succinate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises succinate buffer. In one embodiment, the pH of the formulation is about 5.2, and the

formulation comprises succinate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises succinate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises succinate buffer. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises succinate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises succinate buffer at a concentration of 10 mM. In one embodiment, a succinate buffer is the only buffer present in the formulation.

[0100] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises histidine buffer. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises histidine buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises histidine buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises histidine buffer. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises histidine buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises histidine buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises histidine buffer. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises histidine buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises histidine buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises histidine buffer. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises histidine buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises histidine buffer at a concentration of 10 mM. In one embodiment, a histidine buffer is the only buffer present in the formulation.

[0101] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises citrate buffer. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises citrate buffer at a concentration

of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises citrate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises citrate buffer. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises citrate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises citrate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises citrate buffer. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises citrate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises citrate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises citrate buffer. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises citrate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises citrate buffer at a concentration of 10 mM. In one embodiment, a citrate buffer is the only buffer present in the formulation.

[0102] In some embodiments, the pharmaceutical formulation further comprises a surfactant. In certain embodiments, the surfactant is a polysorbate. In one embodiment, the polysorbate is polysorbate-20. In one embodiment, the polysorbate is polysorbate-40. In one embodiment, the polysorbate is polysorbate-60. In one embodiment, the polysorbate is polysorbate-80.

[0103] In one embodiment, the concentration of the surfactant is from 0.001-0.1% (w/v). In one embodiment, the concentration of the surfactant is from 0.001-0.01% (w/v). In one embodiment, the concentration of the surfactant is 0.05% (w/v). In one embodiment, the concentration of the surfactant is about 0.005% (w/v). In one embodiment, the concentration of the surfactant is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-20 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.01% (w/v). In one embodiment, the

concentration of the polysorbate-40 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-40 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-60 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-80 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.005% (w/v).

[0104] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer. In one embodiment, the pH of the formulation is about 5.2, and the formulation

comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a acetate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) an acetate buffer at a concentration of 10 mM. In one embodiment, a acetate buffer is the only buffer present in the formulation. In one embodiment, the surfactant is a polysorbate. In one embodiment, the polysorbate is polysorbate-20. In one embodiment, the polysorbate is polysorbate-40. In one embodiment, the polysorbate is polysorbate-60. In one embodiment, the polysorbate is polysorbate-80. In one embodiment, the concentration of the surfactant is from 0.001-0.1% (w/v). In one embodiment, the concentration of the surfactant is from 0.001-0.01% (w/v). In one embodiment, the concentration of the surfactant is 0.05% (w/v). In one embodiment, the concentration of the surfactant is about 0.005% (w/v). In one embodiment, the concentration of the surfactant is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-20 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-40 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.05% (w/v). In one embodiment, the

concentration of the polysorbate-60 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-80 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.005% (w/v).

[0105] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises

(i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a succinate buffer at a concentration of 10 mM. In one embodiment, a succinate buffer is the only buffer present in the formulation. In one embodiment, the surfactant is a polysorbate. In one embodiment, the polysorbate is polysorbate-20. In one embodiment, the polysorbate is polysorbate-40. In one embodiment, the polysorbate is polysorbate-60. In one embodiment, the polysorbate is polysorbate-80. In one embodiment, the concentration of the surfactant is from 0.001-0.1% (w/v). In one embodiment, the concentration of the surfactant is from 0.001-0.01% (w/v). In one embodiment, the concentration of the surfactant is 0.05% (w/v). In one embodiment, the concentration of the surfactant is about 0.005% (w/v). In one embodiment, the concentration of the surfactant is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-20 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-40 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-60 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-80 is

about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.005% (w/v).

[0106] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding

fragment provided herein, (ii) a surfactant, and (iii) a histidine buffer at a concentration of 10 mM. In one embodiment, a histidine buffer is the only buffer present in the formulation. In one embodiment, the surfactant is a polysorbate. In one embodiment, the polysorbate is polysorbate-20. In one embodiment, the polysorbate is polysorbate-40. In one embodiment, the polysorbate is polysorbate-60. In one embodiment, the polysorbate is polysorbate-80. In one embodiment, the concentration of the surfactant is from 0.001-0.1% (w/v). In one embodiment, the concentration of the surfactant is from 0.001-0.01% (w/v). In one embodiment, the concentration of the surfactant is 0.05% (w/v). In one embodiment, the concentration of the surfactant is about 0.005% (w/v). In one embodiment, the concentration of the surfactant is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-20 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-40 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-60 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-80 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.005% (w/v).

[0107] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises a (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer. In one embodiment, the pH of the formulation is

within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer at a concentration of 10 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer at a concentration of from 5 mM to 15 mM. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, and (iii) a citrate buffer at a concentration of 10 mM. In one embodiment, a citrate buffer is the only buffer present in the formulation. In one embodiment, the surfactant is a polysorbate. In one embodiment, the polysorbate is polysorbate-20. In one embodiment, the polysorbate is polysorbate-40. In one embodiment, the polysorbate is polysorbate-60. In one embodiment, the polysorbate is polysorbate-80. In one embodiment, the concentration of the

surfactant is from 0.001-0.1% (w/v). In one embodiment, the concentration of the surfactant is from 0.001-0.01% (w/v). In one embodiment, the concentration of the surfactant is 0.05% (w/v). In one embodiment, the concentration of the surfactant is about 0.005% (w/v). In one embodiment, the concentration of the surfactant is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-20 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-40 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-60 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-80 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.005% (w/v).

[0108] In some embodiments, the pharmaceutical formulation further comprises a polyol. In certain embodiments, the polyol is a sugar, sugar alcohol, or sugar acid. In one embodiment, the polyol is a sugar. In another embodiment, the polyol is a sugar alcohol. In yet another embodiment, the polyol is a sugar acid. In one specific embodiment, the polyol is sucrose. In one embodiment, the concentration of the sucrose is from 5-10% (w/v). In one embodiment, the concentration of the sucrose is from 8-9% (w/v). In another embodiment, the concentration of the sucrose is 9% (w/v). In another embodiment, the concentration of the sucrose is about 8.5% (w/v). In another embodiment, the concentration of the sucrose is 8.5% (w/v). In one specific embodiment, the polyol is maltose. In one embodiment, the concentration of the maltose is from

5-10% (w/v). In one embodiment, the concentration of the maltose is from 8-9% (w/v). In another embodiment, the concentration of the maltose is 9% (w/v). In another embodiment, the concentration of the maltose is about 8.5% (w/v). In another embodiment, the concentration of the maltose is 8.5% (w/v). In one specific embodiment, the polyol is trehalose. In one embodiment, the concentration of the trehalose is from 5-10% (w/v). In one embodiment, the concentration of the trehalose is from 8-9% (w/v). In another embodiment, the concentration of the trehalose is 9% (w/v). In another embodiment, the concentration of the trehalose is about 8.5% (w/v). In another embodiment, the concentration of the trehalose is 8.5% (w/v). In one specific embodiment, the polyol is mannitol. In one embodiment, the concentration of the mannitol is from 5-10% (w/v). In one embodiment, the concentration of the mannitol is from 8-9% (w/v). In another embodiment, the concentration of the mannitol is 9% (w/v). In another embodiment, the concentration of the mannitol is about 8.5% (w/v). In another embodiment, the concentration of the mannitol is 8.5% (w/v). In one specific embodiment, the polyol is sorbitol. In one embodiment, the concentration of the sorbitol is from 5-10% (w/v). In one embodiment, the concentration of the sorbitol is from 8-9% (w/v). In another embodiment, the concentration of the sorbitol is 9% (w/v). In another embodiment, the concentration of the sorbitol is about 8.5% (w/v). In another embodiment, the concentration of the sorbitol is 8.5% (w/v).

[0109] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In

one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) an acetate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, an acetate buffer is the only buffer present in the formulation. In certain embodiments, the polyol is a sugar, sugar alcohol, or sugar acid. In one embodiment, the polyol is a sugar. In another embodiment, the polyol is a sugar alcohol. In yet another embodiment, the polyol is a sugar acid. In one specific embodiment, the polyol is sucrose. In one embodiment, the concentration of the sucrose is from 5-10% (w/v). In one embodiment, the concentration of the sucrose is from 8-9% (w/v). In another embodiment, the concentration of the sucrose is 9% (w/v). In another embodiment, the concentration of the sucrose is about 8.5% (w/v). In another embodiment, the concentration of the sucrose is 8.5% (w/v). In one specific embodiment, the polyol is maltose. In one embodiment, the concentration of the maltose is from 5-10% (w/v). In one embodiment, the concentration of the maltose is from 8-9% (w/v). In another embodiment, the concentration of the maltose is 9% (w/v). In another embodiment, the concentration of the maltose is about 8.5% (w/v). In another embodiment, the concentration of the maltose is 8.5% (w/v). In one specific embodiment, the polyol is trehalose. In one embodiment, the concentration

of the trehalose is from 5-10% (w/v). In one embodiment, the concentration of the trehalose is from 8-9% (w/v). In another embodiment, the concentration of the trehalose is 9% (w/v). In another embodiment, the concentration of the trehalose is about 8.5% (w/v). In another embodiment, the concentration of the trehalose is 8.5% (w/v). In one specific embodiment, the polyol is mannitol. In one embodiment, the concentration of the mannitol is from 5-10% (w/v). In one embodiment, the concentration of the mannitol is from 8-9% (w/v). In another embodiment, the concentration of the mannitol is 9% (w/v). In another embodiment, the concentration of the mannitol is about 8.5% (w/v). In another embodiment, the concentration of the mannitol is 8.5% (w/v). In one specific embodiment, the polyol is sorbitol. In one embodiment, the concentration of the sorbitol is from 5-10% (w/v). In one embodiment, the concentration of the sorbitol is from 8-9% (w/v). In another embodiment, the concentration of the sorbitol is 9% (w/v). In another embodiment, the concentration of the sorbitol is about 8.5% (w/v). In another embodiment, the concentration of the sorbitol is 8.5% (w/v). In one embodiment, the surfactant is a polysorbate. In one embodiment, the polysorbate is polysorbate-20. In one embodiment, the polysorbate is polysorbate-40. In one embodiment, the polysorbate is polysorbate-60. In one embodiment, the polysorbate is polysorbate-80. In one embodiment, the concentration of the surfactant is from 0.001-0.1% (w/v). In one embodiment, the concentration of the surfactant is from 0.001-0.01% (w/v). In one embodiment, the concentration of the surfactant is 0.05% (w/v). In one embodiment, the concentration of the surfactant is about 0.005% (w/v). In one embodiment, the concentration of the surfactant is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-20 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-40 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.01% (w/v). In one

embodiment, the concentration of the polysorbate-60 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-60 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-80 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.005% (w/v).

[0110] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1

antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a succinate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, a succinate buffer is the only buffer present in the formulation. In certain embodiments, the polyol is a sugar, sugar alcohol, or sugar acid. In one embodiment, the polyol is a sugar. In another embodiment, the polyol is a sugar alcohol. In yet another embodiment, the polyol is a sugar acid. In one specific embodiment, the polyol is sucrose. In one embodiment, the concentration of the sucrose is from 5-10% (w/v). In one embodiment, the concentration of the sucrose is from 8-9% (w/v). In another embodiment, the concentration of the sucrose is 9% (w/v). In another embodiment, the concentration of the sucrose is about 8.5% (w/v). In another embodiment, the concentration of the sucrose is 8.5% (w/v). In one specific embodiment, the polyol is maltose. In one embodiment, the concentration of the maltose is from 5-10% (w/v). In one embodiment, the concentration of the maltose is from 8-9% (w/v). In another embodiment, the concentration of the maltose is 9% (w/v). In another embodiment, the concentration of the maltose is about 8.5% (w/v). In another embodiment, the concentration of the maltose is 8.5% (w/v). In one specific embodiment, the polyol is trehalose. In one embodiment, the concentration of the trehalose is from 5-10% (w/v). In one embodiment, the concentration of the trehalose is from 8-9% (w/v). In another embodiment, the concentration of the trehalose is 9% (w/v). In another embodiment, the concentration of the trehalose is about 8.5% (w/v). In another embodiment, the concentration of the trehalose is 8.5% (w/v). In one specific embodiment, the polyol is mannitol. In one embodiment, the concentration of the mannitol is from 5-10% (w/v). In one embodiment, the concentration of the mannitol is from 8-9% (w/v). In another embodiment, the concentration of the mannitol is 9% (w/v). In another embodiment, the concentration of the mannitol is about 8.5% (w/v). In another embodiment, the concentration of the mannitol is 8.5% (w/v). In one specific embodiment, the polyol is sorbitol. In one

embodiment, the concentration of the sorbitol is from 5-10% (w/v). In one embodiment, the concentration of the sorbitol is from 8-9% (w/v). In another embodiment, the concentration of the sorbitol is 9% (w/v). In another embodiment, the concentration of the sorbitol is about 8.5% (w/v). In another embodiment, the concentration of the sorbitol is 8.5% (w/v). In one embodiment, the surfactant is a polysorbate. In one embodiment, the polysorbate is polysorbate-20. In one embodiment, the polysorbate is polysorbate-40. In one embodiment, the polysorbate is polysorbate-60. In one embodiment, the polysorbate is polysorbate-80. In one embodiment, the concentration of the surfactant is from 0.001-0.1% (w/v). In one embodiment, the concentration of the surfactant is from 0.001-0.01% (w/v). In one embodiment, the concentration of the surfactant is 0.05% (w/v). In one embodiment, the concentration of the surfactant is about 0.005% (w/v). In one embodiment, the concentration of the surfactant is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-20 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-40 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-60 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-80 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.005% (w/v).

[0111] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a histidine buffer at a concentration of 10 mM, and (iv) a polyol.

surfactant, (iii) a histidine buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, a histidine buffer is the only buffer present in the formulation. In certain embodiments, the polyol is a sugar, sugar alcohol, or sugar acid. In one embodiment, the polyol is a sugar. In another embodiment, the polyol is a sugar alcohol. In yet another embodiment, the polyol is a sugar acid. In one specific embodiment, the polyol is sucrose. In one embodiment, the concentration of the sucrose is from 5-10% (w/v). In one embodiment, the concentration of the sucrose is from 8-9% (w/v). In another embodiment, the concentration of the sucrose is 9% (w/v). In another embodiment, the concentration of the sucrose is about 8.5% (w/v). In another embodiment, the concentration of the sucrose is 8.5% (w/v). In one specific embodiment, the polyol is maltose. In one embodiment, the concentration of the maltose is from 5-10% (w/v). In one embodiment, the concentration of the maltose is from 8-9% (w/v). In another embodiment, the concentration of the maltose is 9% (w/v). In another embodiment, the concentration of the maltose is about 8.5% (w/v). In another embodiment, the concentration of the maltose is 8.5% (w/v). In one specific embodiment, the polyol is trehalose. In one embodiment, the concentration of the trehalose is from 5-10% (w/v). In one embodiment, the concentration of the trehalose is from 8-9% (w/v). In another embodiment, the concentration of the trehalose is 9% (w/v). In another embodiment, the concentration of the trehalose is about 8.5% (w/v). In another embodiment, the concentration of the trehalose is 8.5% (w/v). In one specific embodiment, the polyol is mannitol. In one embodiment, the concentration of the mannitol is from 5-10% (w/v). In one embodiment, the concentration of the mannitol is from 8-9% (w/v). In another embodiment, the concentration of the mannitol is 9% (w/v). In another embodiment, the concentration of the mannitol is about 8.5% (w/v). In another embodiment, the concentration of the mannitol is 8.5% (w/v). In one specific embodiment, the polyol is sorbitol. In one embodiment, the concentration of the sorbitol is from 5-10% (w/v). In one embodiment, the concentration of the sorbitol is from 8-9% (w/v). In another embodiment, the concentration of the sorbitol is 9% (w/v). In another embodiment, the concentration of the sorbitol is about 8.5% (w/v). In another embodiment, the concentration of the sorbitol is 8.5% (w/v). In one embodiment, the surfactant is a polysorbate. In one embodiment, the polysorbate is polysorbate-20. In one embodiment, the polysorbate is polysorbate-40. In one embodiment, the polysorbate is polysorbate-60. In one embodiment, the polysorbate is polysorbate-80. In one embodiment, the concentration of the surfactant is from 0.001-0.1% (w/v). In one embodiment, the concentration

of the surfactant is from 0.001-0.01% (w/v). In one embodiment, the concentration of the surfactant is 0.05% (w/v). In one embodiment, the concentration of the surfactant is about 0.005% (w/v). In one embodiment, the concentration of the surfactant is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-20 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-40 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-60 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-80 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.005% (w/v).

[0112] In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4 and 6.5, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is

within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is within the range of pH 4.7 and 5.7, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is about 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer at a concentration of from 5 mM to 15 mM, and (iv) a polyol. In one embodiment, the pH of the formulation is 5.2, and the formulation comprises (i) a PD-1 antibody or antigen-binding fragment provided herein, (ii) a surfactant, (iii) a citrate buffer at a concentration of 10 mM, and (iv) a polyol. In one embodiment, a citrate buffer is the only buffer present in the formulation. In certain embodiments, the polyol is a sugar, sugar alcohol, or sugar acid. In one embodiment, the polyol is a sugar. In another embodiment, the polyol is a sugar alcohol. In yet another embodiment, the polyol is a sugar acid. In one specific embodiment, the polyol is sucrose. In one embodiment, the concentration of the sucrose is from 5-10% (w/v). In one embodiment, the concentration of the sucrose is from 8-9% (w/v). In another embodiment, the concentration of the sucrose is 9% (w/v). In another embodiment, the concentration of the sucrose is about 8.5% (w/v). In another embodiment, the concentration of the sucrose is 8.5% (w/v). In one specific embodiment, the

polyol is maltose. In one embodiment, the concentration of the maltose is from 5-10% (w/v). In one embodiment, the concentration of the maltose is from 8-9% (w/v). In another embodiment, the concentration of the maltose is 9% (w/v). In another embodiment, the concentration of the maltose is about 8.5% (w/v). In another embodiment, the concentration of the maltose is 8.5% (w/v). In one specific embodiment, the polyol is trehalose. In one embodiment, the concentration of the trehalose is from 5-10% (w/v). In one embodiment, the concentration of the trehalose is from 8-9% (w/v). In another embodiment, the concentration of the trehalose is 9% (w/v). In another embodiment, the concentration of the trehalose is about 8.5% (w/v). In another embodiment, the concentration of the trehalose is 8.5% (w/v). In one specific embodiment, the polyol is mannitol. In one embodiment, the concentration of the mannitol is from 5-10% (w/v). In one embodiment, the concentration of the mannitol is from 8-9% (w/v). In another embodiment, the concentration of the mannitol is 9% (w/v). In another embodiment, the concentration of the mannitol is about 8.5% (w/v). In another embodiment, the concentration of the mannitol is 8.5% (w/v). In one specific embodiment, the polyol is sorbitol. In one embodiment, the concentration of the sorbitol is from 5-10% (w/v). In one embodiment, the concentration of the sorbitol is from 8-9% (w/v). In another embodiment, the concentration of the sorbitol is 9% (w/v). In another embodiment, the concentration of the sorbitol is about 8.5% (w/v). In another embodiment, the concentration of the sorbitol is 8.5% (w/v). In one embodiment, the surfactant is a polysorbate. In one embodiment, the polysorbate is polysorbate-20. In one embodiment, the polysorbate is polysorbate-40. In one embodiment, the polysorbate is polysorbate-60. In one embodiment, the polysorbate is polysorbate-80. In one embodiment, the concentration of the surfactant is from 0.001-0.1% (w/v). In one embodiment, the concentration of the surfactant is from 0.001-0.01% (w/v). In one embodiment, the concentration of the surfactant is 0.05% (w/v). In one embodiment, the concentration of the surfactant is about 0.005% (w/v). In one embodiment, the concentration of the surfactant is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-20 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-20 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-20 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the

polysorbate-40 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-40 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-40 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-60 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-60 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-60 is 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.1% (w/v). In one embodiment, the concentration of the polysorbate-80 is from 0.001-0.01% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.05% (w/v). In one embodiment, the concentration of the polysorbate-80 is about 0.005% (w/v). In one embodiment, the concentration of the polysorbate-80 is 0.005% (w/v).

[0113] In a specific embodiment, provided herein is a pharmaceutical formulation comprising an antibody that binds to PD-1, wherein the formulation has a pH of 5.2 and comprises (i) 10 mM sodium acetate buffer, (ii) 8.5% (w/v) sucrose, and (iii) 0.005% (w/v) polysorbate-80. In another specific embodiment, provided herein is a pharmaceutical formulation comprising an antigen-binding fragment that binds to PD-1, wherein the formulation has a pH of 5.2 and comprises (i) 10 mM sodium acetate buffer, (ii) 8.5% (w/v) sucrose, and (iii) 0.005% (w/v) polysorbate-80.

[0114] In certain embodiment of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody. In other embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antigen-binding fragment.

[0115] In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VL comprising VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in **Table 1**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-1 as set forth in **Table 1**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VL comprising VL CDR1, VL CDR2, and VL CDR3

of PD1AB-2 as set forth in **Table 1**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-3 as set forth in **Table 1**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-4 as set forth in **Table 1**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-5 as set forth in **Table 1**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-6 as set forth in **Table 1**.

[0116] In other embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VH comprising VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in **Table 2**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-1 as set forth in **Table 2**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-2 as set forth in **Table 2**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-3 as set forth in **Table 2**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-4 as set forth in **Table 2**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-5 as set forth in **Table 2**. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-6 as set forth in **Table 2**.

[0117] In other embodiments of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising (a) a VL comprising VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in **Table 1**, and (b) a VH comprising VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in **Table 2**. In one embodiment of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising (a) a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-1 as set forth in **Table 1**, and (b) a VH comprising VH CDR1, VH CDR2, and VH CDR3 of any one of PD1AB-1 as set forth in **Table 2**. In one embodiment of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising (a) a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-2 as set forth in **Table 1**, and (b) a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-2 as set forth in **Table 2**. In one embodiment of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising (a) a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-3 as set forth in **Table 1**, and (b) a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-3 as set forth in **Table 2**. In one embodiment of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising (a) a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-4 as set forth in **Table 1**, and (b) a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-4 as set forth in **Table 2**. In one embodiment of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising (a) a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-5 as set forth in **Table 1**, and (b) a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-5 as set forth in **Table 2**. In one embodiment of the various pharmaceutical formulations provided herein, the formulation comprises a PD-1 antibody comprising (a) a VL comprising VL CDR1, VL CDR2, and VL CDR3 of PD1AB-6 as set forth in **Table 1**, and (b) a VH comprising VH CDR1, VH CDR2, and VH CDR3 of PD1AB-6 as set forth in **Table 2**.

[0118] In certain embodiments of the various pharmaceutical formulations provided herein, the formulation comprises PD1AB-1. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises PD1AB-2. In other embodiments of the various pharmaceutical formulations provided herein, the formulation comprises PD1AB-3. In

some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises PD1AB-4. In other embodiments of the various pharmaceutical formulations provided herein, the formulation comprises PD1AB-5. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises PD1AB-6. In certain embodiments, the pharmaceutical formulation comprises a PD-1 antibody that is an IgG1 antibody. In some embodiments, the pharmaceutical formulation comprises a PD-1 antibody that is an IgG1 variant antibody. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises PD1AB-6-K3. In some embodiments of the various pharmaceutical formulations provided herein, the formulation comprises PD1AB-6-4P.

[0119] In some embodiments, the various pharmaceutical formulations provided herein are aqueous pharmaceutical formulations.

[0120] In certain embodiments, the various pharmaceutical formulations provided herein are stable. Stability of the pharmaceutical formulations provided herein can be measured at a selected temperature for a selected time period. In one embodiment, the antibody in the liquid formulations is stable in a liquid form for at least about 3 months. In one embodiment, the antibody in the liquid formulations is stable in a liquid form for at least about 4 months. In one embodiment, the antibody in the liquid formulations is stable in a liquid form for at least about 5 months. In one embodiment, the antibody in the liquid formulations is stable in a liquid form for at least about 6 months. In one embodiment, the antibody in the liquid formulations is stable in a liquid form for at least about 12 months. In one embodiment, the antibody in the liquid formulations is stable in a liquid form for at least about 18 months. In one embodiment, the antibody in the liquid formulations is stable in a liquid form for at least about 24 months. Values and ranges intermediate to the above recited time periods are also contemplated, *e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months. In addition, ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included. In some embodiments, the pharmaceutical formulation is stable at -70 °C. In some embodiments, the pharmaceutical formulation is stable at 4 °C. In some embodiments, the pharmaceutical formulation is stable at 25 °C. In some embodiments, the pharmaceutical formulation is stable at 30 °C. In a specific embodiment, the pharmaceutical formulation is stable for at least 12 months when stored at -70 °C ± 10 °C. In other

embodiments, the pharmaceutical formulation is stable for at least 6 months when stored at 5 °C $\pm$ 3 °C.

[0121] Further provided herein is a method of making the various pharmaceutical formulations disclosed herein, comprising: (a) culturing a cell in a medium, wherein the cell comprises one or more polynucleotides comprising nucleotide sequences encoding a heavy chain, a light chain, or both a heavy chain and a light chain of the antibody or antigen-binding fragment thereof provided herein; (b) harvesting the medium; and (c) subjecting the medium to a series of purification steps.

[0122] In certain embodiments of the methods, the purification steps comprise: (i) an affinity chromatography; (ii) a viral inactivation; (iii) an ion exchange chromatography; (iv) a viral filtration; and (v) an ultrafiltration/diafiltration. In one embodiment, the affinity chromatography is a protein A affinity chromatography. In another embodiment, the viral inactivation step is a low-pH viral inactivation step. In yet another embodiment, the ion exchange chromatography is an anion exchange chromatography. In still another embodiment, the affinity chromatography is a protein A affinity chromatography, the viral inactivation step is a low-pH viral inactivation step, and the ion exchange chromatography is an anion exchange chromatography.

[0123] In certain embodiments of the methods, the purification steps comprise: (i) a protein A affinity chromatography; (ii) a low-pH viral inactivation step; (iii) an anion exchange chromatography; (iv) a viral filtration step; and (v) an ultrafiltration/diafiltration.

[0124] In some embodiments, the method of making the various pharmaceutical formulations disclosed herein further comprises a formulation step.

4. BRIEF DESCRIPTION OF THE FIGURES

[0125] **FIGS. 1A-1B** show that the T cell attenuating anti-PD-1 antibodies (PD1AB) do not compete with PD-L1 (PD-L1-DyL650 denotes PD-L1 conjugated with the dye DyL650) binding to PD-1: **(A)** PD1AB-1, PD1AB-2, and PD1AB-6; **(B)** PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, and PD1AB-5. MDX 4H1, an antagonist antibody, blocks PD-L1 binding to PD-1.

[0126] **FIG. 2** depicts that the PD-1:PD1AB-6 Fab interaction site is at a distal side of PD-1 relative to the PD-1:PD-L1 interaction site.

[0127] **FIG. 3** depicts that PD1AB-6 Fab binds against a PD-1 β sheet, with substantial interactions formed with a PD-1 loop composed of residues 100-105.

[0128] **FIG. 4** shows the amino acid sequences of heavy chain (HC) and light chain (LC) of PD1AB-6-IgG1 and HC of its variants PD1AB-6-K3 and PD1AB-6-4P.

[0129] **FIGS. 5A-5B** depict the PD1AB-6-IgG1 affinity for cynomolgus **(A)** or human **(B)** PD-1 expressed on CHO cells.

[0130] **FIG. 6** depicts the binding of PD1AB-6-IgG1, isotype control, and human PD-L1 Fc fusion protein (hPD-L1 Fc) to activated human PBMC gated on CD4⁺ T cells.

[0131] **FIG. 7** depicts the binding of PD1AB-6-IgG1, isotype control, and human PD-L1 Fc fusion protein (hPD-L1 Fc) to activated cynomolgus PBMC gated on CD4⁺ T cells.

[0132] **FIGS. 8A-8D** show the PD1AB-6 variants binding to FcγRI **(A)**, FcγRIIIa (V158) **(B)**, or FcγRIIb **(C)** expressed on HEK293 cells using Cisbio Tag-lite™ detection, and **(D)** the EC₅₀ values of the PD1AB-6 variants binding to FcγRI, FcγRIIIa (V158), or FcγRIIb.

[0133] **FIGS. 9A-9C** depict the PD1AB-6 variants binding to FcγRIIIa (V158) **(A)** or FcγRI **(B)** expressed on CHO cells using FACS, and **(C)** the EC₅₀ values of the PD-1 antibody variants binding to FcγRI or FcγRIIIa.

[0134] **FIGS. 10A-10B** depict the ADCC activity of the PD1AB-6 variants and a control human IgG1 Fc among two representatives of four individual healthy donors: **(A)** Donor 7 and **(B)** Donor 8.

[0135] **FIG. 11** depicts the CDC activity of the PD1AB-6 variants. Data are representative of 3 independent experiments: (i) CDC activity of PD1AB-6-IgG1 and anti-human CD20 IgG1; (ii) CDC activity of PD1AB-6-IgG1 and PD1AB-6-K3; (iii) CDC activity of PD1AB-6-4P and commercial human IgG4 isotype control antibody and human IgG1 Fc protein.

[0136] **FIG. 12** depicts the potent attenuating activity of PD1AB-6 variants in human PBMC assay, measured by IL-2 levels in culture supernatants at 24 hours post-stimulation.

[0137] **FIG. 13** depicts the activity of PD1AB-6-K3 in human whole blood assay. The graph shows a representative curve from donor 4 used to calculate EC₅₀ of IFN-γ inhibition. The table shows EC₅₀ values of IFN-γ inhibition for 4 healthy donors with PD1AB-6 variants and CTLA4Ig.

[0138] **FIGS. 14A-14C** depict downregulation of PD-1 expression by PD1AB-6-IgG1 as determined by **(A)** isotype vs. PD-1 staining on CD3⁺ T cells in human PBMC activated with anti-CD3 + anti-CD28 for 48 hours, **(B)** PD-1 expression in isotype IgG1 vs. PD1AB-6-IgG1 treated PBMC (the detection anti-PD-1 antibody is not blocked by PD1AB-6), and **(C)** PD-1

expression on CD3⁺ T cells in human PBMC from 3 different donors, activated with anti-CD3 + anti-CD28 and three different concentrations of either isotype IgG1 or PD1AB-6-IgG1.

[0139] **FIGS. 15A-15C** show **(A)** PD1AB-6-IgG1, **(B)** PD1AB-6-4P, and **(C)** PD1AB-6-K3 binding to PD-1 antigen on Biacore[®] T200.

[0140] **FIG. 16** shows differential scanning calorimetry analysis of PD1AB-6 variants.

[0141] **FIG. 17** shows PD1AB-6-K3 stability at 40 °C, as measured by the weekly change in monomer content over a range of pH.

[0142] **FIG. 18** shows increase in submicron particle size over 8 weeks at the 40 °C thermal stress condition, as measured by DLS over a range of buffers and pH for PD1AB-6-K3 expressed in CHO cells.

[0143] **FIG. 19** shows rate of increase in turbidity over 8 weeks at the 40 °C thermal stress condition, as measured by A360 over a range of buffers and pH for PD1AB-6-K3 expressed in CHO cells.

[0144] **FIG. 20** shows PD1AB-6-K3 stability at 5 °C, as measured by the weekly change in monomer content over a range of pH.

[0145] **FIGS. 21A-21B** illustrate the flow diagrams of manufacturing process of PD1AB-6-K3 drug substance with **(A)** showing the upstream cell culture and harvest steps, and **(B)** showing the downstream purification steps.

[0146] **FIG. 22** is a schematic illustration of the experimental design for a two-arm (2×2) full factorial modeling of the effects of pH and surfactant concentration (*e.g.*, PS-80) on formulations samples containing 10 mM sodium acetate, 9% (w/v) sucrose and 125 mg/ml of PD1AB-6-K3 antibodies

[0147] **FIGS. 23A-23D** depict the results of Size Exclusion Chromatography (SEC) at different time points to quantify the fraction of monomer, high molecular weight (HMW) species (aggregates), and low molecular weight (LMW) species (fragments or clips) of the antibody in candidate formulations. **(A)** Results of SEC analysis of candidate antibody formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, 0.005% (w/v) PS-80, and adjusted to different pH (*i.e.*, pH 5.2, 5.5 and 5.8) after being stored at 4 °C for 12 weeks. A control formulation stored at -80 °C was included. The left panel is an enlarged view of the lower area between 10 and 20 (minutes of elution time) in the right panel. Shown is the change within **(B)** 12 weeks, **(C)** 26 weeks, or **(D)** 14 months of the fraction (%) of HMW of the antibody in

candidate formulations stored at 4 °C. Error bars are the standard deviations of replicate injections of an internal standard and represent the precision of the method/integration.

[0148] FIGS. 24A-24C depict the results of SEC at different time points to quantify the fraction of monomer, HMW species (aggregates), and LMW species (fragments or clips) of the antibody in candidate formulations **(A)** Results of SEC analysis of candidate antibody formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, 0.005% (w/v) PS-80, and adjusted to different pH (*i.e.*, pH 5.2, 5.5 and 5.8) after being stored at 25 °C for 12 weeks. A control formulation stored at -80 °C was included. The left panel is an enlarged view of the lower area between 10 and 20 (minutes of elution time) in the right panel. Shown is the change within **(B)** 12 weeks or **(C)** 26 weeks of the fraction (%) of HMW of the antibody in candidate formulations stored at 25 °C. Error bars are the standard deviations of replicate injections of an internal standard and represent the precision of the method/integration.

[0149] FIGS. 25A-25C depict the results of SEC at different time points to quantify the fraction of monomer HMW species (aggregates), and LMW species (fragments or clips) of the antibody in candidate formulations. **(A)** Results of SEC analysis of candidate antibody formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, 0.005% (w/v) PS-80, and adjusted to different pH (*i.e.*, pH 5.2, 5.5 and 5.8) after being stored at 40 °C for 4 weeks. A control formulation stored at -80 °C was included. The left panel is an enlarged view of the lower area between 10 and 20 (minutes of elution time) in the right panel. Shown is the change within 4 weeks of the fraction (%) of **(B)** HMW or **(C)** LMW of the antibody in candidate formulations stored at 40 °C. Error bars are the standard deviations of replicate injections of an internal standard and represent the precision of the method/integration.

[0150] FIG. 26 shows the results of CE-SDS analysis of candidate antibody formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH 5.2 to pH 5.8) after the candidate formulations have been stored at 5 °C, 25 °C or 40 °C for 4 weeks. Each bar shows the quantitation of the LMW fraction (%) of the antibody in candidate formulations as detected by the CE-SDS. A control formulation stored at - 80 °C was included.

[0151] FIG. 27 shows the results of CE-SDS analysis of candidate antibody formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH

5.2 to pH 5.8) after the candidate formulations have been stored at 4 °C for 26 weeks. Peaks representing the HMW, the monomer, and the LMW fractions are shown.

[0152] FIGS. 28A-28B show the results of flow imaging microscopy of candidate antibody formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH 5.2 to pH 5.8) after the candidate formulations have been stored at **(A)** 4 °C for 12 weeks or **(B)** 25 °C for 12 weeks. Densities (counts/ml) of subvisible particles in the $\geq 2 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$ size ranges are shown.

[0153] FIG. 29 shows the results of flow imaging microscopy of candidate antibody formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH 5.2 to pH 5.8) after the candidate formulations have been stored at 4 °C for 12 and/or 26 weeks. Densities (counts/ml) of subvisible particles in the $\geq 10 \mu\text{m}$ and $\geq 25 \mu\text{m}$ size ranges are shown.

[0154] FIGS. 30A-30C depict the results of charge isoform distribution to the antibodies in candidate formulations evaluated using cation exchange chromatograph (CEX). **(A)** Representative result of the CEX analysis on formulated antibodies at time zero (T0, *i.e.*, before the candidate formulations are stored at 4 °C or 25 °C). Three peaks respectively representing the main species, the acid species and the basic species of the formulated antibody are shown. Also shown is quantitation of the **(B)** main antibody species (main peak) or **(C)** acidic antibody species (acidic peak) identified by the CEX analysis of candidate formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH 5.2 to pH 5.8) after the candidate formulations have been stored at 4 °C or 25 °C for 12 weeks. Data at T0 are included as a control.

[0155] FIG. 31 shows quantitation of the main antibody species (main peak) identified by the CEX analysis of candidate formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH 5.2 to pH 5.8) after the candidate formulations have been stored at 4 °C for 12 weeks or 26 weeks. Data at T0 are included as a control.

[0156] **FIG. 32** shows the representative results of reversed-phase high performance liquid chromatography (RP-HPLC) of candidate antibody formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH 5.2 to pH 5.8) after the candidate formulations have been stored at 4 °C for 12 weeks or at 25 °C for 12 weeks. HC: heavy chain; LC: light chain.

[0157] **FIGS. 33A-33B** depict results of Biacore® analysis of antibodies in the formulation samples. **(A)** Representative Biacore® assay results for candidate formulation stored at 40 °C for 4 weeks (left) and at T0 (right). **(B)** Quantitation of the K_D (nM) values for candidate antibody formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH 5.2 to pH 5.8) at T0, or after the candidate formulation has been stored at 25 °C for 4 weeks, or at 40 °C for 4 weeks, or at 4 °C for 12 weeks, or at 25 °C for 12 weeks.

[0158] **FIGS. 34A-34B** depict results of the effect of agitation on liquid stability of candidate formulations was examined with SEC and MFI. **(A)** Results of SEC analysis of candidate formulations having 125 mg/ml antibody, 10 mM sodium acetate (pH 5.2), 8.5% (w/v) sucrose, 0.001% (w/v) or 0.015% (w/v) PS-80, after the candidate formulations were agitated at 4 °C for up to 24 hours. Quantitation of the HMW fraction at 0, 4-, 8- and 24-hour time points was shown. **(B)** Result of flow-imaging microscopy of candidate formulations having 125 mg/ml antibody, 10 mM sodium acetate (pH 5.2), 8.5% (w/v) sucrose, 0.001% (w/v) or 0.015% (w/v) PS-80, after the candidate formulations were agitated at 4 °C for 24 hours. Densities (counts/ml) of subvisible particles in the $\geq 2 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$ size ranges were shown.

[0159] **FIGS. 35A-35C** show the effect of repeated freeze-thaw cycles on liquid stability of candidate formulation was examined with SEC and MFI. **(A)** Results of SEC analysis of candidate formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9% (w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH 5.2 to pH 5.8) after the candidate formulations have gone through repeated cycles. Quantitation of the monomer fraction after 0, 3 or 5 freeze-thaw cycles was shown. Densities of subvisible particles in the **(B)** $\geq 10 \mu\text{m}$ and **(C)** $\geq 25 \mu\text{m}$ size ranges remained well below the USP standards for intravenous administration as determined by flow imaging microscopy of candidate formulations having 125 mg/ml antibody, 10 mM sodium acetate, 9%

(w/v) sucrose, and different combinations of PS-80 content (ranging from 0.005% (w/v)) and pH values (ranging from pH 5.2 to pH 5.8) after the candidate formulations have gone through 5 freeze-thaw cycles.

5. DETAILED DESCRIPTION

[0160] Provided herein are pharmaceutical formulations of binding proteins, such as antibodies that bind to PD-1 including human and/or cynomolgus PD-1, and methods of making such pharmaceutical formulations.

[0161] In some embodiments of the various pharmaceutical formulations provided herein, the antibodies bind to human and/or cynomolgus PD-1. In some embodiments, the binding proteins, such as antibodies that bind to human and/or cynomolgus PD-1, do not bind to rodent PD-1. In certain embodiments, the PD-1 binding proteins, including antibodies disclosed herein, are agonists (*e.g.*, can mimic the effect of PD-1 ligand and induce PD-1 signaling). In some embodiments, the binding proteins such as antibodies to PD-1 provided herein (i) bind to human and/or cynomolgus PD-1, (ii) do not compete for binding with PD-1 ligand (*e.g.*, PD-L1 and/or PD-L2), and/or (iii) induce PD-1 signaling. In one embodiment, the PD-1 antibodies bind to human PD-1. In one embodiment, the PD-1 antibodies bind to cynomolgus PD-1. In one embodiment, the PD-1 antibodies bind to both human PD-1 and cynomolgus PD-1. In some embodiments, the PD-1 antibodies do not compete with PD-L1 for binding to PD-1. In other embodiments, the PD-1 antibodies do not compete with PD-L2 for binding to PD-1. In yet other embodiments, the PD-1 antibodies do not compete with either PD-L1 or PD-L2 for binding to PD-1. In other embodiments, the PD-1 antibodies induce PD-1 signaling. In specific embodiments, the PD-1 antibodies provided herein bind to both human PD-1 and cynomolgus PD-1, do not compete for binding to PD-1 with either PD-L1 or PD-L2, and induce PD-1 signaling. In some embodiments, the binding, competition, and/or signaling is assayed *in vitro*, *e.g.*, in a cell-based assay. In other embodiments, the binding, competition, and/or signaling is assayed *ex vivo*, *e.g.*, in a T cell function assay. In other embodiments, the binding, competition, and/or signaling is assayed using a sample from a subject (*e.g.*, a human subject). In certain embodiments, assays include (1) a human or cynomolgus PBMC assay (*see, e.g.*, Examples 5.2.1 and 5.2.2); (2) a human whole blood sample assay (*see, e.g.*, Example 5.2.1). In certain embodiments, binding proteins, such as anti-PD-1 antibodies, as described herein, exhibit

activities that are consistent with the natural biological function of PD-L1 and/or PD-L2. In some embodiments, the activities are exhibited *in vitro*. In other embodiments, the activities are exhibited *ex vivo*.

[0162] In specific embodiments of various pharmaceutical formulations provided herein, the binding proteins, such as antibodies that bind to PD-1, provided herein share the common feature of competing with each other for the binding of PD-1. This competitive inhibition can indicate that each antibody binds to the same region of PD-1 (*e.g.*, the same epitope), thereby asserting similar effects. In certain embodiments, anti-PD-1 antibodies provided herein include humanized anti-PD-1 antibodies, such as those derived from or based on antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, and/or PD1AB-6. In other embodiments, anti-PD-1 antibodies provided herein compete for binding with an antibody derived from or based on PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, and/or PD1AB-6. In some embodiments, the anti-PD-1 antibodies have CDR sequences as described in **Tables 1-2**. In certain embodiments, the anti-PD-1 antibodies bind to a specific domain or epitope of human PD-1 (*e.g.*, residues 100-105; *see* Example 5.1.4). Moreover, such binding can be largely attributed to particular amino acid residues within the region (*e.g.*, G103 and R104; *see* Example 5.1.4), which comprise the epitope recognized by the anti-PD-1 antibodies provided herein. Taken together, the results described herein demonstrate that the effects observed for an anti-PD-1 antibody that is derived from or based on PD1AB-6, including an antibody having one or more CDRs described in **Tables 1-2**, can be extrapolated to other anti-PD-1 antibodies provided herein having the same or similar epitope specificity (*e.g.*, the same or similar CDRs). For example, the activities of antibodies as shown in Examples 5.1.2-3, 5.1.7-10, 5.2.1-3, and 5.3.1, for an exemplary humanized anti-PD-1 antibody, are representative of the activities and effects of the anti-PD-1 antibodies provided herein.

[0163] In some embodiments of various pharmaceutical formulations provided herein, the binding proteins such as anti-PD-1 antibodies may comprise immunoglobulin variable regions which comprise one or more CDRs as described in **Tables 1-2**. In such binding proteins (*e.g.*, anti-PD-1 antibodies), the CDRs may be joined with one or more scaffold regions or framework regions (FRs), which orient(s) the CDR(s) such that the proper antigen-binding properties of the CDR(s) is achieved. Such binding proteins, including anti-PD-1 antibodies as described herein, can induce PD-1 signaling.

5.1 General Techniques

[0164] Techniques and procedures described or referenced herein include those that are generally well understood and/or commonly employed using conventional methodology by those skilled in the art, such as, for example, the widely utilized methodologies described in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual (3d ed. 2001); Current Protocols in Molecular Biology (Ausubel *et al.* eds., 2003); Therapeutic Monoclonal Antibodies: From Bench to Clinic (An ed. 2009); Monoclonal Antibodies: Methods and Protocols (Albitar ed. 2010); and Antibody Engineering Vols 1 and 2 (Kontermann and Dübel eds., 2d ed. 2010).

5.2 Terminology

[0165] Unless described otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. For purposes of interpreting this specification, the following description of terms will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa. All patents, applications, published applications, and other publications are incorporated by reference in their entirety. In the event that any description of terms set forth conflicts with any document incorporated herein by reference, the description of term set forth below shall control.

[0166] The terms “Programmed Death 1,” “Programmed Cell Death 1,” “Protein PD-1,” “PD-1,” “PD-1 polypeptide,” or “PD1” encompasses a polypeptide (“polypeptide” and “protein” are used interchangeably herein), including any native polypeptide, from any vertebrate source, including mammals such as primates (*e.g.*, humans and cynomolgus monkeys (cynomolgus)), dogs, and rodents (*e.g.*, mice and rats), unless otherwise indicated. In certain embodiments, the terms include “related PD-1 polypeptides,” including SNP variants thereof. The term “PD-1” also encompasses “full-length,” unprocessed PD-1 as well as any form of PD-1 that results from processing in the cell. In some embodiments, the PD1 has an amino acid sequence of SEQ ID NO:43. GenBank™ accession number U64863 provides another exemplary human PD-1 nucleic acid sequence.

[0167] “Related PD-1 polypeptides” include allelic variants (*e.g.*, SNP variants); splice variants; fragments; derivatives; substitution, deletion, and insertion variants; fusion polypeptides; and interspecies homologs, which can retain PD-1 activity. As those skilled in the art will appreciate, an anti-PD-1 antibody provided herein can bind to a PD-1 polypeptide, a

PD-1 polypeptide fragment, a PD-1 antigen, and/or a PD-1 epitope. An “epitope” may be part of a larger PD-1 antigen, which may be part of a larger PD-1 polypeptide fragment, which, in turn, may be part of a larger PD-1 polypeptide. PD-1 may exist in a native or denatured form. PD-1 polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. Orthologs to the PD-1 polypeptide are also well known in the art.

[0168] A PD-1 polypeptide “extracellular domain” or “ECD” refers to a form of the PD-1 polypeptide that is essentially free of the transmembrane and cytoplasmic domains. For example, a PD-1 polypeptide ECD may have less than 1% of such transmembrane and/or cytoplasmic domains and can have less than 0.5% of such domains.

[0169] The terms “PD1AB-6-IgG1,” “PD1AB-6 IgG1,” “PD1AB-6_IgG1,” “IgG1_PD1AB-6,” and “IgG1-PD1AB-6” are used interchangeably, and refer to the antibody PD1AB-6 having an IgG1 Fc region. In certain embodiments, the antibody PD1AB-6 comprises a light chain amino acid sequence of LC_PD1AB-6-IgG1 (SEQ ID NO:31) and a heavy chain amino acid sequence of HC_PD1AB-6-IgG1 (SEQ ID NO:32), *e.g.*, as shown in **FIG. 4**.

[0170] The terms “PD1AB-6-K3,” “PD1AB-6-IgG1-K322A,” “PD1AB-6-K322A,” “IgG1_PD1AB-6_K322A,” “IgG1_PD1AB-6_K3,” “IgG1-PD1AB-6-K322A,” and “IgG1-PD1AB-6-K3” are used interchangeably and refer to the PD1AB-6 variant having a K322A substitution in the IgG1 Fc region. In certain embodiments, the PD1AB-6 variant has a heavy chain amino acid sequence of HC_PD1AB-6-IgG1-K322A (SEQ ID NO:33), *e.g.*, as shown in **FIG. 4**.

[0171] The terms “PD1AB-6-4P,” “IgG4P_PD1AB-6,” “IgG4P-PD1AB-6,” “PD1AB-6_IgG4P,” and “PD1AB-6-IgG4P” are used interchangeably and refer to the PD1AB-6 variant having an IgG4P Fc region. In certain embodiments, the PD-1 antibody variant has a heavy chain amino acid sequence of HC_PD1AB-6-IgG4P (SEQ ID NO:34), *e.g.*, as shown in **FIG. 4**.

[0172] The terms “PD1AB-6-4PE,” “IgG4PE_PD1AB-6,” “IgG4PE-PD1AB-6,” and “PD1AB-6_IgG4PE,” and “PD1AB-6-IgG4PE” are used interchangeably and refer to the PD1AB-6 variant having an IgG4PE heavy chain amino acid sequence as HC_PD1AB-6-IgG4PE (SEQ ID NO:35).

[0173] The term “PD-1 ligand” refers to a molecule that binds to PD-1, *e.g.*, *in vivo* or *in vitro*. Non-limiting examples of PD-1 ligand include naturally occurring ligands, *e.g.*, PD-1 ligand 1 (PD-L1, also known as B7-H1 or CD274) and PD-1 ligand 2 (PD-L2, also known as B7-DC or CD273), and artificially generated ligands.

[0174] The terms “PD-L1” and “PDL-1” are used interchangeably herein and refer to PD-1 ligand 1 (also known as B7-H1 or CD274).

[0175] The terms “PD-1 activity,” “PD-1 signaling,” and “PD-1 ligand-like signaling” when applied to a binding protein such as an antibody that binds to PD-1 of the present disclosure, means that the binding protein (*e.g.*, antibody) mimics or modulates a biological effect induced by the binding of PD-1 ligand, and induces a biological response that otherwise would result from PD-1 ligand binding to PD-1, *e.g.*, *in vivo* or *in vitro*. In assessing the binding specificity of anti-PD-1 antibody, for example, an antibody or fragment thereof that binds to PD-1 (*e.g.*, human PD-1), the antibody is deemed to induce a biological response when the response is equal to or greater than 5%, such as equal to or greater than 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, or 200% of the activity of a wild type PD-1 ligand standard. In one embodiment, the anti-PD-1 antibody or the PD-1 ligand is immobilized (for example, on a plastic surface or bead). In certain embodiments, the antibody has the following properties: exhibits an efficacy level of equal to or more than 5% of a PD-1 ligand standard, with an EC₅₀ of equal to or less than 100 nM, *e.g.*, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 2 nM, 1 nM, 0.5 nM, 0.2 nM, or 0.1 nM in (1) human or cynomolgus PBMC assay (*see, e.g.*, Examples 4.2.1 and 4.2.2); or (2) human whole blood sample assay (*see, e.g.*, Example 4.2.1).

[0176] The term “binding protein” refers to a protein comprising a portion (*e.g.*, one or more binding regions such as CDRs) that binds to PD-1, including human and/or cynomolgus PD-1 and, optionally, a scaffold or framework portion (*e.g.*, one or more scaffold or framework regions) that allows the binding portion to adopt a conformation that promotes binding of the binding protein to a PD-1 polypeptide, fragment, or epitope. Examples of such binding proteins include antibodies, such as a human antibody, a humanized antibody, a chimeric antibody, a recombinant antibody, a single chain antibody, a diabody, a triabody, a tetrabody, a Fab fragment, a F(ab')₂ fragment, an IgD antibody, an IgE antibody, an IgM antibody, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, or an IgG4 antibody, and fragments thereof. The

binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. *See, e.g.,* Korndorfer *et al.*, 2003, *Proteins: Structure, Function, and Bioinformatics* 53(1):121-29; and Roque *et al.*, 2004, *Biotechnol. Prog.* 20:639-54. In addition, peptide antibody mimetics (“PAMs”) can be used, as well as scaffolds based on antibody mimetics utilizing fibronectin components as a scaffold. In the context of the present disclosure, a binding protein is said to specifically bind or selectively bind to PD-1, for example, when the dissociation constant (K_D) is $\leq 10^{-7}$ M. In some embodiments, the binding proteins (*e.g.*, antibodies) may specifically bind to PD-1 with a K_D of from about 10^{-7} M to about 10^{-12} M. In certain embodiments, the binding protein (*e.g.*, antibody) may specifically bind to PD-1 with high affinity when the K_D is $\leq 10^{-8}$ M or K_D is $\leq 10^{-9}$ M. In one embodiment, the binding proteins (*e.g.*, antibodies) may specifically bind to purified human PD-1 with a K_D of from 1×10^{-9} M to 10×10^{-9} M as measured by Biacore[®]. In another embodiment, the binding proteins (*e.g.*, antibodies) may specifically bind to purified human PD-1 with a K_D of from 0.1×10^{-9} M to 1×10^{-9} M as measured by KinExA[™] (Sapidyne, Boise, ID). In yet another embodiment, the binding proteins (*e.g.*, antibodies) specifically bind to human PD-1 expressed on cells with a K_D of from 0.1×10^{-9} M to 10×10^{-9} M. In certain embodiments, the binding proteins (*e.g.*, antibodies) specifically bind to human PD-1 expressed on cells with a K_D of from 0.1×10^{-9} M to 1×10^{-9} M. In some embodiments, the binding proteins (*e.g.*, antibodies) specifically bind to human PD-1 expressed on cells with a K_D of 1×10^{-9} M to 10×10^{-9} M. In certain embodiments, the binding proteins (*e.g.*, antibodies) specifically bind to human PD-1 expressed on cells with a K_D of about 0.1×10^{-9} M, about 0.5×10^{-9} M, about 1×10^{-9} M, about 5×10^{-9} M, about 10×10^{-9} M, or any range or interval thereof. In still another embodiment, the binding proteins (*e.g.*, antibodies) may specifically bind to cynomolgus PD-1 expressed on cells with a K_D of 0.1×10^{-9} M to 10×10^{-9} M. In certain embodiments, the binding proteins (*e.g.*, antibodies) specifically bind to cynomolgus PD-1 expressed on cells with a K_D of from 0.1×10^{-9} M to 1×10^{-9} M. In some embodiments, the binding proteins (*e.g.*, antibodies) specifically bind to cynomolgus PD-1 expressed on cells with a K_D of 1×10^{-9} M to 10×10^{-9} M. In certain embodiments, the binding proteins (*e.g.*, antibodies) specifically bind to cynomolgus

PD-1 expressed on cells with a K_D of about 0.1×10^{-9} M, about 0.5×10^{-9} M, about 1×10^{-9} M, about 5×10^{-9} M, about 10×10^{-9} M, or any range or interval thereof.

[0177] The term “antibody,” “immunoglobulin,” or “Ig” is used interchangeably herein, and is used in the broadest sense and specifically encompasses, for example, individual anti-PD-1 monoclonal antibodies (including agonist, antagonist, neutralizing antibodies, full length or intact monoclonal antibodies), anti-PD-1 antibody compositions with polyepitopic or monoepitopic specificity, polyclonal or monovalent antibodies, multivalent antibodies, multispecific antibodies (*e.g.*, bispecific antibodies so long as they exhibit the desired biological activity), formed from at least two intact antibodies, single chain anti-PD-1 antibodies, and fragments of anti-PD-1 antibodies, as described below. An antibody can be human, humanized, chimeric and/or affinity matured, as well as an antibody from other species, for example, mouse and rabbit, *etc.* The term “antibody” is intended to include a polypeptide product of B cells within the immunoglobulin class of polypeptides that is able to bind to a specific molecular antigen and is composed of two identical pairs of polypeptide chains, wherein each pair has one heavy chain (about 50-70 kDa) and one light chain (about 25 kDa), each amino-terminal portion of each chain includes a variable region of about 100 to about 130 or more amino acids, and each carboxy-terminal portion of each chain includes a constant region. *See, e.g., Antibody Engineering* (Borrebaeck ed., 2d ed. 1995); and Kuby, *Immunology* (3d ed. 1997). In specific embodiments, the specific molecular antigen can be bound by an antibody provided herein, including a PD-1 polypeptide, a PD-1 fragment, or a PD-1 epitope. Antibodies also include, but are not limited to, synthetic antibodies, recombinantly produced antibodies, camelized antibodies, intrabodies, anti-idiotypic (anti-Id) antibodies, and functional fragments (*e.g.*, antigen-binding fragments such as PD-1-binding fragments) of any of the above, which refers to a portion of an antibody heavy or light chain polypeptide that retains some or all of the binding activity of the antibody from which the fragment was derived. Non-limiting examples of functional fragments (*e.g.*, antigen-binding fragments such as PD-1-binding fragments) include single-chain Fvs (scFv) (*e.g.*, including monospecific, bispecific, *etc.*), Fab fragments, F(ab') fragments, F(ab)₂ fragments, F(ab')₂ fragments, disulfide-linked Fvs (dsFv), Fd fragments, Fv fragments, diabody, triabody, tetrabody, and minibody. In particular, antibodies provided herein include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, for example, antigen-binding domains or molecules that contain an antigen-binding

site that binds to a PD-1 antigen (*e.g.*, one or more CDRs of an anti-PD-1 antibody). Such antibody fragments can be found in, for example, Harlow and Lane, Antibodies: A Laboratory Manual (1989); Mol. Biology and Biotechnology: A Comprehensive Desk Reference (Myers ed., 1995); Huston *et al.*, 1993, Cell Biophysics 22:189-224; Plückthun and Skerra, 1989, Meth. Enzymol. 178:497-515; and Day, Advanced Immunochimistry (2d ed. 1990). The antibodies provided herein can be of any class (*e.g.*, IgG, IgE, IgM, IgD, and IgA) or any subclass (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2) of immunoglobulin molecule. Anti-PD-1 antibodies may be agonistic antibodies or antagonistic antibodies. Provided herein are agonistic antibodies to PD-1, including antibodies that induce PD-1 signaling. In specific embodiments, agonistic antibodies to PD-1 do not compete for the binding of PD-L1 and/or PD-L2 to PD-1.

[0178] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *e.g.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts, and each monoclonal antibody will typically recognize a single epitope on the antigen. In specific embodiments, a “monoclonal antibody,” as used herein, is an antibody produced by a single hybridoma or other cell, wherein the antibody binds to only a PD-1 epitope as determined, for example, by ELISA or other antigen-binding or competitive binding assay known in the art. The term “monoclonal” is not limited to any particular method for making the antibody. For example, the monoclonal antibodies useful in the present disclosure may be prepared by the hybridoma methodology first described by Kohler *et al.*, 1975, Nature 256:495, or may be made using recombinant DNA methods in bacterial or eukaryotic animal or plant cells (*see, e.g.*, U.S. Pat. No. 4,816,567). The “monoclonal antibodies” may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, 1991, Nature 352:624-28 and Marks *et al.*, 1991, J. Mol. Biol. 222:581-97, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies expressed thereby are well known in the art. *See, e.g.*, Short Protocols in Molecular Biology (Ausubel *et al.* eds., 5th ed. 2002).

Exemplary methods of producing monoclonal antibodies are provided in the Examples herein.

[0179] “Polyclonal antibodies” as used herein refer to an antibody population generated in an immunogenic response to a protein having many epitopes and thus includes a variety of different antibodies directed to the same or different epitopes within the protein. Methods for producing

polyclonal antibodies are known in the art (*See, e.g., Short Protocols in Molecular Biology* (Ausubel *et al.* eds., 5th ed. 2002)).

[0180] In the context of a peptide or polypeptide, the term “fragment” as used herein refers to a peptide or polypeptide that comprises less than the full length amino acid sequence. Such a fragment may arise, for example, from a truncation at the amino terminus, a truncation at the carboxy terminus, and/or an internal deletion of a residue(s) from the amino acid sequence. Fragments may, for example, result from alternative RNA splicing or from *in vivo* protease activity. In certain embodiments, PD-1 fragments or anti-PD-1 antibody fragments include polypeptides comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 30 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino acid residues, at least 70 contiguous amino acid residues, at least 80 contiguous amino acid residues, at least 90 contiguous amino acid residues, at least 100 contiguous amino acid residues, at least 125 contiguous amino acid residues, at least 150 contiguous amino acid residues, at least 175 contiguous amino acid residues, at least 200 contiguous amino acid residues, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, or at least 950 contiguous amino acid residues of the amino acid sequence of a PD-1 polypeptide or an anti-PD-1 antibody. In a specific embodiment, a fragment of a PD-1 polypeptide or an anti-PD-1 antibody retains at least 1, at least 2, at least 3, or more functions of the polypeptide or antibody.

[0181] An “antigen” is a predetermined antigen to which an antibody can selectively bind. A target antigen may be a polypeptide, carbohydrate, nucleic acid, lipid, hapten, or other naturally occurring or synthetic compound. In some embodiments, the target antigen is a polypeptide.

[0182] The terms “antigen-binding fragment,” “antigen-binding domain,” “antigen-binding region,” and similar terms refer to that portion of an antibody, which comprises the amino acid residues that interact with an antigen and confer on the binding agent its specificity and affinity for the antigen (*e.g.*, the CDRs).

[0183] An “epitope” is the site on the surface of an antigen molecule to which a single antibody molecule binds, such as a localized region on the surface of an antigen, such as a PD-1

polypeptide or a PD-1 polypeptide fragment, that is capable of being bound to one or more antigen binding regions of an antibody, and that has antigenic or immunogenic activity in an animal, such as a mammal (*e.g.*, a human), that is capable of eliciting an immune response. An epitope having immunogenic activity is a portion of a polypeptide that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of a polypeptide to which an antibody binds as determined by any method well known in the art, including, for example, by an immunoassay. Antigenic epitopes need not necessarily be immunogenic. Epitopes often consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics. Antibody epitopes may be linear epitopes or conformational epitopes. Linear epitopes are formed by a continuous sequence of amino acids in a protein. Conformational epitopes are formed of amino acids that are discontinuous in the protein sequence, but which are brought together upon folding of the protein into its three-dimensional structure. Induced epitopes are formed when the three dimensional structure of the protein is in an altered conformation, such as following activation or binding of another protein or ligand. In certain embodiments, a PD-1 epitope is a three-dimensional surface feature of a PD-1 polypeptide. In other embodiments, a PD-1 epitope is linear feature of a PD-1 polypeptide. Generally an antigen has several or many different epitopes and may react with many different antibodies.

[0184] An antibody binds “an epitope,” “essentially the same epitope,” or “the same epitope” as a reference antibody, when the two antibodies recognize identical, overlapping, or adjacent epitopes in a three-dimensional space. The most widely used and rapid methods for determining whether two antibodies bind to identical, overlapping, or adjacent epitopes in a three-dimensional space are competition assays, which can be configured in a number of different formats, for example, using either labeled antigen or labeled antibody. In some assays, the antigen is immobilized on a 96-well plate, or expressed on a cell surface, and the ability of unlabeled antibodies to block the binding of labeled antibodies is measured using radioactive, fluorescent, or enzyme labels.

[0185] “Epitope mapping” is the process of identifying the binding sites, or epitopes, of antibodies on their target antigens. “Epitope binning” is the process of grouping antibodies based on the epitopes they recognize. More particularly, epitope binning comprises methods and systems for discriminating the epitope recognition properties of different antibodies, using

competition assays combined with computational processes for clustering antibodies based on their epitope recognition properties and identifying antibodies having distinct binding specificities.

[0186] The terms “binds” or “binding” refer to an interaction between molecules including, for example, to form a complex. Interactions can be, for example, non-covalent interactions including hydrogen bonds, ionic bonds, hydrophobic interactions, and/or van der Waals interactions. A complex can also include the binding of two or more molecules held together by covalent or non-covalent bonds, interactions, or forces. The strength of the total non-covalent interactions between a single antigen-binding site on an antibody and a single epitope of a target molecule, such as PD-1, is the affinity of the antibody or functional fragment for that epitope. The ratio of dissociation rate (k_{off}) to association rate (k_{on}) of an antibody to a monovalent antigen ($k_{\text{off}}/k_{\text{on}}$) is the dissociation constant K_D , which is inversely related to affinity. The lower the K_D value, the higher the affinity of the antibody. The value of K_D varies for different complexes of antibody and antigen and depends on both k_{on} and k_{off} . The dissociation constant K_D for an antibody provided herein can be determined using any method provided herein or any other method well known to those skilled in the art. The affinity at one binding site does not always reflect the true strength of the interaction between an antibody and an antigen. When complex antigens containing multiple, repeating antigenic determinants, such as a polyvalent PD-1, come in contact with antibodies containing multiple binding sites, the interaction of antibody with antigen at one site will increase the probability of a reaction at a second site. The strength of such multiple interactions between a multivalent antibody and antigen is called the avidity. The avidity of an antibody can be a better measure of its binding capacity than is the affinity of its individual binding sites. For example, high avidity can compensate for low affinity as is sometimes found for pentameric IgM antibodies, which can have a lower affinity than IgG, but the high avidity of IgM, resulting from its multivalence, enables it to bind antigen effectively.

[0187] The terms “antibodies that specifically bind to PD-1,” “antibodies that specifically bind to a PD-1 epitope,” and analogous terms are also used interchangeably herein and refer to antibodies that specifically bind to a PD-1 polypeptide, such as a PD-1 antigen, or fragment, or epitope (*e.g.*, human PD-1 such as a human PD-1 polypeptide, antigen, or epitope). An antibody that specifically binds to PD-1 (*e.g.*, human PD-1) may bind to the extracellular domain or a peptide derived from the extracellular domain of PD-1. An antibody that specifically binds to a

PD-1 antigen (*e.g.*, human PD-1) may be cross-reactive with related antigens (*e.g.*, cynomolgus PD-1). In certain embodiments, an antibody that specifically binds to a PD-1 antigen does not cross-react with other antigens. An antibody that specifically binds to a PD-1 antigen can be identified, for example, by immunoassays, Biacore[®], or other techniques known to those of skill in the art. An antibody binds specifically to a PD-1 antigen when it binds to a PD-1 antigen with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as radioimmunoassays (RIA) and enzyme linked immunosorbent assays (ELISAs).

Typically a specific or selective reaction will be at least twice background signal or noise and may be more than 10 times background. See, *e.g.*, Fundamental Immunology 332-36 (Paul ed., 2d ed. 1989) for a discussion regarding antibody specificity. An antibody which “binds an antigen of interest” (*e.g.*, a target antigen such as PD-1) is one that binds the antigen with sufficient affinity such that the antibody is useful as a therapeutic agent in targeting a cell or tissue expressing the antigen, and does not significantly cross-react with other proteins. In such embodiments, the extent of binding of the antibody to a “non-target” protein will be less than about 10% of the binding of the antibody to its particular target protein, for example, as determined by fluorescence activated cell sorting (FACS) analysis or RIA. With regard to the binding of an antibody to a target molecule, the term “specific binding,” “specifically binds to,” or “is specific for” a particular polypeptide or an epitope on a particular polypeptide target means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. The term “anti-PD-1 antibody” or “an antibody that binds to PD-1” includes an antibody that is capable of binding PD-1 with sufficient affinity such that the antibody is useful, for example, as a diagnostic agent in targeting PD-1. The term “specific binding,” “specifically binds to,” or “is specific for” a particular polypeptide or an epitope on a particular polypeptide target as used herein refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. In certain embodiments, an antibody that binds to PD-1 has a dissociation

constant (K_D) of less than or equal to 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.9 nM, 0.8 nM, 0.7 nM, 0.6 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, or 0.1 nM. In certain embodiments, anti-PD-1 antibody binds to an epitope of PD-1 that is conserved among PD-1 from different species (*e.g.*, between human and cynomolgus PD-1).

[0188] The term “compete” when used in the context of anti-PD-1 antibodies (*e.g.*, agonistic antibodies and binding proteins that bind to PD-1 and compete for the same epitope or binding site on a target) means competition as determined by an assay in which the antibody (or binding fragment) thereof under study prevents or inhibits the specific binding of a reference molecule (*e.g.*, a reference ligand or reference antigen-binding protein, such as a reference antibody) to a common antigen (*e.g.*, PD-1 or a fragment thereof). Numerous types of competitive binding assays can be used to determine if a test antibody competes with a reference antibody for binding to PD-1 (*e.g.*, human PD-1). Examples of assays that can be employed include solid phase direct or indirect RIA, solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (*see, e.g.*, Stahli *et al.*, 1983, *Methods in Enzymology* 9:242-53), solid phase direct biotin-avidin EIA (*see, e.g.*, Kirkland *et al.*, 1986, *J. Immunol.* 137:3614-19), solid phase direct labeled assay, solid phase direct labeled sandwich assay (*see, e.g.*, Harlow and Lane, Antibodies, A Laboratory Manual (1988)), solid phase direct label RIA using I-125 label (*see, e.g.*, Morel *et al.*, 1988, *Mol. Immunol.* 25:7-15), and direct labeled RIA (Moldenhauer *et al.*, 1990, *Scand. J. Immunol.* 32:77-82). Typically, such an assay involves the use of a purified antigen (*e.g.*, PD-1 such as human PD-1) bound to a solid surface, or cells bearing either of an unlabeled test antigen-binding protein (*e.g.*, test anti-PD-1 antibody) or a labeled reference antigen-binding protein (*e.g.*, reference anti-PD-1 antibody). Competitive inhibition may be measured by determining the amount of label bound to the solid surface or cells in the presence of the test antigen-binding protein. Usually the test antigen-binding protein is present in excess. Antibodies identified by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and/or antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference for antibodies steric hindrance to occur. Additional details regarding methods for determining competitive binding are described herein. Usually, when a competing antibody protein is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 30%, for example 40%, 45%, 50%, 55%,

60%, 65%, 70%, or 75%. In some instance, binding is inhibited by at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more.

[0189] An “isolated” antibody is substantially free of cellular material or other contaminating proteins from the cell or tissue source and/or other contaminant components from which the antibody is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language “substantially free of cellular material” includes preparations of an antibody in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of antibody having less than about 30%, 25%, 20%, 15%, 10%, 5%, or 1% (by dry weight) of heterologous protein (also referred to herein as a “contaminating protein”). In certain embodiments, when the antibody is recombinantly produced, it is substantially free of culture medium, *e.g.*, culture medium represents less than about 20%, 15%, 10%, 5%, or 1% of the volume of the protein preparation. In certain embodiments, when the antibody is produced by chemical synthesis, it is substantially free of chemical precursors or other chemicals, for example, it is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. Accordingly such preparations of the antibody have less than about 30%, 25%, 20%, 15%, 10%, 5%, or 1% (by dry weight) of chemical precursors or compounds other than the antibody of interest. Contaminant components can also include, but are not limited to, materials that would interfere with therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In certain embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method (Lowry *et al.*, 1951, J. Bio. Chem. 193: 265-75), such as 96%, 97%, 98%, or 99%, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody’s natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step. In specific embodiments, antibodies provided herein are isolated.

[0190] A 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. In the case of IgGs, the 4-chain unit is

generally about 150,000 daltons. Each L chain is linked to an H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (VH) followed by three constant domains (CH) for each of the α and γ chains and four CH domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (VL) followed by a constant domain (CL) at its other end. The VL is aligned with the VH, and the CL is aligned with the first constant domain of the heavy chain (CH1). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a VH and VL together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, for example, Basic and Clinical Immunology 71 (Stites *et al.* eds., 8th ed. 1994).

[0191] The term “heavy chain” when used in reference to an antibody refers to a polypeptide chain of about 50-70 kDa, wherein the amino-terminal portion includes a variable region of about 120 to 130 or more amino acids, and a carboxy-terminal portion includes a constant region. The constant region can be one of five distinct types, (*e.g.*, isotypes) referred to as alpha (α), delta (δ), epsilon (ϵ), gamma (γ), and mu (μ), based on the amino acid sequence of the heavy chain constant region. The distinct heavy chains differ in size: α , δ , and γ contain approximately 450 amino acids, while μ and ϵ contain approximately 550 amino acids. When combined with a light chain, these distinct types of heavy chains give rise to five well known classes (*e.g.*, isotypes) of antibodies, IgA, IgD, IgE, IgG, and IgM, respectively, including four subclasses of IgG, namely IgG1, IgG2, IgG3, and IgG4. A heavy chain can be a human heavy chain.

[0192] The term “light chain” when used in reference to an antibody refers to a polypeptide chain of about 25 kDa, wherein the amino-terminal portion includes a variable region of about 100 to about 110 or more amino acids, and a carboxy-terminal portion includes a constant region. The approximate length of a light chain is 211 to 217 amino acids. There are two distinct types, referred to as kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. A light chain can be a human light chain.

[0193] The term “variable region,” “variable domain,” “V region,” or “V domain” refers to a portion of the light or heavy chains of an antibody that is generally located at the amino-terminal of the light or heavy chain and has a length of about 120 to 130 amino acids in the heavy chain

and about 100 to 110 amino acids in the light chain, and are used in the binding and specificity of each particular antibody for its particular antigen. The variable region of the heavy chain may be referred to as “VH.” The variable region of the light chain may be referred to as “VL.” The term “variable” refers to the fact that certain segments of the variable regions differ extensively in sequence among antibodies. The V region mediates antigen binding and defines specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable regions. Instead, the V regions consist of less variable (*e.g.*, relatively invariant) stretches called framework regions (FRs) of about 15-30 amino acids separated by shorter regions of greater variability (*e.g.*, extreme variability) called “hypervariable regions” that are each about 9-12 amino acids long. The variable regions of heavy and light chains each comprise four FRs, largely adopting a β sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases form part of, the β sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (*see, e.g.*, Kabat *et al.*, Sequences of Proteins of Immunological Interest (5th ed. 1991)). The constant regions are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). The variable regions differ extensively in sequence between different antibodies. In specific embodiments, the variable region is a human variable region.

[0194] The term “variable region residue numbering as in Kabat” or “amino acid position numbering as in Kabat”, and variations thereof, refer to the numbering system used for heavy chain variable regions or light chain variable regions of the compilation of antibodies in Kabat *et al.*, *supra*. Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, an FR or CDR of the variable domain. For example, a heavy chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 and three inserted residues (*e.g.*, residues 82a, 82b, and 82c, *etc.* according to Kabat) after residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a “standard” Kabat numbered sequence. The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately

residues 1-107 of the light chain and residues 1-113 of the heavy chain) (*e.g.*, Kabat *et al.*, *supra*). The “EU numbering system” or “EU index” is generally used when referring to a residue in an immunoglobulin heavy chain constant region (*e.g.*, the EU index reported in Kabat *et al.*, *supra*). The “EU index as in Kabat” refers to the residue numbering of the human IgG 1 EU antibody. Other numbering systems have been described, for example, by AbM, Chothia, Contact, IMGT, and AHon.

[0195] A “CDR” refers to one of three hypervariable regions (H1, H2 or H3) within the non-framework region of the immunoglobulin (Ig or antibody) VH β -sheet framework, or one of three hypervariable regions (L1, L2 or L3) within the non-framework region of the antibody VL β -sheet framework. Accordingly, CDRs are variable region sequences interspersed within the framework region sequences. CDR regions are well known to those skilled in the art and have been defined by, for example, Kabat as the regions of most hypervariability within the antibody variable (V) domains (Kabat *et al.*, 1997, J. Biol. Chem. 252:6609-16; Kabat, 1978, Adv. Prot. Chem. 32:1-75). CDR region sequences also have been defined structurally by Chothia as those residues that are not part of the conserved β -sheet framework, and thus are able to adapt different conformations (Chothia and Lesk, 1987, J. Mol. Biol. 196:901-17). Both terminologies are well recognized in the art. CDR region sequences have also been defined by AbM, Contact, and IMGT. The positions of CDRs within a canonical antibody variable region have been determined by comparison of numerous structures (Al-Lazikani *et al.*, 1997, J. Mol. Biol. 273:927-48; Morea *et al.*, 2000, Methods 20:267-79). Because the number of residues within a hypervariable region varies in different antibodies, additional residues relative to the canonical positions are conventionally numbered with a, b, c and so forth next to the residue number in the canonical variable region numbering scheme (Al-Lazikani *et al.*, *supra*). Such nomenclature is similarly well known to those skilled in the art.

[0196] The term “hypervariable region,” “HVR,” or “HV,” when used herein refers to the regions of an antibody variable region that are hypervariable in sequence and/or form structurally defined loops. Generally, antibodies comprise six hypervariable regions, three in the VH (H1, H2, H3) and three in the VL (L1, L2, L3). A number of hypervariable region delineations are in use and are encompassed herein. The Kabat Complementarity Determining Regions (CDRs) are based on sequence variability and are the most commonly used (*see, e.g.*, Kabat *et al.*, *supra*). Chothia refers instead to the location of the structural loops (*see, e.g.*, Chothia and Lesk, 1987, J.

Mol. Biol. 196:901-17). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (*see, e.g., Antibody Engineering* Vol. 2 (Kontermann and Dübel eds., 2d ed. 2010)). The "contact" hypervariable regions are based on an analysis of the available complex crystal structures. The residues from each of these hypervariable regions or CDRs are noted below.

[0197] Recently, a universal numbering system has been developed and widely adopted, ImMunoGeneTics (IMGT) Information System[®] (Lafranc *et al.*, 2003, Dev. Comp. Immunol. 27(1):55-77). IMGT is an integrated information system specializing in immunoglobulins (IG), T cell receptors (TCR), and major histocompatibility complex (MHC) of human and other vertebrates. Herein, the CDRs are referred to in terms of both the amino acid sequence and the location within the light or heavy chain. As the "location" of the CDRs within the structure of the immunoglobulin variable domain is conserved between species and present in structures called loops, by using numbering systems that align variable domain sequences according to structural features, CDR and framework residues are readily identified. This information can be used in grafting and replacement of CDR residues from immunoglobulins of one species into an acceptor framework from, typically, a human antibody. An additional numbering system (AHon) has been developed by Honegger and Plückthun, 2001, J. Mol. Biol. 309: 657-70. Correspondence between the numbering system, including, for example, the Kabat numbering and the IMGT unique numbering system, is well known to one skilled in the art (*see, e.g., Kabat, supra; Chothia and Lesk, supra; Martin, supra; Lefranc et al., supra*). In some embodiments, the CDRs are as defined by the IMGT numbering system. In other embodiments, the CDRs are as defined by the Kabat numbering system. In certain embodiments, the CDRs are as defined by the AbM numbering system. In other embodiments, the CDRs are as defined by the Chothia system. In yet other embodiments, the CDRs are as defined by the Contact numbering system.

	<u>IMGT</u>	<u>Kabat</u>	<u>AbM</u>	<u>Chothia</u>	<u>Contact</u>
V _H CDR1	27-38	31-35	26-35	26-32	30-35
V _H CDR2	56-65	50-65	50-58	53-55	47-58
V _H CDR3	105-117	95-102	95-102	96-101	93-101
V _L CDR1	27-38	24-34	24-34	26-32	30-36
V _L CDR2	56-65	50-56	50-56	50-52	46-55
V _L CDR3	105-117	89-97	89-97	91-96	89-96

[0198] Hypervariable regions may comprise “extended hypervariable regions” as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2), and 89-97 or 89-96 (L3) in the VL, and 26-35 or 26-35A (H1), 50-65 or 49-65 (H2), and 93-102, 94-102, or 95-102 (H3) in the VH. As used herein, the terms “HVR” and “CDR” are used interchangeably.

[0199] The term “constant region” or “constant domain” refers to a carboxy terminal portion of the light and heavy chain which is not directly involved in binding of the antibody to antigen but exhibits various effector function, such as interaction with the Fc receptor. The term refers to the portion of an immunoglobulin molecule having a more conserved amino acid sequence relative to the other portion of the immunoglobulin, the variable region, which contains the antigen binding site. The constant region may contain the CH1, CH2, and CH3 regions of the heavy chain and the CL region of the light chain.

[0200] The term “framework” or “FR” refers to those variable region residues flanking the CDRs. FR residues are present, for example, in chimeric, humanized, human, domain antibodies, diabodies, linear antibodies, and bispecific antibodies. FR residues are those variable domain residues other than the hypervariable region residues or CDR residues.

[0201] The term “Fc region” herein is used to define a C-terminal region of an immunoglobulin heavy chain, including, for example, native sequence Fc regions, recombinant Fc regions, and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is often defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the

antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue.

[0202] A “functional Fc region” possesses an “effector function” of a native sequence Fc region. Exemplary “effector functions” include C1q binding; CDC; Fc receptor binding; ADCC; phagocytosis; downregulation of cell surface receptors (*e.g.*, B cell receptor), *etc.* Such effector functions generally require the Fc region to be combined with a binding region or binding domain (*e.g.*, an antibody variable region or domain) and can be assessed using various assays as disclosed.

[0203] A “native sequence Fc region” comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature, and not manipulated, modified, and/or changed (*e.g.*, isolated, purified, selected, including or combining with other sequences such as variable region sequences) by a human. Native sequence human IgG1 Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof. For example, a native human IgG1 Fc region amino acid sequence is provided below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO:36, K322 emphasized).

An exemplary native human IgG4 Fc region sequence is provided below:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYTCNVNHHKPSNTKVDKRVERESKYGPPCPSCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO:38, S228 and L235 emphasized).

[0204] A “variant Fc region” comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification (*e.g.*, substituting, addition, or deletion). In certain embodiments, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, for example, from about one to about ten amino acid substitutions, or from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of a parent polypeptide. The variant Fc region herein can possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, or at least about 90% homology therewith, for example, at least about 95% homology therewith. For example, a variant with one amino acid K change to A at 322 position in the human IgG1 Fc amino acid sequence, IgG1-K322A Fc region, is provided below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO:37, K322A substitution emphasized).

An exemplary variant with one amino acid S change to P at 228 position in the human IgG4 Fc amino acid sequence, IgG4P Fc region, is provided below:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYTCNVNHHKPSNTKVDKRVERESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO:39, S228P substitution emphasized).

An exemplary variant with two amino acid changes at 228 and 235 positions in the human IgG4 Fc amino acid sequence, IgG4PE Fc region, is provided below:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYTCNVNHHKPSNTKVDKRVERESKYGPPCPPCPAPEFEGGPSVFLFPPKPK
DTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD

WLNQKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO:40, S228P and L235E substitutions emphasized).

[0205] The term “variant” when used in relation to PD-1 or to an anti-PD-1 antibody may refer to a peptide or polypeptide comprising one or more (such as, for example, about 1 to about 25, about 1 to about 20, about 1 to about 15, about 1 to about 10, or about 1 to about 5) amino acid sequence substitutions, deletions, and/or additions as compared to a native or unmodified sequence. For example, a PD-1 variant may result from one or more (such as, for example, about 1 to about 25, about 1 to about 20, about 1 to about 15, about 1 to about 10, or about 1 to about 5) changes to an amino acid sequence of a native PD-1. Also by way of example, a variant of an anti-PD-1 antibody may result from one or more (such as, for example, about 1 to about 25, about 1 to about 20, about 1 to about 15, about 1 to about 10, or about 1 to about 5) changes to an amino acid sequence of a native or previously unmodified anti-PD-1 antibody. Variants may be naturally occurring, such as allelic or splice variants, or may be artificially constructed. Polypeptide variants may be prepared from the corresponding nucleic acid molecules encoding the variants. In specific embodiments, the PD-1 variant or anti-PD-1 antibody variant at least retains PD-1 or anti-PD-1 antibody functional activity, respectively. In specific embodiments, an anti-PD-1 antibody variant binds PD-1 and/or is antagonistic to PD-1 activity. In specific embodiments, an anti-PD-1 antibody variant binds PD-1 and/or is agonistic to PD-1 activity. In certain embodiments, the variant is encoded by a single nucleotide polymorphism (SNP) variant of a nucleic acid molecule that encodes PD-1 or anti-PD-1 antibody VH or VL regions or subregions, such as one or more CDRs.

[0206] An “intact” antibody is one comprising an antigen-binding site as well as a CL and at least heavy chain constant regions, CH1, CH2 and CH3. The constant regions may include human constant regions or amino acid sequence variants thereof. In certain embodiments, an intact antibody has one or more effector functions.

[0207] “Antibody fragments” comprise a portion of an intact antibody, such as the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include, without limitation, Fab, Fab’, F(ab’)₂, and Fv fragments; diabodies and di-diabodies (*see, e.g.*, Holliger *et al.*, 1993, Proc. Natl. Acad. Sci. 90:6444-48; Lu *et al.*, 2005, J. Biol. Chem. 280:19665-72; Hudson *et al.*, 2003, Nat. Med. 9:129-34; WO 93/11161; and U.S. Pat. Nos.

5,837,242 and 6,492,123); single-chain antibody molecules (*see, e.g.*, U.S. Pat. Nos. 4,946,778; 5,260,203; 5,482,858; and 5,476,786); dual variable domain antibodies (*see, e.g.*, U.S. Pat. No. 7,612,181); single variable domain antibodies (sdAbs) (*see, e.g.*, Woolven *et al.*, 1999, Immunogenetics 50: 98-101; and Streltsov *et al.*, 2004, Proc Natl Acad Sci USA. 101:12444-49); and multispecific antibodies formed from antibody fragments.

[0208] A “functional fragment,” “binding fragment,” or “antigen-binding fragment” of a therapeutic antibody will exhibit at least one if not some or all of the biological functions attributed to the intact antibody, the function comprising at least binding to the target antigen (*e.g.*, a PD-1 binding fragment or fragment that binds to PD-1).

[0209] The term “fusion protein” as used herein refers to a polypeptide that comprises an amino acid sequence of an antibody and an amino acid sequence of a heterologous polypeptide or protein (*e.g.*, a polypeptide or protein not normally a part of the antibody (*e.g.*, a non-anti-PD-1 antigen-binding antibody)). The term “fusion” when used in relation to PD-1 or to an anti-PD-1 antibody refers to the joining of a peptide or polypeptide, or fragment, variant, and/or derivative thereof, with a heterologous peptide or polypeptide. In certain embodiments, the fusion protein retains the biological activity of the PD-1 or anti-PD-1 antibody. In certain embodiments, the fusion protein comprises a PD-1 antibody VH region, VL region, VH CDR (one, two, or three VH CDRs), and/or VL CDR (one, two, or three VL CDRs), wherein the fusion protein binds to a PD-1 epitope, a PD-1 fragment, and/or a PD-1 polypeptide.

[0210] The term “native” when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to those which are found in nature and not manipulated, modified, and/or changed (*e.g.*, isolated, purified, selected) by a human being.

[0211] The antibodies provided herein can include “chimeric” antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (*see* U.S. Pat. No. 4,816,567; and Morrison *et al.*, 1984, Proc. Natl. Acad. Sci. USA 81:6851-55).

[0212] “Humanized” forms of nonhuman (*e.g.*, murine) antibodies are chimeric antibodies that include human immunoglobulins (*e.g.*, recipient antibody) in which the native CDR residues are replaced by residues from the corresponding CDR of a nonhuman species (*e.g.*, donor antibody) such as mouse, rat, rabbit, or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, one or more FR region residues of the human immunoglobulin are replaced by corresponding nonhuman residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. A humanized antibody heavy or light chain can comprise substantially all of at least one or more variable regions, in which all or substantially all of the CDRs correspond to those of a nonhuman immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. In certain embodiments, the humanized antibody will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see, Jones *et al.*, 1986, *Nature* 321:522-25; Riechmann *et al.*, 1988, *Nature* 332:323-29; Presta, 1992, *Curr. Opin. Struct. Biol.* 2:593-96; Carter *et al.*, 1992, *Proc. Natl. Acad. Sci. USA* 89:4285-89; U.S. Pat. Nos: 6,800,738; 6,719,971; 6,639,055; 6,407,213; and 6,054,297.

[0213] A “human antibody” is one that possesses an amino acid sequence which corresponds to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries (Hoogenboom and Winter, 1991, *J. Mol. Biol.* 227:381; Marks *et al.*, 1991, *J. Mol. Biol.* 222:581) and yeast display libraries (Chao *et al.*, 2006, *Nature Protocols* 1: 755-68). Also available for the preparation of human monoclonal antibodies are methods described in Cole *et al.*, Monoclonal Antibodies and Cancer Therapy 77 (1985); Boerner *et al.*, 1991, *J. Immunol.* 147(1):86-95; and van Dijk and van de Winkel, 2001, *Curr. Opin. Pharmacol.* 5: 368-74. Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, *e.g.*, mice (*see, e.g.*, Jakobovits, 1995, *Curr. Opin. Biotechnol.* 6(5):561-66; Brüggemann and Taussing, 1997, *Curr. Opin. Biotechnol.* 8(4):455-58; and U.S. Pat. Nos. 6,075,181 and 6,150,584 regarding XENOMOUSETM technology). See also, for

example, Li *et al.*, 2006, Proc. Natl. Acad. Sci. USA 103:3557-62 regarding human antibodies generated via a human B-cell hybridoma technology.

[0214] An “affinity matured” antibody is one with one or more alterations (*e.g.*, amino acid sequence variations, including changes, additions, and/or deletions) in one or more HVRs thereof which result in an improvement in the affinity of the antibody for antigen, compared to a parent antibody which does not possess those alteration(s). Affinity matured antibodies can have nanomolar or even picomolar affinities for the target antigen. Affinity matured antibodies are produced by procedures known in the art. For review, see Hudson and Souriau, 2003, Nature Medicine 9:129-34; Hoogenboom, 2005, Nature Biotechnol. 23:1105-16; Quiroz and Sinclair, 2010, Revista Ingeneria Biomedica 4:39-51.

[0215] A “blocking” antibody or an “antagonist” antibody is one which inhibits or reduces biological activity of the antigen it binds. For example, blocking antibodies or antagonist antibodies may substantially or completely inhibit the biological activity of the antigen.

[0216] An “agonist” antibody is an antibody that triggers a response, *e.g.*, one that mimics at least one of the functional activities of a polypeptide of interest (*e.g.*, PD-L1). An agonist antibody includes an antibody that is a ligand mimetic, for example, wherein a ligand binds to a cell surface receptor and the binding induces cell signaling or activities via an intercellular cell signaling pathway and wherein the antibody induces a similar cell signaling or activation. An “agonist” of PD-1 refers to a molecule that is capable of activating or otherwise increasing one or more of the biological activities of PD-1, such as in a cell expressing PD-1. In some embodiments, an agonist of PD-1 (*e.g.*, an agonistic antibody as described herein) may, for example, act by activating or otherwise increasing the activation and/or cell signaling pathways of a cell expressing a PD-1 protein, thereby increasing a PD-1-mediated biological activity of the cell relative to the PD-1-mediated biological activity in the absence of agonist. In some embodiments the antibodies provided herein are agonistic anti-PD-1 antibodies, including antibodies that induce PD-1 signaling.

[0217] “Binding affinity” generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (*e.g.*, a binding protein such as an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a binding molecule X for

its binding partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein.

Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for purposes of the present disclosure. Specific illustrative embodiments include the following. In one embodiment, the " K_D " or " K_D value" may be measured by assays known in the art, for example by a binding assay. The K_D may be measured in a RIA, for example, performed with the Fab version of an antibody of interest and its antigen (Chen *et al.*, 1999, J. Mol Biol 293:865-81). The K_D or K_D value may also be measured by using surface plasmon resonance assays by Biacore[®], using, for example, a Biacore[®]TM-2000 or a Biacore[®]TM-3000, or by biolayer interferometry using, for example, the Octet[®]QK384 system. An "on-rate" or "rate of association" or "association rate" or " k_{on} " may also be determined with the same surface plasmon resonance or biolayer interferometry techniques described above using, for example, a Biacore[®]TM-2000 or a Biacore[®]TM-3000, or the Octet[®]QK384 system.

[0218] The term "inhibition" or "inhibit," when used herein, refers to partial (such as, 1%, 2%, 5%, 10%, 20%, 25%, 50%, 75%, 90%, 95%, 99%) or complete (*i.e.*, 100%) inhibition.

[0219] The term "attenuate," "attenuation," or "attenuated," when used herein, refers to partial (such as, 1%, 2%, 5%, 10%, 20%, 25%, 50%, 75%, 90%, 95%, 99%) or complete (*i.e.*, 100%) reduction in a property, activity, effect, or value.

[0220] "Antibody effector functions" refer to the biological activities attributable to the Fc region (*e.g.*, a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include but are not limited to: C1q binding; CDC; Fc receptor binding; ADCC; phagocytosis; downregulation of cell surface receptors (*e.g.*, B cell receptor); and B cell activation.

[0221] "T cell effector functions" refer to the biological activities attributable to various types of T cells, including but not limited to cytotoxic T cells, T helper cells, and memory T cells. Examples of T cell effector functions include: increasing T cell proliferation, secreting cytokines, releasing cytotoxins, expressing membrane-associated molecules, killing target cells, activating macrophages, and activating B cells.

[0222] “Antibody-dependent cell-mediated cytotoxicity” or “ADCC” refers to a form of cytotoxicity in which secreted immunoglobulin bound onto Fc receptors (FcRs) present on certain cytotoxic cells (*e.g.*, Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies “arm” the cytotoxic cells and are absolutely required for such killing. NK cells, the primary cells for mediating ADCC, express FcγRIII only, whereas monocytes express FcγRI, FcγRII, and FcγRIII. FcR expression on hematopoietic cells is known (*see, e.g.*, Ravetch and Kinet, 1991, *Annu. Rev. Immunol.* 9:457-92). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay (*see, e.g.*, US Pat. Nos. 5,500,362 and 5,821,337) can be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, for example, in an animal model (*see, e.g.*, Clynes *et al.*, 1998, *Proc. Natl. Acad. Sci. USA* 95:652-56). Antibodies with little or no ADCC activity may be selected for use.

[0223] “Antibody-dependent cellular phagocytosis” or “ADCP” refers to the destruction of target cells via monocyte or macrophage-mediated phagocytosis when immunoglobulin bound onto Fc receptors (FcRs) present on certain phagocytotic cells (*e.g.*, neutrophils, monocytes, and macrophages) enable these phagocytotic cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell. To assess ADCP activity of a molecule of interest, an *in vitro* ADCP assay (*see, e.g.*, Bracher *et al.*, 2007, *J. Immunol. Methods* 323:160-71) can be performed. Useful phagocytotic cells for such assays include peripheral blood mononuclear cells (PBMC), purified monocytes from PBMC, or U937 cells differentiated to the mononuclear type. Alternatively or additionally, ADCP activity of the molecule of interest may be assessed *in vivo*, for example, in an animal model (*see, e.g.*, Wallace *et al.*, 2001, *J. Immunol. Methods* 248:167-82). Antibodies with little or no ADCP activity may be selected for use.

[0224] “Fc receptor” or “FcR” describes a receptor that binds to the Fc region of an antibody. An exemplary FcR is a native sequence human FcR. Moreover, an exemplary FcR is one that binds an IgG antibody (*e.g.*, a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an “activating receptor”) and FcγRIIB (an “inhibiting receptor”), which have similar amino acid sequences that differ primarily in the cytoplasmic

domains thereof (*see, e.g.*, Daëron, 1997, *Annu. Rev. Immunol.* 15:203-34). Various FcRs are known (*see, e.g.*, Ravetch and Kinet, 1991, *Annu. Rev. Immunol.* 9:457-92; Capel *et al.*, 1994, *Immunomethods* 4:25-34; and de Haas *et al.*, 1995, *J. Lab. Clin. Med.* 126:330-41). Other FcRs, including those to be identified in the future, are encompassed by the term “FcR” herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (*see, e.g.*, Guyer *et al.*, 1976, *J. Immunol.* 117:587-93; and Kim *et al.*, 1994, *Eu. J. Immunol.* 24:2429-34). Antibody variants with improved or diminished binding to FcRs have been described (*see, e.g.*, WO 2000/42072; U.S. Pat. Nos. 7,183,387; 7,332,581; and 7,335,742; Shields *et al.* 2001, *J. Biol. Chem.* 9(2):6591-604).

[0225] “Complement dependent cytotoxicity” or “CDC” refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay (*see, e.g.*, Gazzano-Santoro *et al.*, 1996, *J. Immunol. Methods* 202:163) may be performed. Polypeptide variants with altered Fc region amino acid sequences (polypeptides with a variant Fc region) and increased or decreased C1q binding capability have been described (*see, e.g.*, US Pat. No. 6,194,551; WO 1999/51642; Idusogie *et al.*, 2000, *J. Immunol.* 164: 4178-84).

Antibodies with little or no CDC activity may be selected for use.

[0226] The term “identity” refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by aligning and comparing the sequences. “Percent (%) amino acid sequence identity” with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, or MEGALIGN (DNASTar, Inc.) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[0227] A “modification” of an amino acid residue/position refers to a change of a primary amino acid sequence as compared to a starting amino acid sequence, wherein the change results from a sequence alteration involving said amino acid residue/position. For example, typical modifications include substitution of the residue with another amino acid (*e.g.*, a conservative or non-conservative substitution), insertion of one or more (*e.g.*, generally fewer than 5, 4, or 3) amino acids adjacent to said residue/position, and/or deletion of said residue/position.

[0228] In the context of a polypeptide, the term “analog” as used herein refers to a polypeptide that possesses a similar or identical function as a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody but does not necessarily comprise a similar or identical amino acid sequence of a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody, or possess a similar or identical structure of a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody. A polypeptide that has a similar amino acid sequence refers to a polypeptide that satisfies at least one of the followings: (a) a polypeptide having an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody provided herein; (b) a polypeptide encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody (or VH or VL region thereof) described herein at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues (*see, e.g.*, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual (2001); and Maniatis *et al.*, Molecular Cloning: A Laboratory Manual (1982)); or (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the nucleotide sequence encoding a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody (or VH or VL region thereof) described herein. A

polypeptide with similar structure to a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody provided herein refers to a polypeptide that has a similar secondary, tertiary, or quaternary structure of a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody provided herein. The structure of a polypeptide can be determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

[0229] In the context of a polypeptide, the term “derivative” as used herein refers to a polypeptide that comprises an amino acid sequence of a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an antibody that binds to a PD-1 polypeptide which has been altered by the introduction of amino acid residue substitutions, deletions, or additions. The term “derivative” as used herein also refers to a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an antibody that binds to a PD-1 polypeptide which has been chemically modified, *e.g.*, by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody may be chemically modified, *e.g.*, by increase or decrease of glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, chemical cleavage, linkage to a cellular ligand or other protein, *etc.* The derivatives are modified in a manner that is different from naturally occurring or starting peptide or polypeptides, either in the type or location of the molecules attached. Derivatives further include deletion of one or more chemical groups which are naturally present on the peptide or polypeptide. Further, a derivative of a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a PD-1 polypeptide, a fragment of a PD-1 polypeptide, or an anti-PD-1 antibody provided herein.

[0230] The term “host” as used herein refers to an animal, such as a mammal (*e.g.*, a human).

[0231] The term “host cell” as used herein refers to a particular subject cell that may be transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[0232] The term “vector” refers to a substance that is used to carry or include a nucleic acid sequence, including for example, a nucleic acid sequence encoding an anti-PD-1 antibody as described herein, in order to introduce a nucleic acid sequence into a host cell. Vectors applicable for use include, for example, expression vectors, plasmids, phage vectors, viral vectors, episomes, and artificial chromosomes, which can include selection sequences or markers operable for stable integration into a host cell’s chromosome. Additionally, the vectors can include one or more selectable marker genes and appropriate expression control sequences. Selectable marker genes that can be included, for example, provide resistance to antibiotics or toxins, complement auxotrophic deficiencies, or supply critical nutrients not in the culture media. Expression control sequences can include constitutive and inducible promoters, transcription enhancers, transcription terminators, and the like, which are well known in the art. When two or more nucleic acid molecules are to be co-expressed (*e.g.*, both an antibody heavy and light chain or an antibody VH and VL), both nucleic acid molecules can be inserted, for example, into a single expression vector or in separate expression vectors. For single vector expression, the encoding nucleic acids can be operationally linked to one common expression control sequence or linked to different expression control sequences, such as one inducible promoter and one constitutive promoter. The introduction of nucleic acid molecules into a host cell can be confirmed using methods well known in the art. Such methods include, for example, nucleic acid analysis such as Northern blots or polymerase chain reaction (PCR) amplification of mRNA, immunoblotting for expression of gene products, or other suitable analytical methods to test the expression of an introduced nucleic acid sequence or its corresponding gene product. It is understood by those skilled in the art that the nucleic acid molecules are expressed in a sufficient amount to produce a desired product (*e.g.*, an anti-PD-1 antibody as described herein), and it is further understood that expression levels can be optimized to obtain sufficient expression using methods well known in the art.

[0233] An “isolated nucleic acid” is a nucleic acid, for example, an RNA, DNA, or a mixed nucleic acids, which is substantially separated from other genome DNA sequences as well as proteins or complexes such as ribosomes and polymerases, which naturally accompany a native sequence. An “isolated” nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Moreover, an “isolated” nucleic acid molecule, such as a cDNA molecule, can be substantially free of other

cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. In a specific embodiment, one or more nucleic acid molecules encoding an antibody as described herein are isolated or purified. The term embraces nucleic acid sequences that have been removed from their naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogues or analogues biologically synthesized by heterologous systems. A substantially pure molecule may include isolated forms of the molecule.

[0234] “Polynucleotide” or “nucleic acid,” as used interchangeably herein, refers to polymers of nucleotides of any length and includes DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase or by a synthetic reaction. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. “Oligonucleotide,” as used herein, refers to short, generally single-stranded, synthetic polynucleotides that are generally, but not necessarily, fewer than about 200 nucleotides in length. The terms “oligonucleotide” and “polynucleotide” are not mutually exclusive. The description above for polynucleotides is equally and fully applicable to oligonucleotides. A cell that produces an anti-PD-1 antibody of the present disclosure may include a parent hybridoma cell, as well as bacterial and eukaryotic host cells into which nucleic acids encoding the antibodies have been introduced. Suitable host cells are disclosed below.

[0235] Unless specified otherwise, the left-hand end of any single-stranded polynucleotide sequence disclosed herein is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA transcript that are 5' to the 5' end of the RNA transcript are referred to as “upstream sequences”; sequence regions on the DNA strand having the same sequence as the RNA transcript that are 3' to the 3' end of the RNA transcript are referred to as “downstream sequences.”

[0236] The term “encoding nucleic acid” or grammatical equivalents thereof as it is used in reference to nucleic acid molecule refers to a nucleic acid molecule in its native state or when manipulated by methods well known to those skilled in the art that can be transcribed to produce mRNA, which is then translated into a polypeptide and/or a fragment thereof. The antisense

strand is the complement of such a nucleic acid molecule, and the encoding sequence can be deduced therefrom.

[0237] The term “recombinant antibody” refers to an antibody that is prepared, expressed, created, or isolated by recombinant means. Recombinant antibodies can be antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial antibody library, antibodies isolated from an animal (*e.g.*, a mouse or cow) that is transgenic and/or transchromosomal for human immunoglobulin genes (*see, e.g.*, Taylor *et al.*, 1992, Nucl. Acids Res. 20:6287-95), or antibodies prepared, expressed, created, or isolated by any other means that involves splicing of immunoglobulin gene sequences to other DNA sequences. Such recombinant antibodies can have variable and constant regions, including those derived from human germline immunoglobulin sequences (*See Kabat et al., supra*). In certain embodiments, however, such recombinant antibodies may be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis), thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0238] The term “detectable probe” refers to a composition that provides a detectable signal. The term includes, without limitation, any fluorophore, chromophore, radiolabel, enzyme, antibody or antibody fragment, and the like, that provide a detectable signal via its activity.

[0239] The term “detectable agent” refers to a substance that can be used to ascertain the existence or presence of a desired molecule, such as an anti-PD-1 antibody as described herein, in a sample or subject. A detectable agent can be a substance that is capable of being visualized or a substance that is otherwise able to be determined and/or measured (*e.g.*, by quantitation).

[0240] The term “diagnostic agent” refers to a substance administered to a subject that aids in the diagnosis of a disease, disorder, or condition. Such substances can be used to reveal, pinpoint, and/or define the localization of a disease causing process. In certain embodiments, a diagnostic agent includes a substance that is conjugated to an anti-PD-1 antibody as described herein, that when administered to a subject or contacted with a sample from a subject aids in the diagnosis of a PD-1-mediated disease.

[0241] The term “composition” is intended to encompass a product containing the specified ingredients (*e.g.*, an antibody provided herein) in, optionally, the specified amounts.

[0242] “Carriers” as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers, such as phosphate, citrate, and other organic acids; antioxidants, including ascorbic acid; low molecular weight (*e.g.*, fewer than about 10 amino acid residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers, such as polyvinylpyrrolidone; amino acids, such as glycine, glutamine, asparagine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates, including glucose, mannose, or dextrins; chelating agents, such as EDTA; sugar alcohols, such as mannitol or sorbitol; salt-forming counterions, such as sodium; and/or nonionic surfactants, such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™. The term “carrier” can also refer to a diluent, adjuvant (*e.g.*, Freund’s adjuvant (complete or incomplete)), excipient, or vehicle. Such carriers, including pharmaceutical carriers, can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water is an exemplary carrier when a composition (*e.g.*, a pharmaceutical composition) is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable excipients (*e.g.*, pharmaceutical excipients) include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol, and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. Compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations, and the like. Oral compositions, including formulations, can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc.* Examples of suitable pharmaceutical carriers are described in Remington and Gennaro, Remington’s Pharmaceutical Sciences (18th ed. 1990). Compositions, including pharmaceutical compounds, may contain an anti-PD-1 antibody, for example, in isolated or purified form, together with a suitable amount of carriers.

[0243] The term “pharmaceutically acceptable” as used herein means being approved by a regulatory agency of the Federal or a state government, or listed in United States Pharmacopeia, European Pharmacopeia, or other generally recognized Pharmacopeia for use in animals, and more particularly in humans.

[0244] The term “excipient” refers to an inert substance which is commonly used as a diluent, vehicle, preservative, binder, or stabilizing agent, and includes, but is not limited to, proteins (*e.g.*, serum albumin, *etc.*), amino acids (*e.g.*, aspartic acid, glutamic acid, lysine, arginine, glycine, histidine, *etc.*), fatty acids and phospholipids (*e.g.*, alkyl sulfonates, caprylate, *etc.*), surfactants (*e.g.*, SDS, polysorbate, nonionic surfactant, *etc.*), polyols (*e.g.*, sucrose, maltose, trehalose, mannitol, sorbitol, *etc.*). See, also, Remington and Gennaro, Remington’s Pharmaceutical Sciences (18th ed. 1990), which is hereby incorporated by reference in its entirety.

[0245] The terms “subject” and “patient” may be used interchangeably. As used herein, in certain embodiments, a subject is a mammal, such as a non-primate (*e.g.*, cow, pig, horse, cat, dog, rat, *etc.*) or a primate (*e.g.*, monkey and human). In specific embodiments, the subject is a human.

[0246] “Administer” or “administration” refers to the act of injecting or otherwise physically delivering a substance as it exists outside the body (*e.g.*, an anti-PD-1 antibody as described herein) into a patient, such as by mucosal, intradermal, intravenous, intramuscular delivery, and/or any other method of physical delivery described herein or known in the art.

[0247] The term “effective amount” as used herein refers to the amount of an antibody or pharmaceutical composition provided herein which is sufficient to result in the desired outcome.

[0248] The terms “about” and “approximately” mean within 20%, within 15%, within 10%, within 9%, within 8%, within 7%, within 6%, within 5%, within 4%, within 3%, within 2%, within 1%, or less of a given value or range.

[0249] “Substantially all” refers to at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or about 100%.

[0250] The phrase “substantially similar” or “substantially the same” denotes a sufficiently high degree of similarity between two numeric values (*e.g.*, one associated with an antibody of the present disclosure and the other associated with a reference antibody) such that one of skill in

the art would consider the difference between the two values to be of little or no biological and/or statistical significance within the context of the biological characteristic measured by the values (*e.g.*, K_D values). For example, the difference between the two values may be less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, or less than about 5%, as a function of the value for the reference antibody.

[0251] The phrase “substantially increased,” “substantially reduced,” or “substantially different,” as used herein, denotes a sufficiently high degree of difference between two numeric values (*e.g.*, one associated with an antibody of the present disclosure and the other associated with a reference antibody) such that one of skill in the art would consider the difference between the two values to be of statistical significance within the context of the biological characteristic measured by the values. For example, the difference between said two values can be greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, or greater than about 50%, as a function of the value for the reference antibody.

5.3 Compositions and Methods of Making the Same

[0252] Provided herein are pharmaceutical formulations comprising antibodies that bind to a PD-1 polypeptide, a PD-1 polypeptide fragment, a PD-1 peptide, or a PD-1 epitope.

[0253] In certain embodiments, the pharmaceutical formulations provided herein comprise antibodies that bind to human and/or cynomolgus PD-1. In one embodiment, the PD-1 antibodies bind to human PD-1. In one embodiment, the PD-1 antibodies bind to cynomolgus PD-1. In one embodiment, the PD-1 antibodies bind to both human PD-1 and cynomolgus PD-1. In other embodiments, the antibodies provided herein do not bind to rodent PD-1.

[0254] In some embodiments of the various pharmaceutical formulations provided herein, the anti-PD-1 antibodies bind to the extracellular domain (ECD) of PD-1. In certain embodiments, the anti-PD-1 antibodies bind to an epitope in the ECD of PD-1, which is distinct from the PD-L1 binding site. In certain embodiments, the anti-PD-1 antibodies bind to an epitope in the ECD of PD-1, which is distinct from the PD-L2 binding site. In certain embodiments, the anti-PD-1 antibodies bind to an epitope in the ECD of PD-1, which is distinct from both the PD-L1 and PD-L2-binding site.

[0255] In other embodiments, the pharmaceutical formulation comprises an antibody that competitively blocks an anti-PD-1 antibody disclosed herein from binding to a PD-1 polypeptide.

[0256] In other embodiments, the pharmaceutical formulation comprises an antibody that competes for binding to a PD-1 polypeptide with an anti-PD-1 antibody provided herein.

[0257] In some embodiments, the pharmaceutical formulation comprises antibodies that do not block the binding of PD-L1 to a PD-1 polypeptide. In some embodiments, the pharmaceutical formulation comprises antibodies that do not block the binding of PD-L2 to a PD-1 polypeptide. In some embodiments, the pharmaceutical formulation comprises antibodies that do not block the binding of PD-L1 or PD-L2 to a PD-1 polypeptide.

[0258] In some embodiments, the pharmaceutical formulation comprises antibodies that do not compete with PD-L1 for binding to a PD-1 polypeptide. In some embodiments, the pharmaceutical formulation comprises antibodies that do not compete with PD-L2 for binding to a PD-1 polypeptide. In some embodiments, the pharmaceutical formulation comprises antibodies that do not compete with PD-L1 or PD-L2 for binding to a PD-1 polypeptide.

[0259] In certain embodiments, the pharmaceutical formulation comprises antibodies that do not inhibit binding of PD-L1 to PD-1. In other embodiments, the pharmaceutical formulation comprises antibodies that do not inhibit binding of PD-L2 to PD-1. In specific embodiments, the pharmaceutical formulation comprises antibodies that do not inhibit binding of PD-L1 to PD-1 or binding of PD-L2 to PD-1.

[0260] In some embodiments, the pharmaceutical formulation comprises anti-PD-1 antibodies that are conjugated or recombinantly fused, *e.g.*, to a diagnostic agent or detectable agent.

5.3.1 Anti-PD-1 antibodies

[0261] In one embodiment, the present disclosure provides a pharmaceutical formulation comprising anti-PD-1 antibodies that may find use herein as therapeutic agents. In another embodiment, the present disclosure provides a pharmaceutical formulation comprising anti-PD-1 antibodies that may find use herein as diagnostic agents. Exemplary antibodies of the formulations include polyclonal, monoclonal, humanized, human, bispecific, and heteroconjugate antibodies, as well as variants thereof having improved affinity or other properties.

[0262] In some embodiments, provided herein are pharmaceutical formulations comprising antibodies that bind to PD-1, including a PD-1 polypeptide, a PD-1 polypeptide fragment, a PD-1 peptide, or a PD-1 epitope. In certain embodiments, the pharmaceutical formulations comprise

antibodies that bind to human and/or cynomolgus PD-1. In other embodiments, the pharmaceutical formulations comprise antibodies that do not bind to rodent PD-1 (*e.g.*, a mouse PD-1). In one embodiment, the pharmaceutical formulations comprise antibodies that bind to human PD-1. In another embodiment, the pharmaceutical formulations comprise antibodies that bind to cynomolgus PD-1. In another embodiment, the pharmaceutical formulations comprise antibodies that bind to human PD-1 and cynomolgus PD-1. In some embodiments, the pharmaceutical formulations comprise antibodies that bind to human PD-1 and do not bind to a rodent PD-1 (*e.g.*, a mouse PD-1). In some embodiments, the pharmaceutical formulations comprise antibodies that bind to cynomolgus PD-1 and do not bind to a rodent PD-1 (*e.g.*, a mouse PD-1). In some embodiments, the pharmaceutical formulations comprise antibodies that bind to human PD-1, bind to a cynomolgus PD-1, and do not bind to a rodent PD-1 (*e.g.*, a mouse PD-1). In some embodiments, the pharmaceutical formulations comprise antibodies that do not block the binding of PD-L1 to a PD-1 polypeptide. In some embodiments, the anti-PD-1 antibodies do not block the binding of PD-L2 to a PD-1 polypeptide. In some embodiments, the pharmaceutical formulations comprise antibodies that do not block the binding of PD-L1 or PD-L2 to a PD-1 polypeptide. In other embodiments, the pharmaceutical formulations comprise anti-PD-1 antibodies that are humanized antibodies (*e.g.*, comprising human constant regions) that bind to PD-1, including a PD-1 polypeptide, a PD-1 polypeptide fragment, a PD-1 peptide, or a PD-1 epitope.

[0263] In certain embodiments, the pharmaceutical formulations comprises an anti-PD-1 antibody that comprises a VH region, VL region, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of any one of the murine monoclonal antibodies provided herein, such as an amino acid sequence depicted in **Tables 1-6**. Accordingly, in some embodiments, the isolated antibody or functional fragment thereof of the pharmaceutical formulations provided herein comprises one, two, and/or three heavy chain CDRs and/or one, two, and/or three light chain CDRs from: (a) the antibody PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, or (f) the antibody PD1AB-6, as shown in **Tables 1-2**.

Table 1. VL CDR Amino Acid Sequences

Antibody	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
PD1AB-1	KSGQSVLYSSNQKNFLA (SEQ ID NO:1)	WASTRES (SEQ ID NO:2)	HQYLYSWT (SEQ ID NO:3)
PD1AB-2	KSSQSVLYSSNNKNYLA (SEQ ID NO:7)	WASTRES (SEQ ID NO:2)	HQYLYSWT (SEQ ID NO:3)
PD1AB-3	KSGQSVLYSSNQKNFLA (SEQ ID NO:1)	WASTRES (SEQ ID NO:2)	HQYLYSWT (SEQ ID NO:3)
PD1AB-4	KSSQSVLYSSNNKNYLA (SEQ ID NO:7)	WASTRES (SEQ ID NO:2)	HQYLYSWT (SEQ ID NO:3)
PD1AB-5	KSSQSVLYSSNNKNYLA (SEQ ID NO:7)	WASTRES (SEQ ID NO:2)	HQYLYSWT (SEQ ID NO:3)
PD1AB-6	KSGQSVLYSSNQKNFLA (SEQ ID NO:1)	WASTRES (SEQ ID NO:2)	HQYLYSWT (SEQ ID NO:3)

Table 2. VH CDR Amino Acid Sequences

Antibody	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
PD1AB-1	GFNIKDTYMH (SEQ ID NO:4)	RIDPANGDRK (SEQ ID NO:5)	SGPVYYYGSSYVMDY (SEQ ID NO:6)
PD1AB-2	GFNIKDTYMH (SEQ ID NO:4)	RIDPANGDRK (SEQ ID NO:5)	SGPVYYYGSSYVMDY (SEQ ID NO:6)
PD1AB-3	GFNIKDTYMH (SEQ ID NO:4)	RIDPANGDRK (SEQ ID NO:5)	SGPVYYYGSSYVMDY (SEQ ID NO:6)
PD1AB-4	GFNIKDTYMH (SEQ ID NO:4)	RIDPANGDRK (SEQ ID NO:5)	SGPVYYYGSSYVMDY (SEQ ID NO:6)
PD1AB-5	GFNIKDTYMH (SEQ ID NO:4)	RIDPANGDRK (SEQ ID NO:5)	SGPVYYYGSSYVMDY (SEQ ID NO:6)
PD1AB-6	GFNIKDTYMH (SEQ ID NO:4)	RIDPANGDRK (SEQ ID NO:5)	SGPVYYYGSSYVMDY (SEQ ID NO:6)

[0264] In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises or consists of six CDRs, for example, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in **Tables 1-2**. In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that can comprise fewer than six CDRs. In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in **Tables 1-2**. In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of the monoclonal antibody selected from the group consisting of: (a) the antibody

PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, and (f) the antibody PD1AB-6, described herein. Accordingly, in some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises or consists of one, two, three, four, or five CDRs of anyone of the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in **Tables 1-2**.

[0265] In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises one or more (*e.g.*, one, two, or three) VH CDRs listed in **Table 2**. In other embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises one or more (*e.g.*, one, two, or three) VL CDRs listed in **Table 1**. In yet other embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises one or more (*e.g.*, one, two, or three) VH CDRs listed in **Table 2** and one or more VL CDRs listed in **Table 1**. Accordingly, in some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises a VH CDR1 having an amino acid sequence of SEQ ID NO:4. In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises a VH CDR2 having an amino acid sequence of SEQ ID NO:5. In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises a VH CDR3 having an amino acid sequence of SEQ ID NO:6. In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises a VH CDR1 and/or a VH CDR2 and/or a VH CDR3 independently selected from any one of the VH CDR1, VH CDR2, VH CDR3 amino acid sequence(s) as depicted in **Table 2**. In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises a VL CDR1 having an amino acid sequence of any one of SEQ ID NOS:1 and 7. In another embodiment, a pharmaceutical formulation provided herein comprises an antibody that comprises a VL CDR2 having an amino acid sequence of SEQ ID NO:2. In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises a VL CDR3 having an amino acid sequence of SEQ ID NO:3. In some embodiments, a pharmaceutical formulation provided herein comprises an antibody that comprises a VL CDR1 and/or a VL CDR2 and/or a VL CDR3 independently selected from any one of the VL CDR1, VL CDR2, VL CDR3 amino acid sequences as depicted in **Table 1**.

[0266] In certain embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region comprising: (1) a VH CDR1 having an amino acid sequence of SEQ ID

NO:4; (2) a VH CDR2 having an amino acid sequence of SEQ ID NO:5; and (3) a VH CDR3 having an amino acid sequence of SEQ ID NO:6; and a VL region comprising: (1) a VL CDR1 having an amino acid sequence of SEQ ID NO:1; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3.

[0267] In certain embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region comprising: (1) a VH CDR1 having an amino acid sequence of SEQ ID NO:4; (2) a VH CDR2 having an amino acid sequence of SEQ ID NO:5; and (3) a VH CDR3 having an amino acid sequence of SEQ ID NO:6; and a VL region comprising: (1) a VL CDR1 having an amino acid of SEQ ID NOS:7; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3.

[0268] In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region comprising: (1) a VH CDR1 having an amino acid sequence of SEQ ID NO:4; (2) a VH CDR2 having an amino acid sequence of SEQ ID NO:5; and (3) a VH CDR3 having an amino acid sequence of SEQ ID NO:6.

[0269] In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VL region comprising: (1) a VL CDR1 having an amino acid sequence of SEQ ID NO:1; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3.

[0270] In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VL region comprising: (1) a VL CDR1 having an amino acid sequence of SEQ ID NOS: 7; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3.

[0271] Also provided herein are pharmaceutical formulations comprising antibodies that comprise one or more (*e.g.*, one, two, or three) VH CDRs and one or more (*e.g.*, one, two, or three) VL CDRs listed in **Tables 1-2**. In particular, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4) and a VL CDR1 (SEQ ID NOS:1 or 7). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4) and a VL CDR2 (SEQ ID NO:2). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4) and a VL CDR3 (SEQ ID

NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5) and a VL CDR1 (SEQ ID NOS:1 or 7). In some embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5) and a VL CDR2 (SEQ ID NO:2). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5) and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR3 (SEQ ID NO:6) and a VL CDR1 (SEQ ID NOS:1 or 7). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR3 (SEQ ID NO:6) and a VL CDR2 (SEQ ID NO:2). In some embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR3 (SEQ ID NO:6) and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), and a VL CDR1 (SEQ ID NOS:1 or 7). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), and a VL CDR2 (SEQ ID NO:2). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), and a VL CDR3 (SEQ ID NOS:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR1 (SEQ ID NOS:1 or 7). In some embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR2 (SEQ ID NO:2). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), and a VL CDR1 (SEQ ID NOS:1 or 7). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), and a VL CDR2 (SEQ ID NO:2). In some embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), and a VL CDR3 (SEQ ID

NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In some embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In some embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR3 (SEQ ID NO:6), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR1 (SEQ ID NOS:1 or 7). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR2 (SEQ ID NO:2). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In some embodiments, provided herein is a pharmaceutical formulation comprising an

antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In some embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In some embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In other embodiments, provided herein is a pharmaceutical

formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In some embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In one embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In other embodiments, provided herein is a pharmaceutical formulation comprising an antibody that comprises a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, provided herein is a pharmaceutical formulation comprising an antibody that comprises any combination thereof of the VH CDRs and VL CDRs listed in **Tables 1-2**.

[0272] In yet another aspect, the CDRs disclosed herein include consensus sequences derived from groups of related antibodies (*see, e.g., Tables 1-2*). As described herein, a “consensus sequence” refers to amino acid sequences having conserved amino acids common among a number of sequences and variable amino acids that vary within a given amino acid sequences.

[0273] In some embodiments, the isolated antibody or functional fragment thereof of a pharmaceutical formulation provided herein further comprises one, two, three, and/or four heavy chain FRs and/or one, two, three, and/or four light chain FRs from: (a) the antibody PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, or (f) the antibody PD1AB-6, as shown in **Tables 3-4**.

Table 3. VL FR Amino Acid Sequences

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
PD1AB-1	DIVMTQSPDSLAVS LGERATINC (SEQ ID NO:14)	WYQQKPGQPPKLLIY (SEQ ID NO:15)	GVPDRFSGSGSGTDFT LTISSLQAEDVAVYYC (SEQ ID NO:16)	FGQGTKLEIKR (SEQ ID NO:17)
PD1AB-2	DIVMTQSPDSLAVS LGERATINC (SEQ ID NO:14)	WYQQKPGQPPKLLIY (SEQ ID NO:15)	GVPDRFSGSGSGTDFT LTISSLQAEDVAVYYC (SEQ ID NO:16)	FGQGTKLEIKR (SEQ ID NO:17)
PD1AB-3	DIVMTQSPDSLAVS LGERATINC (SEQ ID NO:14)	WYQQKPGQPPKLLIY (SEQ ID NO:15)	GVPDRFSGSGSGTDFT LTISNLQAEDVAVYYC (SEQ ID NO:18)	FGQGTKLEIKR (SEQ ID NO:17)
PD1AB-4	DIVMTQSPDSLAVS LGERATINC (SEQ ID NO:14)	WYQQKPGQPPKLLIY (SEQ ID NO:15)	GVPDRFSGSGSGTDFT LTISSLQAEDVAVYYC (SEQ ID NO:16)	FGQGTKLEIKR (SEQ ID NO:17)
PD1AB-5	DIVMTQSPDSLAVS LGERATINC (SEQ ID NO:14)	WYQQKPGQPPKLLIY (SEQ ID NO:15)	GVPDRFSGSGSGTDFT LTISSLQAEDVAVYYC (SEQ ID NO:16)	FGQGTKLEIKR (SEQ ID NO:17)
PD1AB-6	DIVMTQSPDSLAVS LGERATINC (SEQ ID NO:14)	WYQQKPGQPPKLLIY (SEQ ID NO:15)	GVPDRFSGSGSGTDFT LTISSLQAEDVAVYYC (SEQ ID NO:16)	FGQGTKLEIKR (SEQ ID NO:17)

Table 4. VH FR Amino Acid Sequences

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
PD1AB-1	EVQLVQSGAEVKKP GATVKISKVS (SEQ ID NO:19)	WVQQAPGKGLEWMG (SEQ ID NO:20)	YDPKFQGRVTITADTS TDTAYMELSSLRSED TAVYYCAR (SEQ ID NO:21)	WGQGTTVTVSS (SEQ ID NO:22)
PD1AB-2	EVQLVQSGAEVKKP GATVKISKVS (SEQ ID NO:19)	WVQQAPGKGLEWMG (SEQ ID NO:20)	YDPKFQGRVTITADTS TDTAYMELSSLRSED TAVYYCAR (SEQ ID NO:21)	WGQGTTVTVSS (SEQ ID NO:22)
PD1AB-3	EVQLVQSGAEVKKP GATVKISKVS (SEQ ID NO:19)	WVQQAPGKGLEWMG (SEQ ID NO:20)	YDPKFQGRVTITADTS TNTAYMELSSLRSED TAVYYCAR (SEQ ID NO:23)	WGQGTTVTVSS (SEQ ID NO:22)
PD1AB-4	EVQLVQSGAEVKKP GATVKISKVS (SEQ ID NO:19)	WVQQAPGKGLEWMG (SEQ ID NO:20)	YDPKFQGRVTITADTS TNTAYMELSSLRSED TAVYYCAR (SEQ ID NO:23)	WGQGTTVTVSS (SEQ ID NO:22)
PD1AB-5	EVQLVQSGAEVKKP GATVKISKAS (SEQ ID NO:24)	WVQQAPGKGLEWMG (SEQ ID NO:20)	YDPKFQGRVTITADTS TDTAYMELSSLRSED TAVYYCAR (SEQ ID NO:21)	WGQGTTVTVSS (SEQ ID NO:22)

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
PD1AB-6	EVQLVQSGAEVKKP GATVKISCKAS (SEQ ID NO:24)	WVQQAPGKGLEWMG (SEQ ID NO:20)	YDPKFQGRVTITADTS TDTAYMELSSLRSED T AVYYCAR (SEQ ID NO:21)	WGQGTTVTVSS (SEQ ID NO:22)

[0274] In certain embodiments, the isolated antibody or functional fragment thereof of a pharmaceutical formulation provided herein further comprises one, two, three, and/or four heavy chain FRs from: (a) the antibody PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, or (f) the antibody PD1AB-6, as shown in **Table 4**. In some embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-1. In some embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-2. In other embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-3. In certain embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-4. In other embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-5. In another embodiment, the antibody heavy chain FR(s) is from the antibody PD1AB-6.

[0275] In some embodiments, the isolated antibody or functional fragment thereof of a pharmaceutical formulation provided herein further comprises one, two, three, and/or four light chain FRs from: (a) the antibody PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, or (f) the antibody PD1AB-6, as shown in **Table 3**. In some embodiments, the antibody light chain FR(s) is from the antibody PD1AB-1. In some embodiments, the antibody light chain FR(s) is from the antibody PD1AB-2. In other embodiments, the antibody light chain FR(s) is from the antibody PD1AB-3. In certain embodiments, the antibody light chain FR(s) is from the antibody PD1AB-4. In other embodiments, the antibody light chain FR(s) is from the antibody PD1AB-5. In another embodiment, the antibody light chain FR(s) is from the antibody PD1AB-6.

[0276] In certain embodiments, an antibody or fragment thereof of a pharmaceutical formulation described herein comprises a VH region that comprises: (1) a VH FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS:19 and 24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:21 and 23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In certain embodiments, an antibody or

fragment thereof of a pharmaceutical formulation described herein comprises a VH region that comprises: (1) a VH FR1 having an amino acid of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In certain embodiments, an antibody or fragment thereof of a pharmaceutical formulation described herein comprises a VH region that comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO: 23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In certain embodiments, an antibody or fragment thereof of a pharmaceutical formulation described herein comprises a VH region that comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO: 24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In certain embodiments, an antibody or fragment thereof of a pharmaceutical formulation described herein comprises a VH region that comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO: 23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In specific embodiments, the antibody comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4.

[0277] Accordingly, in some embodiments, the humanized antibody of a pharmaceutical formulation comprises a VH region that includes a VH FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS:19 and 24. In one embodiment, the humanized antibody of a pharmaceutical formulation comprises a VH region that includes a VH FR1 having an amino acid sequence of SEQ ID NO:19. In one embodiment, the humanized antibody of a pharmaceutical formulation comprises a VH region that includes a VH FR1 having an amino acid sequence of SEQ ID NO:24. In some embodiments, the humanized antibody of a pharmaceutical formulation comprises a VH region that includes a VH FR2 having an amino acid sequence of SEQ ID NO: 20. In some embodiments, the humanized antibody of a pharmaceutical formulation comprises a VH region that includes a VH FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:21 and 23. In one embodiment, the humanized antibody of a pharmaceutical formulation comprises a VH region

that includes a VH FR3 having an amino acid sequence of SEQ ID NO:21. In one embodiment, the humanized antibody of a pharmaceutical formulation comprises a VH region that includes a VH FR3 having an amino acid sequence of SEQ ID NO:23. In other embodiments, the humanized antibody of a pharmaceutical formulation comprises a VH region that includes a VH FR4 having an amino acid sequence of SEQ ID NO:22.

[0278] In certain embodiments, an antibody or fragment thereof of a pharmaceutical formulation described herein comprises a VL region that comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:16 and 18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NOS:16; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In other embodiments, the VL region that comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO: 18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17.

[0279] Accordingly, in some embodiments, the humanized antibody of a pharmaceutical formulation comprises a VL region that includes a VL FR1 having an amino acid sequence of SEQ ID NO:14. In certain embodiments, the humanized antibody of a pharmaceutical formulation comprises a VL region that includes a VL FR2 having an amino acid sequence of SEQ ID NO:15. In other embodiments, the humanized antibody of a pharmaceutical formulation comprises a VL region that includes a VL FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:16 and 18. In one embodiment, the humanized antibody of a pharmaceutical formulation comprises a VL region that includes a VL FR3 having an amino acid sequence of SEQ ID NOS:16. In other embodiments, the humanized antibody of a pharmaceutical formulation comprises a VL region that includes a VL FR3 having an amino acid sequence of SEQ ID NO: 18. In yet other embodiments, the humanized antibody of a pharmaceutical formulation comprises a VL region that includes a VL FR4 having an amino acid sequence of SEQ ID NO:17.

[0280] In certain embodiments, an antibody or fragment thereof of a pharmaceutical formulation described herein comprises a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS:19 and 24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:21 and 23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:16 and 18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the antibody of a pharmaceutical formulation comprises a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0281] In some embodiments, an antibody or fragment thereof of a pharmaceutical formulation comprises a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:16; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the antibody of a pharmaceutical formulation comprises a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising

all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0282] In some embodiments, an antibody or fragment thereof of a pharmaceutical formulation comprises a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the antibody of a pharmaceutical formulation comprises a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0283] In some embodiments, an antibody or fragment thereof of a pharmaceutical formulation comprises a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:16; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the antibody of a pharmaceutical formulation comprises a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising

all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0284] In some embodiments, an antibody or fragment thereof of a pharmaceutical formulation comprises a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the antibody of a pharmaceutical formulation comprises a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0285] In some embodiments, an antibody or fragment thereof of a pharmaceutical formulation comprises a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:16; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the antibody of a pharmaceutical formulation comprises a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising

all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0286] In some embodiments, an antibody or fragment thereof of a pharmaceutical formulation comprises a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3 and VH FR4. In other embodiments, the antibody of a pharmaceutical formulation comprises a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3 and VL FR4. In yet other embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0287] In some embodiments, an antibody or fragment thereof of a pharmaceutical formulation comprises a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:16; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the antibody of a pharmaceutical formulation comprises a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising

all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0288] In some embodiments, an antibody or fragment thereof of a pharmaceutical formulation comprises a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the antibody of a pharmaceutical formulation comprises a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the antibody of a pharmaceutical formulation comprises a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0289] Also provided herein are pharmaceutical formulations that comprise antibodies comprising one or more (*e.g.*, one, two, three, or four) VH FRs and one or more (*e.g.*, one, two, three, or four) VL FRs listed in **Tables 3-4**. In particular, provided herein is a pharmaceutical formulation that comprises an antibody comprising a VH FR1 (SEQ ID NOS:19 or 24) and a VL FR1 (SEQ ID NO:14). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24) and a VL FR2 (SEQ ID NO:15). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24) and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24) and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20) and a VL FR1 (SEQ ID NO:14). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20) and a VL FR2 (SEQ ID NO:15). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2

(SEQ ID NO:20) and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20) and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NO:21) and a VL FR1 (SEQ ID NO:14). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NO:21) and a VL FR2 (SEQ ID NO:15). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NO:21) and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NO:21) and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22) and a VL FR1 (SEQ ID NO:14). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22) and a VL FR2 (SEQ ID NO:15). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22) and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22) and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), and a VL FR1 (SEQ ID NO:14). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), and a VL FR2 (SEQ ID NO:15). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), and a VL FR1 (SEQ ID NO:14). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), and a VL FR2 (SEQ ID NO:15). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), and a VL FR3 (SEQ ID NOS:16 or 18). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2

(SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR2 (SEQ ID NO:15) and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR2 (SEQ ID NO:15) and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NO:19 or 24), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR2 (SEQ ID NO:15) and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR2 (SEQ ID NO:15) and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), and a VL FR4

(SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR2 (SEQ ID NO:15) and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR2 (SEQ ID NO:15) and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15) and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15) and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), and a VL FR1 (SEQ ID NO:14). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), and a VL FR2 (SEQ ID NO:15). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), and a VL FR1 (SEQ ID NO:14). In one embodiment, the pharmaceutical formulation comprises an

antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), and a VL FR2 (SEQ ID NO:15). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR1 (SEQ ID NO:14). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR2 (SEQ ID NO:15). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR1 (SEQ ID NO:14). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR2 (SEQ ID NO:15). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody

that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS: 16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NO:21), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NO:21), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NO:21), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NO:21), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NO:21), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NO:21), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an

antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NO:21), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ

ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14),

a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR1 (SEQ ID NO:14). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR2 (SEQ ID NO:15). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19

or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18).

(SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In another embodiment, the

pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that

comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17).

(SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR2 (SEQ ID NO:15). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), and a VL FR4 (SEQ ID NO:17). In one embodiment, the

pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that

comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23),

a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR3 (SEQ ID NOS:16 or 18). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In another embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an

antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR2 (SEQ ID NO:20), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH FR1 (SEQ ID NOS:19 or 24), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In one embodiment, the pharmaceutical formulation comprises an antibody that comprises a VH FR2 (SEQ ID NO:20), a VH FR3 (SEQ ID NOS:21 or 23), a VH FR4 (SEQ ID NO:22), a VL FR1 (SEQ ID NO:14), a VL FR2 (SEQ ID NO:15), a VL FR3 (SEQ ID NOS:16 or 18), and a VL FR4 (SEQ ID NO:17). In some embodiments, the pharmaceutical formulation comprises an antibody that comprises any combination thereof of the VH FRs (SEQ ID NOS:19-24) and the VL FRs (SEQ ID NOS:14-18) listed in **Tables 3-4**.

[0290] In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region or VH domain. In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VL region or VL domain. In certain embodiments, the antibodies of pharmaceutical formulations provided herein have a combination of (i) a VH domain or VH region; and/or (ii) a VL domain or VL region. In yet other embodiments, the antibodies of pharmaceutical formulations provided herein have a combination of (i) a VH domain or VH region; and/or (ii) a VL domain or VL region selected from the group consisting of SEQ ID NOS: 8-13 as set forth in **Tables 5-6**. In still other embodiments, the pharmaceutical formulation comprises an antibody having a combination of (i) a VH domain or VH region; and/or (ii) a VL domain or VL region of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6, as set forth in **Tables 5-6**.

[0291] In certain embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region comprising: (1) a VH CDR1 having an amino acid sequence of SEQ ID NO:4; (2) a VH CDR2 having an amino acid sequence of SEQ ID NO:5; and (3) a VH CDR3 having an amino acid sequence of SEQ ID NO:6; and a VL region selected from the group consisting of SEQ ID NOS:8-10 as set forth in **Table 5**. In some embodiments, the VL region has an amino acid sequence of SEQ ID NO:8. In other embodiments, the VL region has an amino acid sequence of SEQ ID NO:9. In some embodiments, the VL region has an amino acid sequence of SEQ ID NO:10.

[0292] In other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region selected from the group consisting of SEQ ID NOS:11-13 as set forth in **Table 6**; and a VL region comprising: (1) a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS:1 and 7; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3. In yet some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region selected from the group consisting of SEQ ID NOS:11-13 as set forth in **Table 6**; and a VL region comprising: (1) a VL CDR1 having an amino acid sequence of SEQ ID NO:1; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3. In still other embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region selected from the group consisting of SEQ ID NOS:11-13 as set forth in **Table 6**; and a VL region comprising: (1) a VL CDR1 having an amino acid sequence of SEQ ID NO:7; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3. In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region having an amino acid sequence of SEQ ID NO:11. In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region having an amino acid sequence of SEQ ID NO:12. In some embodiments, the pharmaceutical formulation comprises an antibody that comprises a VH region having an amino acid sequence of SEQ ID NO:13.

Table 5. VL Domain Amino Acid Sequences

Antibody	VL (SEQ ID NO:)
PD1AB-1	DIVMTQSPDSLAVSLGERATINCKSGQSVLYSSNQKNFLAWYQQKPGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTITSSSLQAEDVAVYYCHQYLYSWTFGQGGTKLEIKR (SEQ ID NO:8)
PD1AB-2	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTITSSSLQAEDVAVYYCHQYLYSWTFGQGGTKLEIKR (SEQ ID NO:9)
PD1AB-3	DIVMTQSPDSLAVSLGERATINCKSGQSVLYSSNQKNFLAWYQQKPGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTITISNLQAEDVAVYYCHQYLYSWTFGQGGTKLEIKR (SEQ ID NO:10)
PD1AB-4	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTITSSSLQAEDVAVYYCHQYLYSWTFGQGGTKLEIKR (SEQ ID NO:9)
PD1AB-5	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTITSSSLQAEDVAVYYCHQYLYSWTFGQGGTKLEIKR (SEQ ID NO:9)
PD1AB-6	DIVMTQSPDSLAVSLGERATINCKSGQSVLYSSNQKNFLAWYQQKPGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTITSSSLQAEDVAVYYCHQYLYSWTFGQGGTKLEIKR (SEQ ID NO:8)

Table 6. VH Domain Amino Acid Sequences

Antibody	VH (SEQ ID NO:)
PD1AB-1	EVQLVQSGAEVKKPGATVKISCKVSGFNIKDTYMHVWVQQAPGKGLEWMGRIDPANGDRKYDPKFQGRV TITADTSTDTAYMELSSLRSEDTAVYYCARSGPVYYYGSSYVM DYWGQGTTTVTVSS (SEQ ID NO:11)
PD1AB-2	EVQLVQSGAEVKKPGATVKISCKVSGFNIKDTYMHVWVQQAPGKGLEWMGRIDPANGDRKYDPKFQGRV TITADTSTDTAYMELSSLRSEDTAVYYCARSGPVYYYGSSYVM DYWGQGTTTVTVSS (SEQ ID NO:11)
PD1AB-3	EVQLVQSGAEVKKPGATVKISCKVSGFNIKDTYMHVWVQQAPGKGLEWMGRIDPANGDRKYDPKFQGRV TITADTSTNTAYMELSSLRSEDTAVYYCARSGPVYYYGSSYVM DYWGQGTTTVTVSS (SEQ ID NO:12)
PD1AB-4	EVQLVQSGAEVKKPGATVKISCKVSGFNIKDTYMHVWVQQAPGKGLEWMGRIDPANGDRKYDPKFQGRV TITADTSTNTAYMELSSLRSEDTAVYYCARSGPVYYYGSSYVM DYWGQGTTTVTVSS (SEQ ID NO:12)
PD1AB-5	EVQLVQSGAEVKKPGATVKISCKASGFNIKDTYMHVWVQQAPGKGLEWMGRIDPANGDRKYDPKFQGRV TITADTSTDTAYMELSSLRSEDTAVYYCARSGPVYYYGSSYVM DYWGQGTTTVTVSS (SEQ ID NO:13)
PD1AB-6	EVQLVQSGAEVKKPGATVKISCKASGFNIKDTYMHVWVQQAPGKGLEWMGRIDPANGDRKYDPKFQGRV TITADTSTDTAYMELSSLRSEDTAVYYCARSGPVYYYGSSYVM DYWGQGTTTVTVSS (SEQ ID NO:13)

[0293] Also provided herein is a pharmaceutical formulation comprising an antibody encoded by an isolated nucleic acid molecule, *e.g.*, an immunoglobulin heavy chain, light chain, VH region, VL region, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of anti-PD-1 antibodies that bind to a PD-1 polypeptide, a PD-1 polypeptide fragment, a

PD-1 peptide, or a PD-1 epitope. Exemplary nucleic acid sequences for the VL region and the VH region of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, and PD1AB-6 are shown in **Tables 7-8**.

Table 7. VL Nucleic Acid Sequences

Antibody	Nucleotide sequences
PD1AB-1	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCAA CTGCAAGTCCGGTCAAAGTGTTTTATACAGTTCAAATCAGAAGAACTTCTTGGCCTGGTACCAGC AGAAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCCACTAGGGAATCTGGGGTCCCT GACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAAGCTGA AGATGTGGCAGTTTATTACTGTCATCAATACCTCTACTCGTGGACGTTTGGCCAGGGGACCAAGC TGGAGATCAAACGGAC (SEQ ID NO:25)
PD1AB-2	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCAA CTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGC AGAAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCT GACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAAGCTGA AGATGTGGCAGTTTATTACTGTCATCAATACCTCTACTCGTGGACGTTTGGCCAGGGGACCAAGC TGGAGATCAAACGGAC (SEQ ID NO:26)
PD1AB-3	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCAA CTGCAAGTCCGGTCAAAGTGTTTTATACAGTTCAAATCAGAAGAACTTCTTGGCCTGGTACCAGC AGAAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCCACTAGGGAATCTGGGGTCCCT GACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAACCTGCAAGCTGA AGATGTGGCAGTTTATTACTGTCATCAATACCTCTACTCGTGGACGTTTGGCCAGGGGACCAAGC TGGAGATCAAACGGAC (SEQ ID NO:27)
PD1AB-4	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCAA CTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGC AGAAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCT GACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAAGCTGA AGATGTGGCAGTTTATTACTGTCATCAATACCTCTACTCGTGGACGTTTGGCCAGGGGACCAAGC TGGAGATCAAACGGAC (SEQ ID NO:26)
PD1AB-5	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCAA CTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAGAACTACTTAGCTTGGTACCAGC AGAAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCT GACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAAGCTGA AGATGTGGCAGTTTATTACTGTCATCAATACCTCTACTCGTGGACGTTTGGCCAGGGGACCAAGC TGGAGATCAAACGGAC (SEQ ID NO:26)
PD1AB-6	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCAA CTGCAAGTCCGGTCAAAGTGTTTTATACAGTTCAAATCAGAAGAACTTCTTGGCCTGGTACCAGC AGAAACCAGGACAGCCTCCTAAGCTGCTCATTTACTGGGCATCCACTAGGGAATCTGGGGTCCCT GACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAAGCTGA AGATGTGGCAGTTTATTACTGTCATCAATACCTCTACTCGTGGACGTTTGGCCAGGGGACCAAGC TGGAGATCAAACGGAC (SEQ ID NO:25)

Table 8. VH Nucleic Acid Sequences

Antibody	Nucleotide sequences
PD1AB-1	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTACAGTGAAAATCTCCTG CAAGGTTTCTGGATTCAACATTAAAGACACGTATATGCACTGGGTGCAACAGGCCCTGGAAAAG GGCTTGAGTGGATGGGAAGGATTGATCCTGCGAATGGTGATAGGAAATATGACCCGAAGTTCCAG GGCAGAGTCACCATAACCGCGGACACGTCTACAGACACAGCCTACATGGAGCTGAGCAGCCTGAG ATCTGAGGACACGGCCGTGTATTACTGTGCTAGATCAGGCCCTGTTTATTACTACGGTAGTAGCT ACGTTATGGACTACTGGGGTCAAGGAACCACAGTCACCGTCTCCTCA (SEQ ID NO:28)
PD1AB-2	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTACAGTGAAAATCTCCTG CAAGGTTTCTGGATTCAACATTAAAGACACGTATATGCACTGGGTGCAACAGGCCCTGGAAAAG GGCTTGAGTGGATGGGAAGGATTGATCCTGCGAATGGTGATAGGAAATATGACCCGAAGTTCCAG GGCAGAGTCACCATAACCGCGGACACGTCTACAGACACAGCCTACATGGAGCTGAGCAGCCTGAG ATCTGAGGACACGGCCGTGTATTACTGTGCTAGATCAGGCCCTGTTTATTACTACGGTAGTAGCT ACGTTATGGACTACTGGGGTCAAGGAACCACAGTCACCGTCTCCTCA (SEQ ID NO:28)
PD1AB-3	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTACAGTGAAAATCTCCTG CAAGGTTTCTGGATTCAACATTAAAGACACGTATATGCACTGGGTGCAACAGGCCCTGGAAAAG GGCTTGAGTGGATGGGAAGGATTGATCCTGCGAATGGTGATAGGAAATATGACCCGAAGTTCCAG GGCAGAGTCACCATAACCGCGGACACGTCTACAAACACAGCCTACATGGAGCTGAGCAGCCTGAG ATCTGAGGACACGGCCGTGTATTACTGTGCTAGATCAGGCCCTGTTTATTACTACGGTAGTAGCT ACGTTATGGACTACTGGGGTCAAGGAACCACAGTCACCGTCTCCTCA (SEQ ID NO:29)
PD1AB-4	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTACAGTGAAAATCTCCTG CAAGGTTTCTGGATTCAACATTAAAGACACGTATATGCACTGGGTGCAACAGGCCCTGGAAAAG GGCTTGAGTGGATGGGAAGGATTGATCCTGCGAATGGTGATAGGAAATATGACCCGAAGTTCCAG GGCAGAGTCACCATAACCGCGGACACGTCTACAAACACAGCCTACATGGAGCTGAGCAGCCTGAG ATCTGAGGACACGGCCGTGTATTACTGTGCTAGATCAGGCCCTGTTTATTACTACGGTAGTAGCT ACGTTATGGACTACTGGGGTCAAGGAACCACAGTCACCGTCTCCTCA (SEQ ID NO:29)
PD1AB-5	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTACAGTGAAAATCTCCTG CAAGGCTTCTGGATTCAACATTAAAGACACGTATATGCACTGGGTGCAACAGGCCCTGGAAAAG GGCTTGAGTGGATGGGAAGGATTGATCCTGCGAATGGTGATAGGAAATATGACCCGAAGTTCCAG GGCAGAGTCACCATAACCGCGGACACGTCTACAGACACAGCCTACATGGAGCTGAGCAGCCTGAG ATCTGAGGACACGGCCGTGTATTACTGTGCTAGATCAGGCCCTGTTTATTACTACGGTAGTAGCT ACGTTATGGACTACTGGGGTCAAGGAACCACAGTCACCGTCTCCTCA (SEQ ID NO:30)
PD1AB-6	GAGGTCCAGCTGGTACAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTACAGTGAAAATCTCCTG CAAGGCTTCTGGATTCAACATTAAAGACACGTATATGCACTGGGTGCAACAGGCCCTGGAAAAG GGCTTGAGTGGATGGGAAGGATTGATCCTGCGAATGGTGATAGGAAATATGACCCGAAGTTCCAG GGCAGAGTCACCATAACCGCGGACACGTCTACAGACACAGCCTACATGGAGCTGAGCAGCCTGAG ATCTGAGGACACGGCCGTGTATTACTGTGCTAGATCAGGCCCTGTTTATTACTACGGTAGTAGCT ACGTTATGGACTACTGGGGTCAAGGAACCACAGTCACCGTCTCCTCA (SEQ ID NO:30)

[0294] In some embodiments, the pharmaceutical formulation comprises an antibody having a VH and a VL amino acid sequence of PD1AB-1. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH amino acid sequence of SEQ ID NO:11, and a VL amino acid sequence of SEQ ID NO:8.

[0295] In other embodiments, the pharmaceutical formulation comprises an antibody having a VH and a VL amino acid sequence of PD1AB-2. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH amino acid sequence of SEQ ID NO:11, and a VL amino acid sequence of SEQ ID NO:9.

[0296] In some embodiments, the pharmaceutical formulation comprises an antibody having a VH and a VL amino acid sequence of PD1AB-3. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH amino acid sequence of SEQ ID NO:12, and a VL amino acid sequence of SEQ ID NO:10.

[0297] In other embodiments, the pharmaceutical formulation comprises an antibody having a VH and a VL amino acid sequence of PD1AB-4. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH amino acid sequence of SEQ ID NO:12, and a VL amino acid sequence of SEQ ID NO:9.

[0298] In some embodiments, the pharmaceutical formulation comprises an antibody having a VH and a VL amino acid sequence of PD1AB-5. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH amino acid sequence of SEQ ID NO:13, and a VL amino acid sequence of SEQ ID NO:9.

[0299] In other embodiments, the pharmaceutical formulation comprises an antibody having a VH and a VL amino acid sequence of PD1AB-6. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH amino acid sequence of SEQ ID NO:13, and a VL amino acid sequence of SEQ ID NO:8.

[0300] In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-1. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-1. In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-2, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-1. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:11. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:8. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH

CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:11, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:8.

[0301] In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-2. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-2. In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-2, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-2. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:11. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:9. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:11, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:9.

[0302] In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-3. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-3. In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-3, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-3. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:12. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:10. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:12, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:10.

[0303] In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-4. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-4. In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-4, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-4. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:12. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:9. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:12, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:9.

[0304] In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-5. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-5. In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-5, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-5. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:13. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:9. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:13, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:9.

[0305] In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-6. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL

CDR3 of the VL region of PD1AB-6. In other embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region of PD1AB-6, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region of PD1AB-6. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:13. In other embodiments, the pharmaceutical formulation comprises an antibody having a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:8. In some embodiments, the pharmaceutical formulation comprises an antibody having a VH CDR1, VH CDR2 and VH CDR3 of the VH region having amino acid sequence of SEQ ID NO:13, and a VL CDR1, VL CDR2 and VL CDR3 of the VL region having amino acid sequence of SEQ ID NO:8.

[0306] In certain embodiments, the pharmaceutical formulation comprises an antibody or antigen-binding fragment thereof described herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the light chain comprises a constant region having an amino acid sequence of:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YSLSSITLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:41).

[0307] In other embodiments, the pharmaceutical formulation comprises an antibody or antigen-binding fragment thereof described herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain comprises a human IgG1 Fc region having an amino acid sequence of:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTQSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCTPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCK^KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO:36, K322 emphasized).

In some embodiments, the pharmaceutical formulation comprises an antibody or antigen-binding fragment thereof described herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD

of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain does not comprise a human IgG1 Fc region having an amino acid sequence of SEQ ID NO:36.

[0308] In certain embodiments, the pharmaceutical formulation comprises an antibody or antigen-binding fragment thereof described herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain comprises a human IgG1-K322A Fc region having an amino acid sequence of:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO:37, K322A substitution emphasized).

[0309] In some embodiments, the pharmaceutical formulation comprises an antibody or antigen-binding fragment thereof described herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain comprises a human IgG4 Fc region having an amino acid sequence of:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPPEFLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO:38, S228 and L235 emphasized).

[0310] In another embodiment, the pharmaceutical formulation comprises an antibody or antigen-binding fragment thereof described herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain comprises a human IgG4P Fc region having an amino acid sequence of:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS

LSSVVTVPSSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK
DTLMISRTPPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVQLHQT
WLNQKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO:39, S228P substitution emphasized).

[0311] In yet another embodiment, the pharmaceutical formulation comprises an antibody or antigen-binding fragment thereof described herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain comprises a human IgG4PE Fc region having an amino acid sequence of:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK
DTLMISRTPPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVQLHQT
WLNQKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO:40, S228P and L235E substitutions emphasized).

In some embodiments, the pharmaceutical formulation comprises an antibody or antigen-binding fragment thereof described herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain does not comprise a human IgG4PE Fc region having an amino acid sequence of SEQ ID NO:40.

[0312] In still another embodiment, the pharmaceutical formulation comprises an antibody or antigen-binding fragment thereof described herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the light chain comprises a constant region having an amino acid sequence of SEQ ID NO:41; and the heavy chain comprises an Fc region having an amino acid sequence selected from the group consisting of SEQ ID NOS:36-40.

[0313] In certain embodiments, the pharmaceutical formulation comprises an antibody provided herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the light chain comprises an amino acid sequence as follows:

DIVMTQSPDSLAVSLGERATINCKSGQSVLYSSNQKNFLAWYQQKPGQPPKLLIYWASTRESGV
PDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYLYSWTFGQGTKLEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
KHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:31, LC_PD1AB-6-IgG1).

[0314] In some embodiments, the pharmaceutical formulation comprises an antibody provided herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain comprises an amino acid sequence as follows:

EVQLVQSGAEVKKPGATVKISCKASGFNIKDTYMHVWVQQAPGKGLEWMGRIDPANGDRKYDPKF
QGRVTITADTSTDTAYMELSSLRSEDVAVYYCARSGPVYYYGSSYVMDYWGQGTTVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO:32, HC_PD1AB-6-IgG1, K322 emphasized).

[0315] In other embodiments, the pharmaceutical formulation comprises an antibody provided herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain comprises an amino acid sequence as follows:

EVQLVQSGAEVKKPGATVKISCKASGFNIKDTYMHVWVQQAPGKGLEWMGRIDPANGDRKYDPKF
QGRVTITADTSTDTAYMELSSLRSEDVAVYYCARSGPVYYYGSSYVMDYWGQGTTVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO:33, HC_PD1AB-6-IgG1-K322A, K322A substitution emphasized).

[0316] In another embodiment, the pharmaceutical formulation comprises an antibody provided herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for

example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain comprises an amino acid sequence as follows:

EVQLVQSGAEVKKPGATVKISCKASGFNIKDTYMHVWQQAPGKGLEWMGRIDPANGDRKYDPKF
QGRVTITADTSTDYAYMELSSLRSEDYAVYYCARSGPVYYYGSSYVMDYWGQGTTVTVSSASTK
GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDPKPSNTKVDKRVESESKYGPPCP**PC**PAPEFLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLS
PGK (SEQ ID NO:34, HC_PD1AB-6-IgG4P, IgG4P Fc backbone italicized and underlined).

[0317] In yet another embodiment, the pharmaceutical formulation comprises an antibody provided herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein the heavy chain comprises an amino acid sequence as follows:

EVQLVQSGAEVKKPGATVKISCKASGFNIKDTYMHVWQQAPGKGLEWMGRIDPANGDRKYDPKF
QGRVTITADTSTDYAYMELSSLRSEDYAVYYCARSGPVYYYGSSYVMDYWGQGTTVTVSSASTK
GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDPKPSNTKVDKRVESESKYGPPCP**PC**PAPEF**E**GGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLS
PGK (SEQ ID NO:35, HC_PD1AB-6-IgG4PE, IgG4PE Fc backbone italicized and underlined).

[0318] In one particular embodiment, the pharmaceutical formulation comprises an antibody provided herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein (i) the light chain comprises an amino acid sequence of SEQ ID NO:31; and (ii) the heavy chain comprises an amino acid sequence of SEQ ID NO:32.

[0319] In another particular embodiment, the pharmaceutical formulation comprises an antibody provided herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein (i) the light

chain comprises an amino acid sequence of SEQ ID NO:31; and (ii) the heavy chain comprises an amino acid sequence of SEQ ID NO:33.

[0320] In yet another particular embodiment, the pharmaceutical formulation comprises an antibody provided herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein (i) the light chain comprises an amino acid sequence of SEQ ID NO:31; and (ii) the heavy chain comprises an amino acid sequence of SEQ ID NO:34.

[0321] In still another particular embodiment, the pharmaceutical formulation comprises an antibody provided herein, which specifically binds to a PD-1 polypeptide (*e.g.*, an ECD of PD-1, for example human PD-1), and comprises a light chain and a heavy chain, wherein (i) the light chain comprises an amino acid sequence of SEQ ID NO:31; and (ii) the heavy chain comprises an amino acid sequence of SEQ ID NO:35.

[0322] In yet another aspect, the pharmaceutical formulations comprise antibodies that compete with one of the exemplified antibodies or functional fragments for binding to PD-1. Such antibodies may also bind to the same epitope as one of the herein exemplified antibodies, or an overlapping epitope. Antibodies and fragments that compete with or bind to the same epitope as the exemplified antibodies are expected to show similar functional properties. The exemplified antigen-binding proteins and fragments include those with the VH and VL regions, and CDRs provided herein, including those in **Tables 1-6**. Thus, as a specific example, pharmaceutical formulations provided herein comprise antibodies that include those that compete with an antibody comprising: (a) 1, 2, 3, 4, 5, or all 6 of the CDRs listed for an antibody listed in **Tables 1-2**; (b) a VH and a VL selected from the VH and the VL regions listed for an antibody listed in **Tables 5-6**; or (c) two light chains and two heavy chains comprising a VH and a VL as specified for an antibody listed in **Tables 5-6**. In some embodiments, pharmaceutical formulations provided herein comprise an antibody that is PD1AB-1. In some embodiments, pharmaceutical formulations provided herein comprise an antibody that is PD1AB-2. In some embodiments, pharmaceutical formulations provided herein comprise an antibody that is PD1AB-3. In some embodiments, pharmaceutical formulations provided herein comprise an antibody that is PD1AB-4. In some embodiments, pharmaceutical formulations provided herein comprise an antibody that is PD1AB-5. In some embodiments, pharmaceutical formulations provided herein comprise an antibody that is PD1AB-6.

[0323] In another aspect, pharmaceutical formulations provided herein comprise antibodies or antigen-binding fragments thereof that bind to a region, including an epitope, of human PD-1 or cynomolgus PD-1. For example, in some embodiments, pharmaceutical formulations provided herein comprise an antibody that binds to a region of human PD-1 (SEQ ID NO:42) comprising amino acid residues 33 to 109 of human PD-1. In still another aspect, pharmaceutical formulations provided herein comprise an antibody that binds to a specific epitope of human PD-1.

[0324] In certain embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to at least one of residues 100-109 (SEQ ID NO:43) within an amino acid sequence of SEQ ID NO:42. In some embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to at least one of residues 100-105 (SEQ ID NO:44) within an amino acid sequence of SEQ ID NO:42.

[0325] In particular embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to at least one residue selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42. In some embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to at least one residue selected from the group consisting of L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0326] In some embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to two or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0327] In other embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to three or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0328] In certain embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to four or more

residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0329] In one embodiment pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to five or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0330] In another embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to six or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0331] In yet another embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to seven or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0332] In still another embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to eight or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0333] In certain embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to nine or more residues selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0334] In other embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to all ten residues from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.

[0335] In another embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to N33 within an amino acid sequence of SEQ ID NO:42. In another embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to T51 within an amino acid sequence of SEQ ID NO:42. In a particular

embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to S57 within an amino acid sequence of SEQ ID NO:42. In one specific embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to L100 within an amino acid sequence of SEQ ID NO:42. In some embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to N102 within an amino acid sequence of SEQ ID NO:42. In other embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to G103 within an amino acid sequence of SEQ ID NO:42. In another embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to R104 within an amino acid sequence of SEQ ID NO:42. In yet another embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to G103 and R104 within an amino acid sequence of SEQ ID NO:42. In still another embodiment, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to D105 within an amino acid sequence of SEQ ID NO:42. In some embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to H107 within an amino acid sequence of SEQ ID NO:42. In certain embodiments, pharmaceutical formulations provided herein comprise an antibody or antigen-binding fragment thereof, that when bound to PD-1, binds to S109 within an amino acid sequence of SEQ ID NO:42. Any combination of two, three, four, five, six, seven, eight, nine, ten or more of the above-referenced amino acid PD-1 binding sites is also contemplated.

[0336] In one aspect, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to PD-1 and can modulate PD-1 activity and/or expression (*e.g.*, activate PD-1 signaling and/or inhibit PD-1 expression). In certain embodiments, provided herein are pharmaceutical formulations comprising a PD-1 agonist that is an antibody provided herein that specifically binds to an ECD of human PD-1, and activates (*e.g.*, partially activates) at least one PD-1 activity (*e.g.*, inhibiting cytokine production). In certain embodiments, provided herein are pharmaceutical formulations comprising a PD-1 agonist that is an antibody provided herein that specifically binds to an ECD of human PD-1, and downregulates PD-1 expression. In certain

embodiments, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to PD-1 and that (a) attenuate T cell activity, *e.g.*, as determined by inhibition of cytokine production; and/or (b) downregulate PD-1 expression in a cell. In certain embodiments, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to PD-1 and that (a) attenuate T cell activity, *e.g.*, as determined by inhibition of cytokine production; (b) downregulate PD-1 expression in a cell; and/or (c) do not inhibit PD-L1 and/or PD-L2 binding to PD-1. In certain embodiments, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to PD-1, an ECD of human PD-1, or an epitope of an ECD of human PD-1 thereof. In certain embodiments, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to an epitope of an ECD of human PD-1 that is distinct from the PD-L1 binding site. In certain embodiments, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to an epitope of an ECD of human PD-1 that is distinct from the PD-L2 binding site. In certain embodiments, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to an epitope of an ECD of human PD-1 that is distinct from both the PD-L1 and PD-L2 binding sites. In certain embodiments, provided herein are pharmaceutical formulations comprising antibodies that do not inhibit binding of PD-L1 to PD-1. In other embodiments, provided herein are pharmaceutical formulations comprising antibodies that do not inhibit binding of PD-L2 to PD-1. In specific embodiments, provided herein are pharmaceutical formulations comprising antibodies that do not inhibit binding of PD-L1 to PD-1 or binding of PD-L2 to PD-1.

[0337] PD-1 activity can relate to any activity of PD-1 such as those known or described in the art. PD-1 activity and PD-1 signaling are used interchangeably herein. In certain aspects, PD-1 activity is induced by PD-1 ligand (*e.g.*, PD-L1) binding to PD-1. Expression levels of PD-1 can be assessed by methods described herein or known to one of skill in the art (*e.g.*, Western blotting, ELISA, immunohistochemistry, or flow cytometry). In certain embodiments, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to PD-1 and decrease PD-1 expression. In certain embodiments, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to PD-1 and attenuate T cell activity. In certain embodiments, provided herein are pharmaceutical formulations comprising antibodies that specifically bind to PD-1 and inhibit cytokine production. In certain embodiments, provided

herein are pharmaceutical formulations comprising antibodies that specifically bind to PD-1 and activate (*e.g.*, partially activate) PD-1 signaling. In certain embodiments, pharmaceutical formulations provided herein comprise antibodies that specifically bind to PD-1, an ECD of human PD-1, or an epitope of an ECD of human PD-1 thereof. In certain embodiments, pharmaceutical formulations provided herein comprise antibodies that specifically bind to an epitope of an ECD of human PD-1 that is distinct from the PD-L1 binding site. In certain embodiments, pharmaceutical formulations provided herein comprise antibodies that specifically bind to an epitope of an ECD of human PD-1 that is distinct from the PD-L2 binding site. In certain embodiments, pharmaceutical formulations provided herein comprise antibodies that specifically bind to an epitope of an ECD of human PD-1 that is distinct from both the PD-L1 and PD-L2 binding sites. In certain embodiments, pharmaceutical formulations provided herein comprise antibodies that do not inhibit binding of PD-L1 to PD-1. In other embodiments, pharmaceutical formulations provided herein comprise antibodies that do not inhibit binding of PD-L2 to PD-1. In specific embodiments, pharmaceutical formulations provided herein comprise antibodies that do not inhibit binding of PD-L1 to PD-1 or binding of PD-L2 to PD-1.

[0338] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates (*e.g.*, partially attenuates) T cell activity. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 10%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 15%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 20%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 25%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 30%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 35%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 40%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 45%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 50%. In some embodiments, an anti-PD-1 antibody of

a pharmaceutical formulation provided herein attenuates T cell activity by at least about 55%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 60%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 65%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 70%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 75%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 80%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 85%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 90%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 95%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 98%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 99%. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein attenuates T cell activity by at least about 100%. In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein can attenuate (*e.g.*, partially attenuate) T cell activity by at least about 25% to about 65%. In specific embodiments, the T cell activity attenuation is assessed by methods described herein. In some embodiments, the T cell activity attenuation is assessed by methods known to one of skill in the art. In certain embodiments, the T cell activity attenuation is relative to T cell activity in the presence of stimulation without any anti-PD-1 antibody. In certain embodiments, the T cell activity attenuation is relative to T cell activity in the presence of stimulation with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1). A non-limiting example of T cell activity is secretion of a cytokine. In some embodiments, the cytokine is selected from the group consisting of IL-2, IL-17, IFN- γ , or any combination thereof. In certain embodiments, the cytokine is selected from the group consisting of IL-1, IL-2, IL-6, IL-12, IL-17, IL-22, IL-23, GM-CSF, IFN- γ , and TNF- α . In certain embodiments, the cytokine is IL-1. In some embodiments, the cytokine is IL-2. In other embodiments, the cytokine is IL-6. In another embodiment, the cytokine is IL-12. In other

embodiments, the cytokine is IL-17. In yet other embodiments, the cytokine is IL-22. In still other embodiments, the cytokine is IL-23. In some embodiments, the cytokine is GM-CSF. In other embodiments, the cytokine is IFN- γ . In yet other embodiments, the cytokine is TNF- α . In certain embodiments, the cytokine is IL-2 and IL-17. In some embodiments, the cytokine is IL-2 and IFN- γ . In yet other embodiments, the cytokine is IL-17 and IFN- γ . In still other embodiments, the cytokine is IL-2, IL-17, and IFN- γ .

[0339] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit IL-2 secretion (*e.g.*, from a cell, for example, T cells). In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 5%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 10%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 15%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 20%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 25%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 30%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 35%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 40%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 45%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 50%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 55%. In another embodiment, an antibody of a pharmaceutical formulation provided herein

specifically binds to PD-1 and inhibits IL-2 secretion by at least about 60%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 65%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 70%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 75%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 80%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 85%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 90%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 95%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 98%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-2 secretion by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit IL-2 secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-2 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-2 secretion is assessed by methods known to one of skill in the art (*e.g.*, MesoScale™ Discovery (MSD) multiplex assay). In a specific embodiment, the IL-2 secretion is inhibited relative to IL-2 secretion in the absence of anti-PD-1 antibody. In other embodiments, the IL-2 secretion is inhibited relative to IL-2 secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0340] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) inhibits IL-2 secretion. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about

50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 0.5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 0.05 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at most about 0.001 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at least about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at least about 40 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at least about 30 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at least about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC₅₀ of at least about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-

2 secretion with an EC_{50} of at least about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC_{50} of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC_{50} of at least about 0.75 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC_{50} of at least about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC_{50} of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC_{50} of at least about 0.05 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC_{50} of at least about 0.01 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC_{50} of at least about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-2 secretion with an EC_{50} of at least about 0.001 nM. In specific embodiments, the EC_{50} is assessed by methods described herein. In other embodiments, the EC_{50} is assessed by other methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC_{50} is assessed by MSD multiplex assay.

[0341] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit IL-17 secretion (*e.g.*, from a cell, for example, T cells). In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 5%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 10%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 15%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 20%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 25%. In one embodiment, an antibody of a

pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 30%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 35%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 40%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 45%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 50%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 55%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 60%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 65%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 70%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 75%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 80%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 85%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 90%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 95%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 98%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-17 secretion by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit IL-17 secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-17 secretion is assessed by methods described herein. In other embodiments, the

inhibition of IL-17 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-17 secretion is inhibited relative to IL-17 secretion in the absence of anti-PD-1 antibody. In other embodiments, the IL-17 secretion is inhibited relative to IL-17 secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0342] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) inhibits IL-17 secretion. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 50 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 40 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 20 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 1 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 0.75 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 0.5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 0.1 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 0.05 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀

of at most about 0.005 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at most about 0.001 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 50 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 0.5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 0.05 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 0.005 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-17 secretion with an EC₅₀ of at least about 0.001 nM. In specific embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by other methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC₅₀ is assessed by MSD multiplex assay.

[0343] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6

or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit IFN- γ secretion (*e.g.*, from a cell, for example, T cells). In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 5%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 10%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 15%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 20%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 25%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 30%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 35%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 40%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 45%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 50%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 55%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 60%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 65%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 70%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 75%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 80%. In some

embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 85%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 90%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 95%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 98%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IFN- γ secretion by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit IFN- γ secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IFN- γ secretion is assessed by methods described herein. In other embodiments, the inhibition of IFN- γ secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IFN- γ secretion is inhibited relative to IFN- γ secretion in the absence of anti-PD-1 antibody. In other embodiments, the IFN- γ secretion is inhibited relative to IFN- γ secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0344] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) inhibits IFN- γ secretion. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 50 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 40 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 30 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 20 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 10 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein

inhibits IFN- γ secretion with an EC₅₀ of at most about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 0.75 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 0.05 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 0.01 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 0.005 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at most about 0.001 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 50 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 40 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 20 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 10 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 1 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 0.75 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 0.5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 0.1 nM. In

another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 0.05 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 0.005 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IFN- γ secretion with an EC₅₀ of at least about 0.001 nM. In specific embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by other methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC₅₀ is assessed by MSD multiplex assay.

[0345] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit IL-1 secretion (*e.g.*, from a cell, for example, T cells). In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 5%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 10%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 15%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 20%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 25%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 30%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 35%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 40%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 45%. In other embodiments, an antibody of a

pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 50%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 55%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 60%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 65%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 70%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 75%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 80%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 85%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 90%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 95%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 98%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-1 secretion by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit IL-1 secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-1 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-1 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-1 secretion is inhibited relative to IL-1 secretion in the absence of anti-PD-1 antibody. In other embodiments, the IL-1 secretion is inhibited relative to IL-1 secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0346] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4,

PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) inhibits IL-1 secretion. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 0.5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 0.05 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at most about 0.001 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 40 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 30 nM. In another embodiment, an anti-PD-

1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 0.75 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 0.05 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 0.01 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-1 secretion with an EC₅₀ of at least about 0.001 nM. In specific embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by other methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC₅₀ is assessed by MSD multiplex assay.

[0347] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit IL-6 secretion (*e.g.*, from a cell, for example, T cells). In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 5%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 10%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least

about 15%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 20%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 25%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 30%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 35%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 40%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 45%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 50%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 55%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 60%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 65%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 70%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 75%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 80%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 85%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 90%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 95%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-6 secretion by at least about 98%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to

PD-1 and inhibits IL-6 secretion by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit IL-6 secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-6 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-6 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-6 secretion is inhibited relative to IL-6 secretion in the absence of anti-PD-1 antibody. In other embodiments, the IL-6 secretion is inhibited relative to IL-6 secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0348] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) inhibits IL-6 secretion. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 0.5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC₅₀ of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-

6 secretion with an EC_{50} of at most about 0.05 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at most about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at most about 0.001 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 40 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 30 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 0.75 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 0.05 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 0.01 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-6 secretion with an EC_{50} of at least about 0.001 nM. In specific embodiments, the EC_{50} is assessed by methods described herein. In other embodiments,

the EC₅₀ is assessed by other methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC₅₀ is assessed by MSD multiplex assay.

[0349] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit IL-12 secretion (*e.g.*, from a cell, for example, T cells). In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 5%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 10%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 15%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 20%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 25%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 30%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 35%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 40%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 45%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 50%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 55%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 60%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 65%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12

secretion by at least about 70%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 75%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 80%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 85%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 90%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 95%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 98%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-12 secretion by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit IL-12 secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-12 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-12 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-12 secretion is inhibited relative to IL-12 secretion in the absence of anti-PD-1 antibody. In other embodiments, the IL-12 secretion is inhibited relative to IL-12 secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0350] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) inhibits IL-12 secretion. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 30 nM. In some embodiments, an anti-PD-1 antibody

of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 0.5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 0.05 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at most about 0.001 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 40 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 30 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀

of at least about 0.75 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 0.05 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 0.01 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-12 secretion with an EC₅₀ of at least about 0.001 nM. In specific embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by other methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC₅₀ is assessed by MSD multiplex assay.

[0351] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit IL-22 secretion (*e.g.*, from a cell, for example, a T cell). In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 5%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 10%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 15%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 20%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 25%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 30%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least

about 35%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 40%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 45%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 50%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 55%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 60%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 65%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 70%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 75%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 80%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 85%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 90%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 95%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 98%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-22 secretion by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit IL-22 secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-22 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-22 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-22 secretion is inhibited relative to IL-22 secretion in the absence of anti-PD-1 antibody. In other embodiments, the IL-22 secretion is

inhibited relative to IL-22 secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0352] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) inhibits IL-22 secretion. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 0.5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 0.05 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at most about 0.001 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein

inhibits IL-22 secretion with an EC₅₀ of at least about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 40 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 30 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 0.75 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 0.05 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 0.01 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-22 secretion with an EC₅₀ of at least about 0.001 nM. In specific embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by other methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC₅₀ is assessed by MSD multiplex assay.

[0353] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit IL-23 secretion (*e.g.*, from a cell, for example, a T cell). In one

embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 5%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 10%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 15%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 20%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 25%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 30%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 35%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 40%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 45%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 50%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 55%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 60%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 65%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 70%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 75%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 80%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 85%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23

secretion by at least about 90%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 95%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 98%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits IL-23 secretion by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit IL-23 secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-23 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-23 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-23 secretion is inhibited relative to IL-23 secretion in the absence of anti-PD-1 antibody. In other embodiments, the IL-23 secretion is inhibited relative to IL-23 secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0354] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) inhibits IL-23 secretion. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation

provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 0.5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 0.05 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at most about 0.001 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 40 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 30 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 0.75 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 0.05 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 0.01 nM. In

another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits IL-23 secretion with an EC₅₀ of at least about 0.001 nM. In specific embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by other methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC₅₀ is assessed by MSD multiplex assay.

[0355] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit GM-CSF secretion (*e.g.*, from a cell, for example, T cells). In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 5%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 10%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 15%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 20%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 25%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 30%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 35%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 40%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 45%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 50%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF

secretion by at least about 55%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 60%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 65%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 70%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 75%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 80%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 85%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 90%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 95%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 98%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits GM-CSF secretion by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit GM-CSF secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of GM-CSF secretion is assessed by methods described herein. In other embodiments, the inhibition of GM-CSF secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the GM-CSF secretion is inhibited relative to GM-CSF secretion in the absence of anti-PD-1 antibody. In other embodiments, the GM-CSF secretion is inhibited relative to GM-CSF secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0356] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or

PD1AB-6) inhibits GM-CSF secretion. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 0.5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 0.05 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at most about 0.001 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 40 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 30 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 20 nM. In

one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 0.75 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 0.05 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 0.01 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits GM-CSF secretion with an EC_{50} of at least about 0.001 nM. In specific embodiments, the EC_{50} is assessed by methods described herein. In other embodiments, the EC_{50} is assessed by other methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC_{50} is assessed by MSD multiplex assay.

[0357] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and inhibit TNF- α secretion (*e.g.*, from a cell, for example, a T cell). In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 5%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 10%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 15%. In other embodiments, an antibody of a pharmaceutical formulation provided herein

specifically binds to PD-1 and inhibits TNF- α secretion by at least about 20%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 25%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 30%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 35%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 40%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 45%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 50%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 55%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 60%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 65%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 70%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 75%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 80%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 85%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 90%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 95%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 98%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and inhibits TNF- α secretion by at least about 99%. In specific embodiments, antibodies of

a pharmaceutical formulation provided herein specifically bind to PD-1 and inhibit TNF- α secretion by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of TNF- α secretion is assessed by methods described herein. In other embodiments, the inhibition of TNF- α secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the TNF- α secretion is inhibited relative to TNF- α secretion in the absence of anti-PD-1 antibody. In other embodiments, the TNF- α secretion is inhibited relative to TNF- α secretion in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0358] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) inhibits TNF- α secretion. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 0.5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 0.05 nM. In

another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at most about 0.001 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 40 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 30 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 0.75 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 0.05 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 0.01 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein inhibits TNF- α secretion with an EC₅₀ of at least about 0.001 nM. In specific embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by other methods known to one of

skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the EC₅₀ is assessed by MSD multiplex assay.

[0359] In specific embodiments, antibodies of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) specifically bind to PD-1 and downregulate PD-1 expression (*e.g.*, in a cell, for example, T cells). In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 5%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 10%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 15%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 20%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 25%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 30%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 35%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 40%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 45%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 50%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 55%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 60%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 65%. In one embodiment, an antibody of a

pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 70%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 75%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 80%. In some embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 85%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 90%. In other embodiments, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 95%. In one embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 98%. In another embodiment, an antibody of a pharmaceutical formulation provided herein specifically binds to PD-1 and downregulates PD-1 expression by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and downregulates PD-1 expression by at least about 25% or 35%, optionally to about 75%. In some embodiments, the downregulation of PD-1 expression is assessed by methods described herein. In other embodiments, the downregulation of PD-1 expression is assessed by methods known to one of skill in the art (*e.g.*, flow cytometry, Western blotting, Northern blotting, or RT-PCR). In a specific embodiment, the downregulation of PD-1 expression is assessed by flow cytometry. In another embodiment, the downregulation of PD-1 expression is assessed by Western blotting. In yet another embodiment, the downregulation of PD-1 expression is assessed by Northern blotting. In still another embodiment, the downregulation of PD-1 expression is assessed by RT-PCR. In a specific embodiment, the PD-1 expression is downregulated relative to PD-1 expression downregulation in the absence of anti-PD-1 antibody. In other embodiments, the PD-1 expression is downregulated relative to PD-1 expression downregulation in the presence of an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0360] In certain embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein (*e.g.*, any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising

CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6) downregulates PD-1 expression. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 40 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 30 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 10 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 5 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 0.75 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 0.5 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 0.05 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 0.01 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at most about 0.001 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 50 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 40 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical

formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 30 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 20 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 10 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 1 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 0.75 nM. In other embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 0.5 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 0.1 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 0.05 nM. In some embodiments, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 0.01 nM. In another embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 0.005 nM. In one embodiment, an anti-PD-1 antibody of a pharmaceutical formulation provided herein downregulates PD-1 expression with an EC_{50} of at least about 0.001 nM. In specific embodiments, the EC_{50} is assessed by methods described herein. In other embodiments, the EC_{50} is assessed by other methods known to one of skill in the art (*e.g.*, flow cytometry, Western blotting, Northern blotting, or RT-PCR). In a specific embodiment, the EC_{50} is assessed by flow cytometry. In another embodiment, the EC_{50} is assessed by Western blotting. In yet another embodiment, the EC_{50} is assessed by Northern blotting. In still another embodiment, the EC_{50} is assessed by RT-PCR.

[0361] In certain embodiments, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations provided herein. In another embodiment, the downregulation occurs as early as 6 hours after the contact. In yet another embodiment, the

downregulation occurs as early as 8 hours after the contact. In still another embodiment, the downregulation occurs as early as 10 hours after the contact. In one embodiment, the downregulation occurs as early as 12 hours after the contact. In another embodiment, the downregulation occurs as early as 14 hours after the contact. In yet another embodiment, the downregulation occurs as early as 16 hours after the contact. In still another embodiment, the downregulation occurs as early as 18 hours after the contact. In one embodiment, the downregulation occurs as early as 20 hours after the contact. In another embodiment, the downregulation occurs as early as 22 hours after the contact. In yet another embodiment, the downregulation occurs as early as 24 hours after the contact. In some embodiments, the contact is with the antibody. In other embodiments, the contact is with an antigen-binding fragment thereof.

[0362] In some embodiments, the downregulation of PD-1 expression on the surface of T cells precedes cytokine inhibition. In one embodiment, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In another embodiment, the downregulation occurs as early as 6 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 8 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In still another embodiment, the downregulation occurs as early as 10 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In one embodiment, the downregulation occurs as early as 12 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In another embodiment, the downregulation occurs as early as 14 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 16 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In still another embodiment, the downregulation occurs as early as 18 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In one

embodiment, the downregulation occurs as early as 20 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In another embodiment, the downregulation occurs as early as 22 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 24 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and precedes cytokine inhibition.

[0363] In other embodiments, the downregulation of PD-1 expression on the surface of T cells is concurrent with cytokine inhibition. In one embodiment, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In another embodiment, the downregulation occurs as early as 6 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 8 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In still another embodiment, the downregulation occurs as early as 10 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In one embodiment, the downregulation occurs as early as 12 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In another embodiment, the downregulation occurs as early as 14 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 16 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In still another embodiment, the downregulation occurs as early as 18 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In one embodiment, the downregulation occurs as early as 20 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In another embodiment, the downregulation occurs as early as 22 hours after

the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 24 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is concurrent with cytokine inhibition.

[0364] In yet other embodiments, the downregulation of PD-1 expression on the surface of T cells is after cytokine inhibition. In one embodiment, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In another embodiment, the downregulation occurs as early as 6 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 8 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In still another embodiment, the downregulation occurs as early as 10 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In one embodiment, the downregulation occurs as early as 12 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In another embodiment, the downregulation occurs as early as 14 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 16 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In still another embodiment, the downregulation occurs as early as 18 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In one embodiment, the downregulation occurs as early as 20 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In another embodiment, the downregulation occurs as early as 22 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition. In yet another embodiment, the downregulation occurs as early as 24 hours after the contact with the antibody or antigen-binding fragment thereof of pharmaceutical formulations, and is after cytokine inhibition.

5.3.1.1 Polyclonal Antibodies

[0365] The antibodies of pharmaceutical formulations of the present disclosure may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include a PD-1 polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized or to immunize the mammal with the protein and one or more adjuvants. Examples of such immunogenic proteins include, but are not limited to, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Ribi, CpG, Poly 1C, Freund's complete adjuvant, and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation. The mammal can then be bled, and the serum assayed for PD-1 antibody titer. If desired, the mammal can be boosted until the antibody titer increases or plateaus. Additionally or alternatively, lymphocytes may be obtained from the immunized animal for fusion and preparation of monoclonal antibodies from hybridoma as described below.

5.3.1.2 Monoclonal Antibodies

[0366] The antibodies of pharmaceutical formulations of the present disclosure may alternatively be monoclonal antibodies. Monoclonal antibodies may be made using the hybridoma method first described by Kohler *et al.*, 1975, Nature 256:495-97, or may be made by recombinant DNA methods (*see, e.g.*, U.S. Pat. No. 4,816,567).

[0367] In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as described above to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. After immunization, lymphocytes are isolated and then fused with a myeloma cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice 59-103 (1986)).

[0368] The hybridoma cells thus prepared are seeded and grown in a suitable culture medium which, in certain embodiments, contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells (also referred to as fusion partner). For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the selective culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which prevent the growth of HGPRT-deficient cells.

[0369] Exemplary fusion partner myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a selective medium that selects against the unfused parental cells. Exemplary myeloma cell lines are murine myeloma lines, such as SP-2 and derivatives, for example, X63-Ag8-653 cells available from the American Type Culture Collection (Manassas, VA), and those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center (San Diego, CA). Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, 1984, Immunol. 133:3001-05; and Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications 51-63 (1987)).

[0370] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. The binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as RIA or ELISA. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis described in Munson *et al.*, 1980, Anal. Biochem. 107:220-39.

[0371] Once hybridoma cells that produce antibodies of the desired specificity, affinity, and/or activity are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, *supra*). Suitable culture media for this purpose include, for example, DMEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal, for example, by i.p. injection of the cells into mice.

[0372] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional antibody purification procedures such

as, for example, affinity chromatography (*e.g.*, using protein A or protein G-Sepharose) or ion-exchange chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, *etc.*

[0373] DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells can serve as a source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells, such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra *et al.*, 1993, *Curr. Opin. in Immunol.* 5:256-62 and Plückthun, 1992, *Immunol. Revs.* 130:151-88.

[0374] In some embodiments, an antibody of pharmaceutical formulations that binds a PD-1 epitope comprises an amino acid sequence of a VH domain and/or an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes to (1) the complement of a nucleotide sequence encoding any one of the VH and/or VL domain described herein under stringent conditions (*e.g.*, hybridization to filter-bound DNA in 6X sodium chloride/sodium citrate (SSC) at about 45 °C followed by one or more washes in 0.2X SSC/0.1% SDS at about 50-65 °C), under highly stringent conditions (*e.g.*, hybridization to filter-bound nucleic acid in 6X SSC at about 45 °C followed by one or more washes in 0.1X SSC/0.2% SDS at about 68 °C), or under other stringent hybridization conditions which are known to those of skill in the art. *See, e.g., Current Protocols in Molecular Biology* Vol. I, 6.3.1-6.3.6 and 2.10.3 (Ausubel *et al.* eds., 1989).

[0375] In some embodiments, an antibody of pharmaceutical formulations that binds a PD-1 epitope comprises an amino acid sequence of a VH CDR or an amino acid sequence of a VL CDR encoded by a nucleotide sequence that hybridizes to the complement of a nucleotide sequence encoding any one of the VH CDRs and/or VL CDRs depicted in **Tables 1-2** under stringent conditions (*e.g.*, hybridization to filter-bound DNA in 6X SSC at about 45 °C followed by one or more washes in 0.2X SSC/0.1% SDS at about 50-65 °C), under highly stringent conditions (*e.g.*, hybridization to filter-bound nucleic acid in 6X SSC at about 45 °C followed by one or more washes in 0.1X SSC/0.2% SDS at about 68 °C), or under other stringent

hybridization conditions which are known to those of skill in the art (*see, e.g., Ausubel et al., supra*).

[0376] In a further embodiment, monoclonal antibodies or antibody fragments of pharmaceutical formulations can be isolated from antibody phage libraries generated using the techniques described in, for example, Antibody Phage Display: Methods and Protocols (O'Brien and Aitken eds., 2002). In principle, synthetic antibody clones are selected by screening phage libraries containing phages that display various fragments of antibody variable region (Fv) fused to phage coat protein. Such phage libraries are screened against the desired antigen. Clones expressing Fv fragments capable of binding to the desired antigen are adsorbed to the antigen and thus separated from the non-binding clones in the library. The binding clones are then eluted from the antigen and can be further enriched by additional cycles of antigen adsorption/elution.

[0377] Variable domains can be displayed functionally on phage, either as single-chain Fv (scFv) fragments, in which VH and VL are covalently linked through a short, flexible peptide, or as Fab fragments, in which they are each fused to a constant domain and interact non-covalently, as described, for example, in Winter *et al.*, 1994, *Ann. Rev. Immunol.* 12:433-55.

[0378] Repertoires of VH and VL genes can be separately cloned by PCR and recombined randomly in phage libraries, which can then be searched for antigen-binding clones as described in Winter *et al., supra*. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned to provide a single source of human antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths *et al.*, 1993, *EMBO J* 12:725-34. Finally, naive libraries can also be made synthetically by cloning the unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement *in vitro* as described, for example, by Hoogenboom and Winter, 1992, *J. Mol. Biol.* 227:381-88.

[0379] Screening of the libraries can be accomplished by various techniques known in the art. For example, PD-1 (*e.g., a PD-1 polypeptide, fragment, or epitope*) can be used to coat the wells of adsorption plates, expressed on host cells affixed to adsorption plates or used in cell sorting, conjugated to biotin for capture with streptavidin-coated beads, or used in any other method for panning display libraries. The selection of antibodies with slow dissociation kinetics (*e.g., good binding affinities*) can be promoted by use of long washes and monovalent phage

display as described in Bass *et al.*, 1990, Proteins 8:309-14 and WO 92/09690, and by use of a low coating density of antigen as described in Marks *et al.*, 1992, Biotechnol. 10:779-83.

[0380] Anti-PD-1 antibodies of pharmaceutical formulations can be obtained by designing a suitable antigen screening procedure to select for the phage clone of interest followed by construction of a full length anti-PD-1 antibody clone using VH and/or VL sequences (*e.g.*, the Fv sequences), or various CDR sequences from VH and VL sequences, from the phage clone of interest and suitable constant region (*e.g.*, Fc) sequences described in Kabat *et al.*, *supra*.

[0381] In another embodiment, an anti-PD-1 antibody of pharmaceutical formulations is generated by using methods as described in Bowers *et al.*, 2011, Proc Natl Acad Sci USA. 108:20455-60, *e.g.*, the SHM-XHL™ platform (AnaptysBio, San Diego, CA). Briefly, in this approach, a fully human library of IgGs is constructed in a mammalian cell line (*e.g.*, HEK293) as a starting library. Mammalian cells displaying immunoglobulin that binds to a target peptide or epitope are selected (*e.g.*, by FACS sorting), then activation-induced cytidine deaminase (AID)-triggered somatic hypermutation is reproduced *in vitro* to expand diversity of the initially selected pool of antibodies. After several rounds of affinity maturation by coupling mammalian cell surface display with *in vitro* somatic hypermutation, high affinity, high specificity anti-PD-1 antibodies are generated. Further methods that can be used to generate antibody libraries and/or antibody affinity maturation are disclosed, *e.g.*, in U.S. Patent Nos. 8,685,897 and 8,603,930, and U.S. Publ. Nos. 2014/0170705, 2014/0094392, 2012/0028301, 2011/0183855, and 2009/0075378, each of which are incorporated herein by reference.

5.3.1.3 Antibody Fragments

[0382] The present disclosure provides pharmaceutical formulations comprising antibodies and antibody fragments that bind to PD-1. In certain circumstances, there are advantages of using antibody fragments, rather than whole antibodies. The smaller size of the fragments allows for rapid clearance, and may lead to improved access to cells, tissues, or organs. For a review of certain antibody fragments, see Hudson *et al.*, 2003, Nature Med. 9:129-34.

[0383] Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (*see, e.g.*, Morimoto *et al.*, 1992, J. Biochem. Biophys. Methods 24:107-17; and Brennan *et al.*, 1985, Science 229:81-83). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv, and scFv antibody fragments can all be expressed in and secreted from *E. coli*

or yeast cells, thus allowing the facile production of large amounts of these fragments. Antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')₂ fragments (Carter *et al.*, 1992, Bio/Technology 10:163-67). According to another approach, F(ab')₂ fragments can be isolated directly from recombinant host cell culture. Fab and F(ab')₂ fragment with increased *in vivo* half-life comprising salvage receptor binding epitope residues are described in, for example, U.S. Pat. No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In certain embodiments, an antibody is a single chain Fv fragment (scFv) (*see, e.g.*, WO 93/16185; U.S. Pat. Nos. 5,571,894 and 5,587,458). Fv and scFv have intact combining sites that are devoid of constant regions; thus, they may be suitable for reduced nonspecific binding during *in vivo* use. scFv fusion proteins may be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an scFv (*See, e.g.*, Borrebaeck ed., *supra*). The antibody fragment may also be a "linear antibody," for example, as described in the references cited above. Such linear antibodies may be monospecific or multi-specific, such as bispecific.

[0384] Smaller antibody-derived binding structures are the separate variable domains (V domains) also termed single variable domain antibodies (sdAbs). Certain types of organisms, the camelids and cartilaginous fish, possess high affinity single V-like domains mounted on an Fc equivalent domain structure as part of their immune system. (Woolven *et al.*, 1999, Immunogenetics 50: 98-101; and Streltsov *et al.*, 2004, Proc Natl Acad Sci USA. 101:12444-49). The V-like domains (called VhH in camelids and V-NAR in sharks) typically display long surface loops, which allow penetration of cavities of target antigens. They also stabilize isolated VH domains by masking hydrophobic surface patches.

[0385] These VhH and V-NAR domains have been used to engineer sdAbs. Human V domain variants have been designed using selection from phage libraries and other approaches that have resulted in stable, high binding VL- and VH-derived domains.

[0386] Antibodies of a pharmaceutical formulation provided herein include, but are not limited to, immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, for example, molecules that contain an antigen binding site that bind to a PD-1 epitope. The immunoglobulin molecules provided herein can be of any class (*e.g.*, IgG, IgE,

IgM, IgD, and IgA) or any subclass (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2) of immunoglobulin molecule.

[0387] Variants and derivatives of antibodies of pharmaceutical formulations include antibody functional fragments that retain the ability to bind to a PD-1 epitope. Exemplary functional fragments include Fab fragments (*e.g.*, an antibody fragment that contains the antigen-binding domain and comprises a light chain and part of a heavy chain bridged by a disulfide bond); Fab' (*e.g.*, an antibody fragment containing a single antigen-binding domain comprising an Fab and an additional portion of the heavy chain through the hinge region); F(ab')₂ (*e.g.*, two Fab' molecules joined by interchain disulfide bonds in the hinge regions of the heavy chains; the Fab' molecules may be directed toward the same or different epitopes); a bispecific Fab (*e.g.*, a Fab molecule having two antigen binding domains, each of which may be directed to a different epitope); a single chain comprising a variable region, also known as, scFv (*e.g.*, the variable, antigen-binding determinative region of a single light and heavy chain of an antibody linked together by a chain of 10-25 amino acids); a disulfide-linked Fv, or dsFv (*e.g.*, the variable, antigen-binding determinative region of a single light and heavy chain of an antibody linked together by a disulfide bond); a camelized VH (*e.g.*, the variable, antigen-binding determinative region of a single heavy chain of an antibody in which some amino acids at the VH interface are those found in the heavy chain of naturally occurring camel antibodies); a bispecific scFv (*e.g.*, an scFv or a dsFv molecule having two antigen-binding domains, each of which may be directed to a different epitope); a diabody (*e.g.*, a dimerized scFv formed when the VH domain of a first scFv assembles with the VL domain of a second scFv and the VL domain of the first scFv assembles with the VH domain of the second scFv; the two antigen-binding regions of the diabody may be directed towards the same or different epitopes); and a triabody (*e.g.*, a trimerized scFv, formed in a manner similar to a diabody, but in which three antigen-binding domains are created in a single complex; the three antigen-binding domains may be directed towards the same or different epitopes).

5.3.1.4 Humanized Antibodies

[0388] In some embodiments, antibodies of a pharmaceutical formulation provided herein can be humanized antibodies that bind PD-1, including human and/or cynomolgus PD-1. For example, humanized antibodies of pharmaceutical formulations of the present disclosure may comprise one or more CDRs as shown in **Tables 1-2**. Various methods for humanizing non-

human antibodies are known in the art. For example, a humanized antibody can have one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues are often referred to as “import” residues, which are typically taken from an “import” variable domain. Humanization may be performed, for example, following the method of Jones *et al.*, 1986, Nature 321:522-25; Riechmann *et al.*, 1988, Nature 332:323-27; and Verhoeyen *et al.*, 1988, Science 239:1534-36), by substituting hypervariable region sequences for the corresponding sequences of a human antibody.

[0389] In some cases, the humanized antibodies of pharmaceutical formulations are constructed by CDR grafting, in which the amino acid sequences of the six CDRs of the parent non-human antibody (*e.g.*, rodent) are grafted onto a human antibody framework. For example, Padlan *et al.* determined that only about one third of the residues in the CDRs actually contact the antigen, and termed these the “specificity determining residues,” or SDRs (Padlan *et al.*, 1995, FASEB J. 9:133-39). In the technique of SDR grafting, only the SDR residues are grafted onto the human antibody framework (*see, e.g.*, Kashmiri *et al.*, 2005, Methods 36:25-34).

[0390] The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies can be important to reduce antigenicity. For example, according to the so-called “best-fit” method, the sequence of the variable domain of a non-human (*e.g.*, rodent) antibody is screened against the entire library of known human variable-domain sequences. The human sequence that is closest to that of the rodent may be selected as the human framework for the humanized antibody (Sims *et al.*, 1993, J. Immunol. 151:2296-308; and Chothia *et al.*, 1987, J. Mol. Biol. 196:901-17). Another method uses a particular framework derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter *et al.*, 1992, Proc. Natl. Acad. Sci. USA 89:4285-89; and Presta *et al.*, 1993, J. Immunol. 151:2623-32). In some cases, the framework is derived from the consensus sequences of the most abundant human subclasses, V_L6 subgroup I (V_L6I) and V_H subgroup III (V_HIII). In another method, human germline genes are used as the source of the framework regions.

[0391] In an alternative paradigm based on comparison of CDRs, called superhumanization, FR homology is irrelevant. The method consists of comparison of the non-human sequence with the functional human germline gene repertoire. Those genes encoding the same or closely related canonical structures to the murine sequences are then selected. Next, within the genes sharing the

canonical structures with the non-human antibody, those with highest homology within the CDRs are chosen as FR donors. Finally, the non-human CDRs are grafted onto these FRs (*see, e.g., Tan et al., 2002, J. Immunol. 169:1119-25*).

[0392] It is further generally desirable that antibodies of pharmaceutical formulations be humanized with retention of their affinity for the antigen and other favorable biological properties. To achieve this goal, according to one method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. These include, for example, WAM (Whitelegg and Rees, 2000, Protein Eng. 13:819-24), Modeller (Sali and Blundell, 1993, J. Mol. Biol. 234:779-815), and Swiss PDB Viewer (Guex and Peitsch, 1997, Electrophoresis 18:2714-23). Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, *e.g.,* the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

[0393] Another method for antibody humanization is based on a metric of antibody humanness termed Human String Content (HSC). This method compares the mouse sequence with the repertoire of human germline genes, and the differences are scored as HSC. The target sequence is then humanized by maximizing its HSC rather than using a global identity measure to generate multiple diverse humanized variants (Lazar *et al., 2007, Mol. Immunol. 44:1986-98*).

[0394] In addition to the methods described above, empirical methods may be used to generate and select humanized antibodies. These methods include those that are based upon the generation of large libraries of humanized variants and selection of the best clones using enrichment technologies or high throughput screening techniques. Antibody variants may be isolated from phage, ribosome, and yeast display libraries as well as by bacterial colony screening (*see, e.g., Hoogenboom, 2005, Nat. Biotechnol. 23:1105-16; Dufner et al., 2006,*

Trends Biotechnol. 24:523-29; Feldhaus *et al.*, 2003, Nat. Biotechnol. 21:163-70; and Schlapschy *et al.*, 2004, Protein Eng. Des. Sel. 17:847-60).

[0395] In the FR library approach, a collection of residue variants are introduced at specific positions in the FR followed by screening of the library to select the FR that best supports the grafted CDR. The residues to be substituted may include some or all of the “Vernier” residues identified as potentially contributing to CDR structure (*see, e.g.*, Foote and Winter, 1992, J. Mol. Biol. 224:487-99), or from the more limited set of target residues identified by Baca *et al.* (1997, J. Biol. Chem. 272:10678-84).

[0396] In FR shuffling, whole FRs are combined with the non-human CDRs instead of creating combinatorial libraries of selected residue variants (*see, e.g.*, Dall’Acqua *et al.*, 2005, Methods 36:43-60). The libraries may be screened for binding in a two-step process, first humanizing VL, followed by VH. Alternatively, a one-step FR shuffling process may be used. Such a process has been shown to be more efficient than the two-step screening, as the resulting antibodies exhibited improved biochemical and physicochemical properties including enhanced expression, increased affinity, and thermal stability (*see, e.g.*, Damschroder *et al.*, 2007, Mol. Immunol. 44:3049-60).

[0397] The “humaneering” method is based on experimental identification of essential minimum specificity determinants (MSDs) and is based on sequential replacement of non-human fragments into libraries of human FRs and assessment of binding. It begins with regions of the CDR3 of non-human VH and VL chains and progressively replaces other regions of the non-human antibody into the human FRs, including the CDR1 and CDR2 of both VH and VL. This methodology typically results in epitope retention and identification of antibodies from multiple subclasses with distinct human V-segment CDRs. Humaneering allows for isolation of antibodies that are 91-96% homologous to human germline gene antibodies (*see, e.g.*, Alfenito, Cambridge Healthtech Institute’s Third Annual PEGS, The Protein Engineering Summit, 2007).

[0398] The “human engineering” method involves altering a non-human antibody or antibody fragment, such as a mouse or chimeric antibody or antibody fragment, by making specific changes to the amino acid sequence of the antibody so as to produce a modified antibody with reduced immunogenicity in a human that nonetheless retains the desirable binding properties of the original non-human antibodies. Generally, the technique involves classifying amino acid residues of a non-human (*e.g.*, mouse) antibody as “low risk,” “moderate risk,” or

“high risk” residues. The classification is performed using a global risk/reward calculation that evaluates the predicted benefits of making particular substitution (*e.g.*, for immunogenicity in humans) against the risk that the substitution will affect the resulting antibody’s folding. The particular human amino acid residue to be substituted at a given position (*e.g.*, low or moderate risk) of a non-human (*e.g.*, mouse) antibody sequence can be selected by aligning an amino acid sequence from the non-human antibody’s variable regions with the corresponding region of a specific or consensus human antibody sequence. The amino acid residues at low or moderate risk positions in the non-human sequence can be substituted for the corresponding residues in the human antibody sequence according to the alignment. Techniques for making human engineered proteins are described in greater detail in Studnicka *et al.*, 1994, Protein Engineering 7:805-14; U.S. Pat. Nos. 5,766,886; 5,770,196; 5,821,123; and 5,869,619; and PCT Publication WO 93/11794.

5.3.1.5 Human Antibodies

[0399] Human anti-PD-1 antibodies of pharmaceutical formulations can be constructed by combining Fv clone variable domain sequence(s) selected from human-derived phage display libraries with known human constant domain sequences(s). Alternatively, human monoclonal anti-PD-1 antibodies of pharmaceutical formulations of the present disclosure can be made by the hybridoma method. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described, for example, by Kozbor, 1984, J. Immunol. 133:3001-05; Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications 51-63 (1987); and Boerner *et al.*, 1991, J. Immunol. 147:86-95.

[0400] It is also possible to produce transgenic animals (*e.g.*, mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. Transgenic mice that express human antibody repertoires have been used to generate high-affinity human sequence monoclonal antibodies against a wide variety of potential drug targets (*see, e.g.*, Jakobovits, A., 1995, Curr. Opin. Biotechnol. 6(5):561-66; Brüggemann and Taussing, 1997, Curr. Opin. Biotechnol. 8(4):455-58; U.S. Pat. Nos. 6,075,181 and 6,150,584; and Lonberg *et al.*, 2005, Nature Biotechnol. 23:1117-25).

[0401] Alternatively, the human antibody may be prepared via immortalization of human B lymphocytes producing an antibody directed against a target antigen (*e.g.*, such B lymphocytes may be recovered from an individual or may have been immunized *in vitro*) (*see, e.g.*, Cole *et*

al., Monoclonal Antibodies and Cancer Therapy (1985); Boerner *et al.*, 1991, J. Immunol. 147(1):86-95; and U.S. Pat. No. 5,750,373).

[0402] Gene shuffling can also be used to derive human antibodies from non-human, for example, rodent, antibodies, where the human antibody has similar affinities and specificities to the starting non-human antibody. According to this method, which is also called “epitope imprinting” or “guided selection,” either the heavy or light chain variable region of a non-human antibody fragment obtained by phage display techniques as described herein is replaced with a repertoire of human V domain genes, creating a population of non-human chain/human chain scFv or Fab chimeras. Selection with antigen results in isolation of a non-human chain/human chain chimeric scFv or Fab wherein the human chain restores the antigen binding site destroyed upon removal of the corresponding non-human chain in the primary phage display clone (*e.g.*, the epitope guides (imprints) the choice of the human chain partner). When the process is repeated in order to replace the remaining non-human chain, a human antibody is obtained (*see, e.g.*, PCT WO 93/06213; and Osbourn *et al.*, 2005, Methods 36:61-68). Unlike traditional humanization of non-human antibodies by CDR grafting, this technique provides completely human antibodies, which have no FR or CDR residues of non-human origin. Examples of guided selection to humanize mouse antibodies towards cell surface antigens include the folate-binding protein present on ovarian cancer cells (*see, e.g.*, Figini *et al.*, 1998, Cancer Res. 58:991-96) and CD147, which is highly expressed on hepatocellular carcinoma (*see, e.g.*, Bao *et al.*, 2005, Cancer Biol. Ther. 4:1374-80).

[0403] A potential disadvantage of the guided selection approach is that shuffling of one antibody chain while keeping the other constant could result in epitope drift. In order to maintain the epitope recognized by the non-human antibody, CDR retention can be applied (*see, e.g.*, Klimka *et al.*, 2000, Br. J. Cancer. 83:252-60; and Beiboer *et al.*, 2000, J. Mol. Biol. 296:833-49). In this method, the non-human VH CDR3 is commonly retained, as this CDR may be at the center of the antigen-binding site and may be the most important region of the antibody for antigen recognition. In some instances, however, VH CDR3 and VL CDR3, as well as VH CDR2, VL CDR2, and VL CDR1 of the non-human antibody may be retained.

5.3.1.6 Bispecific Antibodies

[0404] Also provided herein are pharmaceutical formulations comprising bispecific antibodies that are monoclonal antibodies that have binding specificities for at least two different

antigens. In certain embodiments, bispecific antibodies are human or humanized antibodies. In certain embodiments, one of the binding specificities is for PD-1 and the other is for any other antigen. In some embodiments, one of the binding specificities is for PD-1, and the other is for another surface antigen expressed on cells expressing PD-1. In certain embodiments, bispecific antibodies may bind to two different epitopes of PD-1. Bispecific antibodies can be prepared as full length antibodies or antibody fragments (*e.g.*, F(ab')₂ bispecific antibodies).

[0405] Methods for making bispecific antibodies are known in the art, such as, by co-expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (*see, e.g.*, Milstein and Cuello, 1983, Nature 305:537-40). For further details of generating bispecific antibodies, *see, for example*, Bispecific Antibodies (Kontermann ed., 2011).

5.3.1.7 Multivalent Antibodies

[0406] A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind. The antibodies of pharmaceutical formulations of the present disclosure can be multivalent antibodies (which are other than of the IgM class) with three or more antigen binding sites (*e.g.*, tetravalent antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or more antigen binding sites. In certain embodiments, the dimerization domain comprises (or consists of) an Fc region or a hinge region. In this scenario, the antibody will comprise an Fc region and three or more antigen binding sites amino-terminal to the Fc region. In certain embodiments, a multivalent antibody comprises (or consists of) three to about eight antigen binding sites. In one such embodiment, a multivalent antibody comprises (or consists of) four antigen binding sites. The multivalent antibody comprises at least one polypeptide chain (*e.g.*, two polypeptide chains), wherein the polypeptide chain(s) comprise two or more variable domains. For instance, the polypeptide chain(s) may comprise VD1-(X1)_n-VD2-(X2)_n-Fc, wherein VD1 is a first variable domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or polypeptide, and n is 0 or 1. For instance, the polypeptide chain(s) may comprise: VH-CH1-flexible linker-VH-CH1-Fc region chain; or VH-CH1-VH-CH1-Fc region chain. The multivalent antibody herein may further comprise at least two (*e.g.*, four) light chain variable domain polypeptides. The

multivalent antibody herein may, for instance, comprise from about two to about eight light chain variable domain polypeptides. The light chain variable domain polypeptides contemplated here comprise a light chain variable domain and, optionally, further comprise a CL domain.

5.3.1.8 Fc Engineering

[0407] It may be desirable to modify an anti-PD-1 antibody of a pharmaceutical formulation provided herein by Fc engineering. In certain embodiments, the modification to the Fc region of the antibody results in the decrease or elimination of an effector function of the antibody. In certain embodiments, the effector function is ADCC, ADCP, and/or CDC. In some embodiments, the effector function is ADCC. In other embodiments, the effector function is ADCP. In other embodiments, the effector function is CDC. In one embodiment, the effector function is ADCC and ADCP. In one embodiment, the effector function is ADCC and CDC. In one embodiment, the effector function is ADCP and CDC. In one embodiment, the effector function is ADCC, ADCP and CDC. This may be achieved by introducing one or more amino acid substitutions in an Fc region of the antibody. For example, substitutions into human IgG1 using IgG2 residues at positions 233-236 and IgG4 residues at positions 327, 330, and 331 were shown to greatly reduce ADCC and CDC (*see, e.g., Armour et al., 1999, Eur. J. Immunol. 29(8):2613-24; and Shields et al., 2001, J. Biol. Chem. 276(9): 6591-604*). Other Fc variants are provided elsewhere herein.

[0408] To increase the serum half life of the antibody of pharmaceutical formulations, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment), for example, as described in U.S. Pat. No. 5,739,277. Term “salvage receptor binding epitope” refers to an epitope of the Fc region of an IgG molecule (*e.g., IgG1, IgG2, IgG3, or IgG4*) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

5.3.1.9 Alternative Binding Agents

[0409] The present disclosure encompasses pharmaceutical formulations comprising non-immunoglobulin binding agents that specifically bind to the same epitope as an anti-PD-1 antibody disclosed herein. In some embodiments, a non-immunoglobulin binding agent is identified as an agent that displaces or is displaced by an anti-PD-1 antibody of the present disclosure in a competitive binding assay. These alternative binding agents may include, for example, any of the engineered protein scaffolds known in the art. Such scaffolds may comprise

one or more CDRs as shown in **Tables 1-2**. Such scaffolds include, for example, anticalins, which are based upon the lipocalin scaffold, a protein structure characterized by a rigid beta-barrel that supports four hypervariable loops which form the ligand binding site. Novel binding specificities may be engineered by targeted random mutagenesis in the loop regions, in combination with functional display and guided selection (*see, e.g.*, Skerra, 2008, FEBS J. 275:2677-83). Other suitable scaffolds may include, for example, adnectins, or monobodies, based on the tenth extracellular domain of human fibronectin III (*see, e.g.*, Koide and Koide, 2007, Methods Mol. Biol. 352: 95-109); affibodies, based on the Z domain of staphylococcal protein A (*see, e.g.*, Nygren et al., 2008, FEBS J. 275:2668-76); DARPins, based on ankyrin repeat proteins (*see, e.g.*, Stumpp *et al.*, 2008, Drug. Discov. Today 13:695-701); fynomers, based on the SH3 domain of the human Fyn protein kinase (*see, e.g.*, Grabulovski *et al.*, 2007, J. Biol. Chem. 282:3196-204); affitins, based on Sac7d from *Sulfolobus acidolarius* (*see, e.g.*, Krehenbrink *et al.*, 2008, J. Mol. Biol. 383:1058-68); affilins, based on human γ -B-crystallin (*see, e.g.*, Ebersbach *et al.*, 2007, J. Mol. Biol. 372:172-85); avimers, based on the A domain of membrane receptor proteins (*see, e.g.*, Silverman *et al.*, 2005, Biotechnol. 23:1556-61); cysteine-rich knottin peptides (*see, e.g.*, Kolmar, 2008, FEBS J. 275:2684-90); and engineered Kunitz-type inhibitors (*see, e.g.*, Nixon and Wood, 2006, Curr. Opin. Drug. Discov. Dev. 9:261-68). For a review, see, for example, Gebauer and Skerra, 2009, Curr. Opin. Chem. Biol. 13:245-55.

5.3.2 Antibody variants

[0410] In some embodiments, amino acid sequence modification(s) of the antibodies that bind to PD-1 or described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody, including but not limited to specificity, thermostability, expression level, effector functions, glycosylation, reduced immunogenicity, or solubility. Thus, in addition to the anti-PD-1 antibodies of a pharmaceutical formulation provided herein, it is contemplated that anti-PD-1 antibody variants can be prepared. For example, anti-PD-1 antibody variants can be prepared by introducing appropriate nucleotide changes into the encoding DNA, and/or by synthesis of the desired antibody or polypeptide. Those skilled in the art who appreciate that amino acid changes may alter post-translational processes of the anti-PD-1 antibody, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

[0411] In some embodiments, antibodies of a pharmaceutical formulation provided herein are chemically modified, for example, by the covalent attachment of any type of molecule to the antibody. The antibody derivatives may include antibodies that have been chemically modified, for example, by increase or decrease of glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, chemical cleavage, proteolytic cleavage, linkage to a cellular ligand or other protein, *etc.* Additionally, the antibody may contain one or more non-classical amino acids.

[0412] Variations may be a substitution, deletion, or insertion of one or more codons encoding the antibody or polypeptide that results in a change in the amino acid sequence as compared with the native sequence antibody or polypeptide. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, *e.g.*, conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. In certain embodiments, the substitution, deletion, or insertion includes fewer than 25 amino acid substitutions, fewer than 20 amino acid substitutions, fewer than 15 amino acid substitutions, fewer than 10 amino acid substitutions, fewer than 5 amino acid substitutions, fewer than 4 amino acid substitutions, fewer than 3 amino acid substitutions, or fewer than 2 amino acid substitutions relative to the original molecule. In a specific embodiment, the substitution is a conservative amino acid substitution made at one or more predicted non-essential amino acid residues. The variation allowed may be determined by systematically making insertions, deletions, or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

[0413] Amino acid sequence insertions 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. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (*e.g.*, for antibody-directed enzyme prodrug therapy) or a polypeptide which increases the serum half-life of the antibody.

[0414] Substantial modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining

(a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Alternatively, conservative (*e.g.*, within an amino acid group with similar properties and/or side chains) substitutions may be made, so as to maintain or not significantly change the properties. Amino acids may be grouped according to similarities in the properties of their side chains (*see, e.g.*, Lehninger, Biochemistry 73-75 (2d ed. 1975)):

(1) non-polar: Ala (A), Val (V), Leu (L), Ile (I), Pro (P), Phe (F), Trp (W), Met (M);
 (2) uncharged polar: Gly (G), Ser (S), Thr (T), Cys (C), Tyr (Y), Asn (N), Gln (Q); (3) acidic: Asp (D), Glu (E); and (4) basic: Lys (K), Arg (R), His(H).

[0415] Alternatively, naturally occurring residues may be divided into groups based on common side-chain properties: (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

[0416] Non-conservative substitutions entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, into the remaining (non-conserved) sites. Accordingly, in one embodiment, an antibody or fragment thereof that binds to a PD-1 epitope comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of a murine monoclonal antibody of a pharmaceutical formulation provided herein. In one embodiment, an antibody or fragment thereof that binds to a PD-1 epitope comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to an amino acid sequence depicted in **Tables 1-6**. In yet another embodiment, an antibody or fragment thereof that binds to a PD-1 epitope comprises a VH CDR and/or a VL CDR amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to a VH CDR amino acid sequence depicted in **Table 2** and/or a VL CDR amino acid sequence depicted in **Table 1**. The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis.

Site-directed mutagenesis (*see, e.g.*, Carter, 1986, Biochem J. 237:1-7; and Zoller *et al.*, 1982, Nucl. Acids Res. 10:6487-500), cassette mutagenesis (*see, e.g.*, Wells *et al.*, 1985, Gene 34:315-23), or other known techniques can be performed on the cloned DNA to produce the anti-PD-1 antibody variant DNA.

[0417] Any cysteine residue not involved in maintaining the proper conformation of the anti-PD-1 antibody also may be substituted, for example, with another amino acid, such as alanine or serine, to improve the oxidative stability of the molecule and to prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the anti-PD-1 antibody to improve its stability (*e.g.*, where the antibody is an antibody fragment such as an Fv fragment).

[0418] In some embodiments, an anti-PD-1 antibody molecule of pharmaceutical formulations of the present disclosure is a “de-immunized” antibody. A “de-immunized” anti-PD-1 antibody is an antibody derived from a humanized or chimeric anti-PD-1 antibody, which has one or more alterations in its amino acid sequence resulting in a reduction of immunogenicity of the antibody, compared to the respective original non-de-immunized antibody. One of the procedures for generating such antibody mutants involves the identification and removal of T cell epitopes of the antibody molecule. In a first step, the immunogenicity of the antibody molecule can be determined by several methods, for example, by *in vitro* determination of T cell epitopes or *in silico* prediction of such epitopes, as known in the art. Once the critical residues for T cell epitope function have been identified, mutations can be made to remove immunogenicity and retain antibody activity. For review, see, for example, Jones *et al.*, 2009, Methods in Molecular Biology 525:405-23.

5.3.2.1 *In vitro* Affinity Maturation

[0419] In some embodiments, antibody variants of pharmaceutical formulations provided herein having an improved property such as affinity, stability, or expression level as compared to a parent antibody may be prepared by *in vitro* affinity maturation. Like the natural prototype, *in vitro* affinity maturation is based on the principles of mutation and selection. Libraries of antibodies are displayed as Fab, scFv, or V domain fragments either on the surface of an organism (*e.g.*, phage, bacteria, yeast, or mammalian cell) or in association (*e.g.*, covalently or non-covalently) with their encoding mRNA or DNA. Affinity selection of the displayed antibodies allows isolation of organisms or complexes carrying the genetic information encoding the antibodies. Two or three rounds of mutation and selection using display methods such as

phage display usually results in antibody fragments with affinities in the low nanomolar range. Affinity matured antibodies can have nanomolar or even picomolar affinities for the target antigen.

[0420] Phage display is a widespread method for display and selection of antibodies. The antibodies are displayed on the surface of Fd or M13 bacteriophages as fusions to the bacteriophage coat protein. Selection involves exposure to antigen to allow phage-displayed antibodies to bind their targets, a process referred to as “panning.” Phage bound to antigen are recovered and used to infect bacteria to produce phage for further rounds of selection. For review, see, for example, Hoogenboom, 2002, *Methods. Mol. Biol.* 178:1-37; and Bradbury and Marks, 2004, *J. Immunol. Methods* 290:29-49.

[0421] In a yeast display system (*see, e.g.,* Boder *et al.*, 1997, *Nat. Biotech.* 15:553–57; and Chao *et al.*, 2006, *Nat. Protocols* 1:755-68), the antibody may be displayed as single-chain variable fusions (scFv) in which the heavy and light chains are connected by a flexible linker. The scFv is fused to the adhesion subunit of the yeast agglutinin protein Aga2p, which attaches to the yeast cell wall through disulfide bonds to Aga1p. Display of a protein via Aga2p projects the protein away from the cell surface, minimizing potential interactions with other molecules on the yeast cell wall. Magnetic separation and flow cytometry are used to screen the library to select for antibodies with improved affinity or stability. Binding to a soluble antigen of interest is determined by labeling of yeast with biotinylated antigen and a secondary reagent such as streptavidin conjugated to a fluorophore. Variations in surface expression of the antibody can be measured through immunofluorescence labeling of either the hemagglutinin or c-Myc epitope tag flanking the scFv. Expression has been shown to correlate with the stability of the displayed protein, and thus antibodies can be selected for improved stability as well as affinity (*see, e.g.,* Shusta *et al.*, 1999, *J. Mol. Biol.* 292:949-56). An additional advantage of yeast display is that displayed proteins are folded in the endoplasmic reticulum of the eukaryotic yeast cells, taking advantage of endoplasmic reticulum chaperones and quality-control machinery. Once maturation is complete, antibody affinity can be conveniently “titrated” while displayed on the surface of the yeast, eliminating the need for expression and purification of each clone. A theoretical limitation of yeast surface display is the potentially smaller functional library size than that of other display methods; however, a recent approach uses the yeast cells’ mating system to create combinatorial

diversity estimated to be 10^{14} in size (see, *e.g.*, U.S. Pat. Publication 2003/0186374; and Blaise *et al.*, 2004, Gene 342:211–18).

[0422] In ribosome display, antibody-ribosome-mRNA (ARM) complexes are generated for selection in a cell-free system. The DNA library coding for a particular library of antibodies is genetically fused to a spacer sequence lacking a stop codon. This spacer sequence, when translated, is still attached to the peptidyl tRNA and occupies the ribosomal tunnel, and thus allows the protein of interest to protrude out of the ribosome and fold. The resulting complex of mRNA, ribosome, and protein can bind to surface-bound ligand, allowing simultaneous isolation of the antibody and its encoding mRNA through affinity capture with the ligand. The ribosome-bound mRNA is then reverse transcribed back into cDNA, which can then undergo mutagenesis and be used in the next round of selection (*see, e.g.*, Fukuda *et al.*, 2006, Nucleic Acids Res. 34:e127). In mRNA display, a covalent bond between antibody and mRNA is established using puromycin as an adaptor molecule (Wilson *et al.*, 2001, Proc. Natl. Acad. Sci. USA 98:3750-55).

[0423] As these methods are performed entirely *in vitro*, they provide two main advantages over other selection technologies. First, the diversity of the library is not limited by the transformation efficiency of bacterial cells, but only by the number of ribosomes and different mRNA molecules present in the test tube. Second, random mutations can be introduced easily after each selection round, for example, by non-proofreading polymerases, as no library must be transformed after any diversification step.

[0424] In a mammalian cell display system (*see, e.g.*, Bowers *et al.*, 2011, Proc Natl Acad Sci USA. 108:20455-60), a fully human library of IgGs is constructed based on germline sequence V-gene segments joined to prerecombined D(J) regions. Full-length V regions for heavy chain and light chain are assembled with human heavy chain and light chain constant regions and transfected into a mammalian cell line (*e.g.*, HEK293). The transfected library is expanded and subjected to several rounds of negative selection against streptavidin (SA)-coupled magnetic beads, followed by a round of positive selection against SA-coupled magnetic beads coated with biotinylated target protein, peptide fragment, or epitope. Positively selected cells are expanded, and then sorted by rounds of FACS to isolate single cell clones displaying antibodies that specifically bind to the target protein, peptide fragment, or epitope. Heavy and light chain pairs from these single cell clones are retransfected with AID for further maturation. Several

rounds of mammalian cell display, coupled with AID-triggered somatic hypermutation, generate high specificity, high affinity antibodies.

[0425] Diversity may also be introduced into the CDRs or the whole V genes of the antibody libraries in a targeted manner or via random introduction. The former approach includes sequentially targeting all the CDRs of an antibody via a high or low level of mutagenesis or targeting isolated hot spots of somatic hypermutations (*see, e.g.,* Ho *et al.*, 2005, J. Biol. Chem. 280:607-17) or residues suspected of affecting affinity on experimental basis or structural reasons. In a specific embodiment, somatic hypermutation is performed by AID-triggered somatic hypermutation, *e.g.,* using the SHM-XELTM platform (AnaptysBio, San Diego, CA). Random mutations can be introduced throughout the whole V gene using *E. coli* mutator strains, error-prone replication with DNA polymerases (*see, e.g.,* Hawkins *et al.*, 1992, J. Mol. Biol. 226:889-96), or RNA replicases. Diversity may also be introduced by replacement of regions that are naturally diverse via DNA shuffling or similar techniques (*see, e.g.,* Lu *et al.*, 2003, J. Biol. Chem. 278:43496-507; U.S. Pat. Nos. 5,565,332 and 6,989,250). Alternative techniques target hypervariable loops extending into framework-region residues (*see, e.g.,* Bond *et al.*, 2005, J. Mol. Biol. 348:699-709) employ loop deletions and insertions in CDRs or use hybridization-based diversification (*see, e.g.,* U.S. Pat. Publication No. 2004/0005709). Additional methods of generating diversity in CDRs are disclosed, for example, in U.S. Pat. No. 7,985,840. Further methods that can be used to generate antibody libraries and/or antibody affinity maturation are disclosed, *e.g.,* in U.S. Patent Nos. 8,685,897 and 8,603,930, and U.S. Publ. Nos. 2014/0170705, 2014/0094392, 2012/0028301, 2011/0183855, and 2009/0075378, each of which are incorporated herein by reference.

[0426] Screening of the libraries can be accomplished by various techniques known in the art. For example, PD-1 can be immobilized onto solid supports, columns, pins, or cellulose/poly(vinylidene fluoride) membranes/other filters, expressed on host cells affixed to adsorption plates or used in cell sorting, or conjugated to biotin for capture with streptavidin-coated beads or used in any other method for panning display libraries.

[0427] For review of *in vitro* affinity maturation methods, *see, e.g.,* Hoogenboom, 2005, Nature Biotechnology 23:1105-16; Quiroz and Sinclair, 2010, Revista Ingeneria Biomedica 4:39-51; and references therein.

5.3.2.2 Modifications of Anti-PD-1 Antibodies

[0428] Covalent modifications of anti-PD-1 antibodies of pharmaceutical formulations provided herein are included within the scope of the present disclosure. Covalent modifications include reacting targeted amino acid residues of an anti-PD-1 antibody with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the anti-PD-1 antibody. Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains (*see, e.g.,* Creighton, Proteins: Structure and Molecular Properties 79-86 (1983)), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

[0429] Other types of covalent modification of the anti-PD-1 antibody included within the scope of this present disclosure include altering the native glycosylation pattern of the antibody or polypeptide (*see, e.g.,* Beck *et al.*, 2008, Curr. Pharm. Biotechnol. 9:482-501; and Walsh, 2010, Drug Discov. Today 15:773-80), and linking the antibody to one of a variety of nonproteinaceous polymers, *e.g.,* polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth, for example, in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; or 4,179,337.

[0430] An anti-PD-1 antibody of pharmaceutical formulations of the present disclosure may also be modified to form chimeric molecules comprising an anti-PD-1 antibody fused to another, heterologous polypeptide or amino acid sequence, for example, an epitope tag (*see, e.g.,* Terpe, 2003, Appl. Microbiol. Biotechnol. 60:523-33) or the Fc region of an IgG molecule (*see, e.g.,* Aruffo, Antibody Fusion Proteins 221-42 (Chamow and Ashkenazi eds., 1999)).

[0431] Also provided herein are fusion proteins comprising an antibody of a pharmaceutical formulation provided herein that binds to a PD-1 antigen and a heterologous polypeptide. In some embodiments, the heterologous polypeptide to which the antibody is fused is useful for targeting the antibody to cells having cell surface-expressed PD-1.

[0432] Also provided herein are panels of antibodies that bind to a PD-1 antigen. In specific embodiments, the panels of antibodies have different association rates, different dissociation rates, different affinities for a PD-1 antigen, and/or different specificities for a PD-1 antigen. In some embodiments, the panels comprise or consist of about 10, about 25, about 50, about 75,

about 100, about 125, about 150, about 175, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1000 antibodies or more. Panels of antibodies can be used, for example, in 96-well or 384-well plates, for assays such as ELISAs.

5.3.3 Preparation of anti-PD-1 antibodies

[0433] Anti-PD-1 antibodies of pharmaceutical formulations provided herein may be produced by culturing cells transformed or transfected with a vector containing anti-PD-1 antibody-encoding nucleic acids. Polynucleotide sequences encoding polypeptide components of the antibody of the present disclosure can be obtained using standard recombinant techniques. Desired polynucleotide sequences may be isolated and sequenced from antibody producing cells such as hybridomas cells. Alternatively, polynucleotides can be synthesized using nucleotide synthesizer or PCR techniques. Once obtained, sequences encoding the polypeptides are inserted into a recombinant vector capable of replicating and expressing heterologous polynucleotides in host cells. Many vectors that are available and known in the art can be used for the purpose of the present disclosure. Selection of an appropriate vector will depend mainly on the size of the nucleic acids to be inserted into the vector and the particular host cell to be transformed with the vector. Host cells suitable for expressing antibodies of the present disclosure include prokaryotes such as Archaeobacteria and Eubacteria, including Gram-negative or Gram-positive organisms, eukaryotic microbes such as filamentous fungi or yeast, invertebrate cells such as insect or plant cells, and vertebrate cells such as mammalian host cell lines. Host cells are transformed with the above-described expression vectors and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. Antibodies produced by the host cells are purified using standard protein purification methods as known in the art.

[0434] Methods for antibody production including vector construction, expression, and purification are further described in Plückthun *et al.*, Antibody Engineering: Producing antibodies in Escherichia coli: From PCR to fermentation 203-52 (McCafferty *et al.* eds., 1996); Kwong and Rader, *E. coli Expression and Purification of Fab Antibody Fragments*, in Current Protocols in Protein Science (2009); Tachibana and Takekoshi, *Production of Antibody Fab Fragments in Escherichia coli*, in Antibody Expression and Production (Al-Rubeai ed., 2011); and Therapeutic Monoclonal Antibodies: From Bench to Clinic (An ed., 2009).

[0435] It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare anti-PD-1 antibodies. For instance, the appropriate amino acid sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques (*see, e.g.,* Stewart *et al.*, Solid-Phase Peptide Synthesis (1969); and Merrifield, 1963, J. Am. Chem. Soc. 85:2149-54). *In vitro* protein synthesis may be performed using manual techniques or by automation. Various portions of the anti-PD-1 antibody may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the desired anti-PD-1 antibody. Alternatively, antibodies may be purified from cells or bodily fluids, such as milk, of a transgenic animal engineered to express the antibody, as disclosed, for example, in U.S. Pat. Nos. 5,545,807 and 5,827,690.

5.3.4 Immunoconjugates

[0436] The present disclosure also provides pharmaceutical formulations that comprise conjugates comprising any one of the anti-PD-1 antibodies of the present disclosure covalently bound by a synthetic linker to one or more non-antibody agents.

[0437] In some embodiments, antibodies of a pharmaceutical formulation provided herein are conjugated or recombinantly fused, *e.g.*, to a diagnostic or detectable molecule. The conjugated or recombinantly fused antibodies can be useful, for example, for monitoring or prognosing the onset, development, progression, and/or severity of a PD-1-mediated disease.

[0438] Such diagnosis and detection can be accomplished, for example, by coupling the antibody to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidin/biotin or avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride, or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as, but not limited to, luciferase, luciferin, or aequorin; chemiluminescent material, such as, but not limited to, an acridinium based compound or a HALOTAG; radioactive materials, such as, but not limited to, iodine (^{131}I , ^{125}I , ^{123}I , and ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{115}In , ^{113}In , ^{112}In , and ^{111}In), technetium (^{99}Tc), thallium (^{201}Tl), gallium (^{68}Ga and ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru , ^{68}Ge , ^{57}Co ,

^{65}Zn , ^{85}Sr , ^{32}P , ^{153}Gd , ^{169}Yb , ^{51}Cr , ^{54}Mn , ^{75}Se , ^{113}Sn , or ^{117}Sn ; positron emitting metals using various positron emission tomographies; and non-radioactive paramagnetic metal ions.

[0439] Also provided herein are antibodies that are recombinantly fused or chemically conjugated (covalent or non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, for example, to a polypeptide of about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90, or about 100 amino acids) to generate fusion proteins, as well as uses thereof. In particular, provided herein are fusion proteins comprising an antigen-binding fragment of an antibody of a pharmaceutical formulation provided herein (*e.g.*, a Fab fragment, Fc fragment, Fv fragment, F(ab)₂ fragment, a VH domain, a VH CDR, a VL domain, or a VL CDR) and a heterologous protein, polypeptide, or peptide. In one embodiment, the heterologous protein, polypeptide, or peptide that the antibody is fused to is useful for targeting the antibody to a particular cell type, such as a cell that expresses PD-1. For example, an antibody that binds to a cell surface receptor expressed by a particular cell type may be fused or conjugated to a modified antibody of a pharmaceutical formulation provided herein.

[0440] Moreover, antibodies of a pharmaceutical formulation provided herein can be fused to marker or “tag” sequences, such as a peptide, to facilitate purification. In specific embodiments, the marker or tag amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (*see, e.g.*, QIAGEN, Inc.), among others, many of which are commercially available. For example, as described in Gentz *et al.*, 1989, Proc. Natl. Acad. Sci. USA 86:821-24, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin (“HA”) tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, 1984, Cell 37:767-78), and the “FLAG” tag.

[0441] Methods for fusing or conjugating moieties (including polypeptides) to antibodies are known (*see, e.g.*, Arnon *et al.*, *Monoclonal Antibodies for Immunotargeting of Drugs in Cancer Therapy*, in Monoclonal Antibodies and Cancer Therapy 243-56 (Reisfeld *et al.* eds., 1985); Hellstrom *et al.*, *Antibodies for Drug Delivery*, in Controlled Drug Delivery 623-53 (Robinson *et al.* eds., 2d ed. 1987); Thorpe, *Antibody Carriers of Cytotoxic Agents in Cancer Therapy: A Review*, in Monoclonal Antibodies: Biological and Clinical Applications 475-506 (Pinchera *et al.* eds., 1985); *Analysis, Results, and Future Prospective of the Therapeutic Use of Radiolabeled Antibody in Cancer Therapy*, in Monoclonal Antibodies for Cancer Detection and Therapy 303-

16 (Baldwin *et al.* eds., 1985); Thorpe *et al.*, 1982, Immunol. Rev. 62:119-58; U.S. Pat. Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,723,125; 5,783,181; 5,908,626; 5,844,095; and 5,112,946; EP 307,434; EP 367,166; EP 394,827; PCT publications WO 91/06570, WO 96/04388, WO 96/22024, WO 97/34631, and WO 99/04813; Ashkenazi *et al.*, 1991, Proc. Natl. Acad. Sci. USA, 88: 10535-39; Traunecker *et al.*, 1988, Nature, 331:84-86; Zheng *et al.*, 1995, J. Immunol. 154:5590-600; and Vil *et al.*, 1992, Proc. Natl. Acad. Sci. USA 89:11337-41).

[0442] Fusion proteins may be generated, for example, through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as “DNA shuffling”). DNA shuffling may be employed to alter the activities of anti-PD-1 antibodies as provided herein, including, for example, antibodies with higher affinities and lower dissociation rates (*see, e.g.*, U.S. Pat. Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458; Patten *et al.*, 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson *et al.*, 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308-13). Antibodies, or the encoded antibodies, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion, or other methods prior to recombination. A polynucleotide encoding an antibody of a pharmaceutical formulation provided herein may be recombined with one or more components, motifs, sections, parts, domains, fragments, *etc.* of one or more heterologous molecules.

[0443] An antibody of a pharmaceutical formulation provided herein can also be conjugated to a second antibody to form an antibody heteroconjugate as described, for example, in U.S. Pat. No. 4,676,980.

[0444] Antibodies that bind to PD-1 as provided herein may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride, or polypropylene.

[0445] The linker may be a “cleavable linker” facilitating release of the conjugated agent in the cell, but non-cleavable linkers are also contemplated herein. Linkers for use in the conjugates of the present disclosure include, without limitation, acid labile linkers (*e.g.*, hydrazone linkers), disulfide-containing linkers, peptidase-sensitive linkers (*e.g.*, peptide linkers comprising amino acids, for example, valine and/or citrulline such as citrulline-valine or phenylalanine-lysine),

photolabile linkers, dimethyl linkers (*see, e.g.*, Chari *et al.*, 1992, Cancer Res. 52:127-31; and U.S. Pat. No. 5,208,020), thioether linkers, or hydrophilic linkers designed to evade multidrug transporter-mediated resistance (*see, e.g.*, Kovtun *et al.*, 2010, Cancer Res. 70:2528-37).

[0446] Conjugates of the antibody and agent may be made using a variety of bifunctional protein coupling agents such as BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate). The present disclosure further contemplates that conjugates of antibodies and agents may be prepared using any suitable methods as disclosed in the art (*see, e.g.*, Bioconjugate Techniques (Hermanson ed., 2d ed. 2008)).

[0447] Conventional conjugation strategies for antibodies and agents have been based on random conjugation chemistries involving the ϵ -amino group of Lys residues or the thiol group of Cys residues, which results in heterogenous conjugates. Recently developed techniques allow site-specific conjugation to antibodies, resulting in homogeneous loading and avoiding conjugate subpopulations with altered antigen-binding or pharmacokinetics. These include engineering of “thiomabs” comprising cysteine substitutions at positions on the heavy and light chains that provide reactive thiol groups and do not disrupt immunoglobulin folding and assembly or alter antigen binding (*see, e.g.*, Junutula *et al.*, 2008, J. Immunol. Meth. 332: 41-52; and Junutula *et al.*, 2008, Nature Biotechnol. 26:925-32). In another method, selenocysteine is cotranslationally inserted into an antibody sequence by recoding the stop codon UGA from termination to selenocysteine insertion, allowing site specific covalent conjugation at the nucleophilic selenol group of selenocysteine in the presence of the other natural amino acids (*see, e.g.*, Hofer *et al.*, 2008, Proc. Natl. Acad. Sci. USA 105:12451-56; and Hofer *et al.*, 2009, Biochemistry 48(50):12047-57).

5.4 Methods of Using the Antibodies and Compositions

[0448] Provided herein are methods of (a) attenuating T cell activity, and/or (b) downregulating PD-1 expression in a subject. In certain embodiments, methods provided herein downregulate PD-1 expression in a cell of a subject. In certain embodiments, methods provided herein attenuate T cell activity in a subject. A non-limiting example of T cell activity is secretion of a cytokine. In certain embodiments, provided herein are methods of inhibiting secretion of a cytokine. In certain embodiments, the cytokine is selected from the group consisting of IL-1, IL-

2, IL-6, IL-12, IL-17, IL-22, IL-23, GM-CSF, IFN- γ , and TNF- α . In some embodiments, the cytokine is IL-2, IL-17, IFN- γ , or any combination thereof. In certain embodiments, the cytokine is IL-2. In other embodiments, the cytokine is IL-17. In yet other embodiments, the cytokine is IFN- γ . In certain embodiments, the cytokine is IL-2 and IL-17. In some embodiments, the cytokine is IL-2 and IFN- γ . In yet other embodiments, the cytokine is IL-17 and IFN- γ . In still other embodiments, the cytokine is IL-2, IL-17, and IFN- γ . In certain embodiments, the cytokine is IL-1. In other embodiments, the cytokine is IL-6. In yet other embodiments, the cytokine is IL-12. In still other embodiments, the cytokine is IL-22. In certain embodiments, the cytokine is IL-23. In some embodiments, the cytokine is GM-CSF. In other embodiments, the cytokine is TNF- α . Other combinations of two, three or more of the above-mentioned cytokines are also contemplated.

[0449] In one embodiment, provided herein is a method of inhibiting secretion of IL-2. In some embodiments, provided herein is a methods of inhibiting secretion of IL-17. In yet another embodiment, the method of attenuating T cell activity is a method of inhibiting secretion of IFN- γ .

[0450] In one aspect, provided herein is a method of attenuating activity of a T cell, comprising contacting the T cell with an effective amount of an antibody or antigen binding fragment thereof of a pharmaceutical formulation provided herein. In other embodiments, the maximal percent attenuation of T cell activity is at least about 10%. In another embodiment, the maximal percent attenuation of T cell activity is at least about 20%. In some embodiments, the maximal percent attenuation of T cell activity is at least about 30%. In one embodiment, the maximal percent attenuation of T cell activity is at least about 40%. In another embodiment, the maximal percent attenuation of T cell activity is at least about 45%. In other embodiments, the maximal percent attenuation of T cell activity is at least about 50%. In one embodiment, the maximal percent attenuation of T cell activity is at least about 55%. In another embodiment, the maximal percent attenuation of T cell activity is at least about 60%. In some embodiments, the maximal percent attenuation of T cell activity is at least about 65%. In other embodiments, the maximal percent attenuation of T cell activity is at least about 70%. In another embodiment, the maximal percent attenuation of T cell activity is at least about 75%. In one embodiment, the maximal percent attenuation of T cell activity is at least about 80%. In other embodiments, the maximal percent attenuation of T cell activity is at least about 85%. In another embodiment, the

maximal percent attenuation of T cell activity is at least about 90%. In one embodiment, the maximal percent attenuation of T cell activity is at least about 95%. In some embodiments, the maximal percent attenuation of T cell activity is at least about 100%.

[0451] In some embodiments, the attenuation of T cell activity is measured by modulation of production of a cytokine. In some embodiments, the attenuation of T cell activity is measured by modulation of secretion of a cytokine. In some embodiments, the attenuation of T cell activity is measured by modulation of expression of a cytokine. In some embodiments, the attenuation of T cell activity is measured by inhibition of production of a cytokine. In some embodiments, the attenuation of T cell activity is measured by inhibition of secretion of a cytokine. In some embodiments, the attenuation of T cell activity is measured by inhibition of expression of a cytokine. In certain embodiments, cytokine production (*e.g.*, cytokine protein production) is modulated. In certain embodiments, cytokine secretion (*e.g.*, cytokine protein secretion) is modulated. In other embodiments, cytokine expression (*e.g.*, cytokine gene expression) is modulated. In some embodiments, the modulation is a decrease, inhibition, or down-regulation of the cytokine. In other embodiments, the modulation is an increase or up-regulation of the cytokine. In certain embodiments, cytokine production (*e.g.*, cytokine protein production) is inhibited. In certain embodiments, cytokine secretion (*e.g.*, cytokine protein secretion) is inhibited. In other embodiments, cytokine expression (*e.g.*, cytokine gene expression) is inhibited. In certain embodiments, cytokine production from a cell is modulated. In certain embodiments, cytokine secretion from a cell is modulated. In certain embodiments, cytokine expression from a cell is modulated. In certain embodiments, cytokine production from a cell is inhibited. In certain embodiments, cytokine secretion from a cell is inhibited. In certain embodiments, cytokine expression from a cell is inhibited. In certain embodiments, the cell is a T cell. In some embodiments, the cell is not a T cell.

[0452] In some embodiments, the cytokine is selected from the group consisting of IL-2, IL-17, IFN- γ , or any combination thereof. In one embodiment, the cytokine is IL-2. In another embodiment, the cytokine is IL-17. In other embodiments, the cytokine is IFN- γ . In some embodiments, the cytokine is IL-2 and IL-17. In some embodiments, the cytokine is IL-2 and IFN- γ . In other embodiments, the cytokine is IL-17 and IFN- γ . In certain embodiments, the cytokine is IL-2, IL-17, and IFN- γ . In certain embodiments, the cytokine is selected from the group consisting of IL-1, IL-2, IL-6, IL-12, IL-17, IL-22, IL-23, GM-CSF, IFN- γ , and TNF- α . In

certain embodiments, the cytokine is IL-1. In other embodiments, the cytokine is IL-6. In yet other embodiments, the cytokine is IL-12. In still other embodiments, the cytokine is IL-22. In certain embodiments, the cytokine is IL-23. In some embodiments, the cytokine is GM-CSF. In other embodiments, the cytokine is TNF- α . Other combinations of two, three or more of the above-mentioned cytokines are also contemplated.

[0453] In some embodiments, the inhibition of cytokine production is concurrent with downregulation of PD-1 expression on the surface of the T cell. In some embodiments, the inhibition of cytokine production is preceded by downregulation of PD-1 expression on the surface of the T cell. In some embodiments, the inhibition of cytokine production precedes downregulation of PD-1 expression on the surface of the T cell. In one embodiment, the downregulation of PD-1 expression on the surface of the T cell occurs as early as 4 hours after contact with the antibody or antigen-binding fragment thereof.

[0454] In one aspect, provided herein is a method of modulating PD-1 activity and/or expression in a cell, comprising contacting the cell with an antibody that specifically binds to PD-1 as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof as described herein. In one embodiment, PD-1 activity is modulated. In another embodiment, PD-1 expression is modulated. In other embodiment, PD-1 activity and PD-1 expression are both modulated. In one embodiment, PD-1 signaling is activated. In another embodiment, PD-1 expression is inhibited. In certain embodiments, the antibody is a PD-1 agonist. In certain embodiments, the antibody of a pharmaceutical formulation provided herein specifically binds to human PD-1, and activates (*e.g.*, partially activates) or otherwise modulates at least one PD-1 activity. In a specific embodiment, the at least one PD-1 activity is inhibition of cytokine production. In certain embodiments, the antibody that specifically binds to PD-1 binds to an ECD of human PD-1, or an epitope of an ECD of human PD-1 thereof. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L1 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L2 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from both the PD-L1 and PD-L2 binding sites. In certain embodiments, binding of PD-L1 to PD-1 is not inhibited by the antibody. In other embodiments, binding of PD-L2 to PD-1 is not inhibited by

the antibody. In specific embodiments, neither binding of PD-L1 to PD-1 nor binding of PD-L2 to PD-1 is inhibited by the antibody.

[0455] In another aspect, provided herein is a method of downregulating PD-1 expression in a cell, comprising contacting the cell with an antibody that specifically binds to PD-1 as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is a PD-1 agonist provided herein. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L1 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L2 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from both the PD-L1 and PD-L2 binding sites. In certain embodiments, binding of PD-L1 to PD-1 is not inhibited by the antibody. In other embodiments, binding of PD-L2 to PD-1 is not inhibited by the antibody. In specific embodiments, neither binding of PD-L1 to PD-1 nor binding of PD-L2 to PD-1 is inhibited by the antibody.

[0456] In another aspect, provided herein is a method of attenuating T cell activity and down-regulating PD-1 expression in a cell, comprising contacting the cell with an antibody that specifically binds to PD-1 as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof as described herein. In certain embodiments, the attenuation of T cell activity is inhibition of cytokine production. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L1 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L2 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from both the PD-L1 and PD-L2 binding sites. In certain embodiments, binding of PD-L1 to PD-1 is not inhibited by the antibody. In other embodiments, binding of PD-L2 to PD-1 is not inhibited by the antibody. In specific embodiments, neither binding of PD-L1 to PD-1 nor binding of PD-L2 to PD-1 is inhibited by the antibody.

[0457] PD-1 activity can relate to any activity of PD-1 such as those known or described in the art. PD-1 activity and PD-1 signaling are used interchangeably herein. In certain aspects, PD-

1 activity is induced by PD-1 ligand (*e.g.*, PD-L1) binding to PD-1. Expression levels of PD-1 can be assessed by methods described herein or known to one of skill in the art (*e.g.*, Western blotting, ELISA, immunohistochemistry, or flow cytometry).

[0458] Also provided herein is a method of inhibiting cytokine production in a cell, comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen binding fragment thereof as described herein. In some embodiments, the antibody binds to an ECD of human PD-1. In some embodiments, the antibody binds to an epitope of an ECD of human PD-1. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L1 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L2 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from both the PD-L1 and PD-L2 binding sites. In certain embodiments, binding of PD-L1 to PD-1 is not inhibited by the antibody. In other embodiments, binding of PD-L2 to PD-1 is not inhibited by the antibody. In specific embodiments, neither binding of PD-L1 to PD-1 nor binding of PD-L2 to PD-1 is inhibited by the antibody.

[0459] Also provided herein are methods of activating PD-1 signaling in a cell, comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof as described herein. In some embodiments, the antibody binds to an ECD of human PD-1. In some embodiments, the antibody binds to an epitope of an ECD of human PD-1. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L1 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L2 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from both the PD-L1 and PD-L2 binding sites. In certain embodiments, binding of PD-L1 to PD-1 is not inhibited by the antibody. In other embodiments, binding of PD-L2 to PD-1 is not inhibited by the antibody. In specific embodiments, neither

binding of PD-L1 to PD-1 nor binding of PD-L2 to PD-1 is inhibited by the antibody. In one embodiment, PD-1 signaling is partially activated.

[0460] In one aspect, provided herein are methods of attenuating T cell activity, comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof as described herein. In some embodiments, the antibody binds to an ECD of human PD-1. In some embodiments, the antibody binds to an epitope of an ECD of human PD-1. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L1 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from the PD-L2 binding site. In certain embodiments, the antibody specifically binds to an epitope of an ECD of human PD-1 that is distinct from both the PD-L1 and PD-L2 binding sites. In certain embodiments, binding of PD-L1 to PD-1 is not inhibited by the antibody. In other embodiments, binding of PD-L2 to PD-1 is not inhibited by the antibody. In specific embodiments, neither binding of PD-L1 to PD-1 nor binding of PD-L2 to PD-1 is inhibited by the antibody. In some embodiments, T cell activity is attenuated by at least about 10%. In some embodiments, T cell activity is attenuated by at least about 15%. In some embodiments, T cell activity is attenuated by at least about 20%. In some embodiments, T cell activity is attenuated by at least about 25%. In some embodiments, T cell activity is attenuated by at least about 30%. In some embodiments, T cell activity is attenuated by at least about 35%. In some embodiments, T cell activity is attenuated by at least about 40%. In some embodiments, T cell activity is attenuated by at least about 45%. In some embodiments, T cell activity is attenuated by at least about 50%. In some embodiments, T cell activity is attenuated by at least about 55%. In some embodiments, T cell activity is attenuated by at least about 60%. In some embodiments, T cell activity is attenuated by at least about 65%. In some embodiments, T cell activity is attenuated by at least about 70%. In some embodiments, T cell activity is attenuated by at least about 75%. In some embodiments, T cell activity is attenuated by at least about 80%. In some embodiments, T cell activity is attenuated by at least about 85%. In some embodiments, T cell activity is attenuated by at least about 90%. In some embodiments, T cell activity is attenuated by at least about 95%. In some embodiments, T cell activity is attenuated by at least about 98%. In some embodiments, T cell

activity is attenuated by at least about 99%. In some embodiments, T cell activity is attenuated by at least about 100%. In certain embodiments, T cell activity is attenuated by at least about 25% to about 65%. In specific embodiments, the T cell activity attenuation is assessed by methods described herein. In some embodiments, the T cell activity attenuation is assessed by methods known to one of skill in the art. In certain embodiments, the T cell activity attenuation is relative to T cell activity in a cell that is not contacted with an anti-PD-1 antibody. In certain embodiments, the T cell activity attenuation is relative to T cell activity that is contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0461] A non-limiting example of T cell activity is secretion of a cytokine. In certain embodiments, the cytokine is selected from the group consisting of IL-1, IL-2, IL-6, IL-12, IL-17, IL-22, IL-23, GM-CSF, IFN- γ , and TNF- α . In some embodiments, the cytokine is IL-2, IL-17, IFN- γ , or any combination thereof. In certain embodiments, the cytokine is IL-2. In other embodiments, the cytokine is IL-17. In yet other embodiments, the cytokine is IFN- γ . In certain embodiments, the cytokine is IL-2 and IL-17. In some embodiments, the cytokine is IL-2 and IFN- γ . In yet other embodiments, the cytokine is IL-17 and IFN- γ . In still other embodiments, the cytokine is IL-2, IL-17, and IFN- γ . In certain embodiments, the cytokine is IL-1. In other embodiments, the cytokine is IL-6. In yet other embodiments, the cytokine is IL-12. In still other embodiments, the cytokine is IL-22. In certain embodiments, the cytokine is IL-23. In some embodiments, the cytokine is GM-CSF. In other embodiments, the cytokine is TNF- α . Other combinations of two, three or more of the above-mentioned cytokines are also contemplated.

[0462] In certain embodiments, cytokine secretion is inhibited as a result of inhibition of cytokine production. In other embodiments, cytokine secretion is inhibited as a result of inhibition of cytokine expression.

[0463] In specific embodiments, provided herein are methods of inhibiting cytokine secretion from a cell, comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4,

PD1AB-5, or PD1AB-6. In certain embodiments, the cytokine is selected from the group consisting of IL-1, IL-2, IL-6, IL-12, IL-17, IL-22, IL-23, GM-CSF, IFN- γ , and TNF- α . In some embodiments, the cytokine is IL-2, IL-17, IFN- γ , or any combination thereof. In certain embodiments, the cytokine is IL-2. In other embodiments, the cytokine is IL-17. In yet other embodiments, the cytokine is IFN- γ . In certain embodiments, the cytokine is IL-2 and IL-17. In some embodiments, the cytokine is IL-2 and IFN- γ . In yet other embodiments, the cytokine is IL-17 and IFN- γ . In still other embodiments, the cytokine is IL-2, IL-17, and IFN- γ . In certain embodiments, the cytokine is IL-1. In other embodiments, the cytokine is IL-6. In yet other embodiments, the cytokine is IL-12. In still other embodiments, the cytokine is IL-22. In certain embodiments, the cytokine is IL-23. In some embodiments, the cytokine is GM-CSF. In other embodiments, the cytokine is TNF- α . Other combinations of two, three or more of the above-mentioned cytokines are also contemplated.

[0464] In some embodiments, provided herein are methods of inhibiting IL-2 secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0465] In one embodiment, IL-2 secretion is inhibited by at least about 5%. In some embodiments, IL-2 secretion is inhibited by at least about 10%. In another embodiment, IL-2 secretion is inhibited by at least about 15%. In other embodiments, IL-2 secretion is inhibited by at least about 20%. In one embodiment, IL-2 secretion is inhibited by at least about 25%. In another embodiment, IL-2 secretion is inhibited by at least about 30%. In some embodiments, IL-2 secretion is inhibited by at least about 35%. In one embodiment, IL-2 secretion is inhibited by at least about 40%. In another embodiment, IL-2 secretion is inhibited by at least about 45%. In other embodiments, IL-2 secretion is inhibited by at least about 50%. In some embodiments, IL-2 secretion is inhibited by at least about 55%. In another embodiment, IL-2 secretion is inhibited by at least about 60%. In one embodiment, IL-2 secretion is inhibited by at least about

65%. In one embodiment, IL-2 secretion is inhibited by at least about 70%. In another embodiment, IL-2 secretion is inhibited by at least about 75%. In some embodiments, IL-2 secretion is inhibited by at least about 80%. In other embodiments, IL-2 secretion is inhibited by at least about 85%. In another embodiment, IL-2 secretion is inhibited by at least about 90%. In one embodiment, IL-2 secretion is inhibited by at least about 95%. In some embodiments, IL-2 secretion is inhibited by at least about 98%. In another embodiment, IL-2 secretion is inhibited by at least about 99%. In specific embodiments, IL-2 secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-2 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-2 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-2 secretion is inhibited relative to IL-2 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-2 secretion is inhibited relative to IL-2 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0466] In certain embodiments, IL-2 secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, IL-2 secretion is inhibited with an EC₅₀ of at most about 40 nM. In another embodiment, IL-2 secretion is inhibited with an EC₅₀ of at most about 30 nM. In some embodiments, IL-2 secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, IL-2 secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, IL-2 secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, IL-2 secretion is inhibited with an EC₅₀ of at most about 1 nM. In some embodiments, IL-2 secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, IL-2 secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other embodiments, IL-2 secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, IL-2 secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, IL-2 secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, IL-2 secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one embodiment, IL-2 secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, IL-2 secretion is inhibited with an EC₅₀ of at least about 50 nM. In other embodiments, IL-2 secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, IL-2 secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, IL-2 secretion is inhibited with an EC₅₀ of at least about

20 nM. In one embodiment, IL-2 secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, IL-2 secretion is inhibited with an EC₅₀ of at least about 5 nM. In another embodiment, IL-2 secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, IL-2 secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, IL-2 secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, IL-2 secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, IL-2 secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some embodiments, IL-2 secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, IL-2 secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, IL-2 secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-2 secretion is inhibited relative to IL-2 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-2 secretion is inhibited relative to IL-2 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0467] In some embodiments, provided herein are methods of inhibiting IL-17 secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0468] In one embodiment, IL-17 secretion is inhibited by at least about 5%. In some embodiments, IL-17 secretion is inhibited by at least about 10%. In another embodiment, IL-17 secretion is inhibited by at least about 15%. In other embodiments, IL-17 secretion is inhibited by at least about 20%. In one embodiment, IL-17 secretion is inhibited by at least about 25%. In another embodiment, IL-17 secretion is inhibited by at least about 30%. In some embodiments, IL-17 secretion is inhibited by at least about 35%. In one embodiment, IL-17 secretion is

inhibited by at least about 40%. In another embodiment, IL-17 secretion is inhibited by at least about 45%. In other embodiments, IL-17 secretion is inhibited by at least about 50%. In some embodiments, IL-17 secretion is inhibited by at least about 55%. In another embodiment, IL-17 secretion is inhibited by at least about 60%. In one embodiment, IL-17 secretion is inhibited by at least about 65%. In one embodiment, IL-17 secretion is inhibited by at least about 70%. In another embodiment, IL-17 secretion is inhibited by at least about 75%. In some embodiments, IL-17 secretion is inhibited by at least about 80%. In other embodiments, IL-17 secretion is inhibited by at least about 85%. In another embodiment, IL-17 secretion is inhibited by at least about 90%. In one embodiment, IL-17 secretion is inhibited by at least about 95%. In some embodiments, IL-17 secretion is inhibited by at least about 98%. In another embodiment, IL-17 secretion is inhibited by at least about 99%. In specific embodiments, IL-17 secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-17 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-17 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-17 secretion is inhibited relative to IL-17 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-17 secretion is inhibited relative to IL-17 secretion in a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0469] In certain embodiments, IL-17 secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, IL-17 secretion is inhibited with an EC₅₀ of at most about 40 nM. In another embodiment, IL-17 secretion is inhibited with an EC₅₀ of at most about 30 nM. In some embodiments, IL-17 secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, IL-17 secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, IL-17 secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, IL-17 secretion is inhibited with an EC₅₀ of at most about 1 nM. In some embodiments, IL-17 secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, IL-17 secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other embodiments, IL-17 secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, IL-17 secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, IL-17 secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, IL-17 secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one

embodiment, IL-17 secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, IL-17 secretion is inhibited with an EC₅₀ of at least about 50 nM. In other embodiments, IL-17 secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, IL-17 secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, IL-17 secretion is inhibited with an EC₅₀ of at least about 20 nM. In one embodiment, IL-17 secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, IL-17 secretion is inhibited with an EC₅₀ of at least about 5 nM. In another embodiment, IL-17 secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, IL-17 secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, IL-17 secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, IL-17 secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, IL-17 secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some embodiments, IL-17 secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, IL-17 secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, IL-17 secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-17 secretion is inhibited relative to IL-17 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-17 secretion is inhibited relative to IL-17 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0470] In some embodiments, provided herein are methods of inhibiting IFN- γ secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0471] In one embodiment, IFN- γ secretion is inhibited by at least about 5%. In some embodiments, IFN- γ secretion is inhibited by at least about 10%. In another embodiment, IFN- γ secretion is inhibited by at least about 15%. In other embodiments, IFN- γ secretion is inhibited by at least about 20%. In one embodiment, IFN- γ secretion is inhibited by at least about 25%. In another embodiment, IFN- γ secretion is inhibited by at least about 30%. In some embodiments, IFN- γ secretion is inhibited by at least about 35%. In one embodiment, IFN- γ secretion is inhibited by at least about 40%. In another embodiment, IFN- γ secretion is inhibited by at least about 45%. In other embodiments, IFN- γ secretion is inhibited by at least about 50%. In some embodiments, IFN- γ secretion is inhibited by at least about 55%. In another embodiment, IFN- γ secretion is inhibited by at least about 60%. In one embodiment, IFN- γ secretion is inhibited by at least about 65%. In one embodiment, IFN- γ secretion is inhibited by at least about 70%. In another embodiment, IFN- γ secretion is inhibited by at least about 75%. In some embodiments, IFN- γ secretion is inhibited by at least about 80%. In other embodiments, IFN- γ secretion is inhibited by at least about 85%. In another embodiment, IFN- γ secretion is inhibited by at least about 90%. In one embodiment, IFN- γ secretion is inhibited by at least about 95%. In some embodiments, IFN- γ secretion is inhibited by at least about 98%. In another embodiment, IFN- γ secretion is inhibited by at least about 99%. In specific embodiments, IFN- γ secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IFN- γ secretion is assessed by methods described herein. In other embodiments, the inhibition of IFN- γ secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IFN- γ secretion is inhibited relative to IFN- γ secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IFN- γ secretion is inhibited relative to IFN- γ secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0472] In certain embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at most about 40 nM. In another embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at most about 30 nM. In some embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at most about 1 nM. In some

embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at least about 50 nM. In other embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at least about 20 nM. In one embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at least about 5 nM. In another embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some embodiments, IFN- γ secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, IFN- γ secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IFN- γ secretion is inhibited relative to IFN- γ secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IFN- γ secretion is inhibited relative to IFN- γ secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0473] In some embodiments, provided herein are methods of inhibiting IL-1 secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective

amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0474] In one embodiment, IL-1 secretion is inhibited by at least about 5%. In some embodiments, IL-1 secretion is inhibited by at least about 10%. In another embodiment, IL-1 secretion is inhibited by at least about 15%. In other embodiments, IL-1 secretion is inhibited by at least about 20%. In one embodiment, IL-1 secretion is inhibited by at least about 25%. In another embodiment, IL-1 secretion is inhibited by at least about 30%. In some embodiments, IL-1 secretion is inhibited by at least about 35%. In one embodiment, IL-1 secretion is inhibited by at least about 40%. In another embodiment, IL-1 secretion is inhibited by at least about 45%. In other embodiments, IL-1 secretion is inhibited by at least about 50%. In some embodiments, IL-1 secretion is inhibited by at least about 55%. In another embodiment, IL-1 secretion is inhibited by at least about 60%. In one embodiment, IL-1 secretion is inhibited by at least about 65%. In one embodiment, IL-1 secretion is inhibited by at least about 70%. In another embodiment, IL-1 secretion is inhibited by at least about 75%. In some embodiments, IL-1 secretion is inhibited by at least about 80%. In other embodiments, IL-1 secretion is inhibited by at least about 85%. In another embodiment, IL-1 secretion is inhibited by at least about 90%. In one embodiment, IL-1 secretion is inhibited by at least about 95%. In some embodiments, IL-1 secretion is inhibited by at least about 98%. In another embodiment, IL-1 secretion is inhibited by at least about 99%. In specific embodiments, IL-1 secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-1 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-1 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-1 secretion is inhibited relative to IL-1 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-1 secretion is inhibited relative to IL-1 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0475] In certain embodiments, IL-1 secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, IL-1 secretion is inhibited with an EC₅₀ of at most about 40 nM.

In another embodiment, IL-1 secretion is inhibited with an EC₅₀ of at most about 30 nM. In some embodiments, IL-1 secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, IL-1 secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, IL-1 secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, IL-1 secretion is inhibited with an EC₅₀ of at most about 1 nM. In some embodiments, IL-1 secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, IL-1 secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other embodiments, IL-1 secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, IL-1 secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, IL-1 secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, IL-1 secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one embodiment, IL-1 secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, IL-1 secretion is inhibited with an EC₅₀ of at least about 50 nM. In other embodiments, IL-1 secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, IL-1 secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, IL-1 secretion is inhibited with an EC₅₀ of at least about 20 nM. In one embodiment, IL-1 secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, IL-1 secretion is inhibited with an EC₅₀ of at least about 5 nM. In another embodiment, IL-1 secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, IL-1 secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, IL-1 secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, IL-1 secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, IL-1 secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some embodiments, IL-1 secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, IL-1 secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, IL-1 secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-1 secretion is inhibited relative to IL-1 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-1 secretion is inhibited relative to IL-1 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0476] In some embodiments, provided herein are methods of inhibiting IL-6 secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0477] In one embodiment, IL-6 secretion is inhibited by at least about 5%. In some embodiments, IL-6 secretion is inhibited by at least about 10%. In another embodiment, IL-6 secretion is inhibited by at least about 15%. In other embodiments, IL-6 secretion is inhibited by at least about 20%. In one embodiment, IL-6 secretion is inhibited by at least about 25%. In another embodiment, IL-6 secretion is inhibited by at least about 30%. In some embodiments, IL-6 secretion is inhibited by at least about 35%. In one embodiment, IL-6 secretion is inhibited by at least about 40%. In another embodiment, IL-6 secretion is inhibited by at least about 45%. In other embodiments, IL-6 secretion is inhibited by at least about 50%. In some embodiments, IL-6 secretion is inhibited by at least about 55%. In another embodiment, IL-6 secretion is inhibited by at least about 60%. In one embodiment, IL-6 secretion is inhibited by at least about 65%. In one embodiment, IL-6 secretion is inhibited by at least about 70%. In another embodiment, IL-6 secretion is inhibited by at least about 75%. In some embodiments, IL-6 secretion is inhibited by at least about 80%. In other embodiments, IL-6 secretion is inhibited by at least about 85%. In another embodiment, IL-6 secretion is inhibited by at least about 90%. In one embodiment, IL-6 secretion is inhibited by at least about 95%. In some embodiments, IL-6 secretion is inhibited by at least about 98%. In another embodiment, IL-6 secretion is inhibited by at least about 99%. In specific embodiments, IL-6 secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-6 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-6 secretion is assessed by methods known to one of skill in the art (*e.g.*, MesoScale™ Discovery (MSD) multiplex assay). In a specific embodiment, the IL-6 secretion is inhibited relative to IL-6 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the

IL-6 secretion is inhibited relative to IL-6 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0478] In certain embodiments, IL-6 secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, IL-6 secretion is inhibited with an EC₅₀ of at most about 40 nM. In another embodiment, IL-6 secretion is inhibited with an EC₅₀ of at most about 30 nM. In some embodiments, IL-6 secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, IL-6 secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, IL-6 secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, IL-6 secretion is inhibited with an EC₅₀ of at most about 1 nM. In some embodiments, IL-6 secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, IL-6 secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other embodiments, IL-6 secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, IL-6 secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, IL-6 secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, IL-6 secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one embodiment, IL-6 secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, IL-6 secretion is inhibited with an EC₅₀ of at least about 50 nM. In other embodiments, IL-6 secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, IL-6 secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, IL-6 secretion is inhibited with an EC₅₀ of at least about 20 nM. In one embodiment, IL-6 secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, IL-6 secretion is inhibited with an EC₅₀ of at least about 5 nM. In another embodiment, IL-6 secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, IL-6 secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, IL-6 secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, IL-6 secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, IL-6 secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some embodiments, IL-6 secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, IL-6 secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, IL-6 secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific

embodiment, the IL-6 secretion is inhibited relative to IL-6 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-6 secretion is inhibited relative to IL-6 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0479] In some embodiments, provided herein are methods of inhibiting IL-12 secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0480] In one embodiment, IL-12 secretion is inhibited by at least about 5%. In some embodiments, IL-12 secretion is inhibited by at least about 10%. In another embodiment, IL-12 secretion is inhibited by at least about 15%. In other embodiments, IL-12 secretion is inhibited by at least about 20%. In one embodiment, IL-12 secretion is inhibited by at least about 25%. In another embodiment, IL-12 secretion is inhibited by at least about 30%. In some embodiments, IL-12 secretion is inhibited by at least about 35%. In one embodiment, IL-12 secretion is inhibited by at least about 40%. In another embodiment, IL-12 secretion is inhibited by at least about 45%. In other embodiments, IL-12 secretion is inhibited by at least about 50%. In some embodiments, IL-12 secretion is inhibited by at least about 55%. In another embodiment, IL-12 secretion is inhibited by at least about 60%. In one embodiment, IL-12 secretion is inhibited by at least about 65%. In one embodiment, IL-12 secretion is inhibited by at least about 70%. In another embodiment, IL-12 secretion is inhibited by at least about 75%. In some embodiments, IL-12 secretion is inhibited by at least about 80%. In other embodiments, IL-12 secretion is inhibited by at least about 85%. In another embodiment, IL-12 secretion is inhibited by at least about 90%. In one embodiment, IL-12 secretion is inhibited by at least about 95%. In some embodiments, IL-12 secretion is inhibited by at least about 98%. In another embodiment, IL-12 secretion is inhibited by at least about 99%. In specific embodiments, IL-12 secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of

IL-12 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-12 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-12 secretion is inhibited relative to IL-12 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-12 secretion is inhibited relative to IL-12 secretion in a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0481] In certain embodiments, IL-12 secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, IL-12 secretion is inhibited with an EC₅₀ of at most about 40 nM. In another embodiment, IL-12 secretion is inhibited with an EC₅₀ of at most about 30 nM. In some embodiments, IL-12 secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, IL-12 secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, IL-12 secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, IL-12 secretion is inhibited with an EC₅₀ of at most about 1 nM. In some embodiments, IL-12 secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, IL-12 secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other embodiments, IL-12 secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, IL-12 secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, IL-12 secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, IL-12 secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one embodiment, IL-12 secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, IL-12 secretion is inhibited with an EC₅₀ of at least about 50 nM. In other embodiments, IL-12 secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, IL-12 secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, IL-12 secretion is inhibited with an EC₅₀ of at least about 20 nM. In one embodiment, IL-12 secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, IL-12 secretion is inhibited with an EC₅₀ of at least about 5 nM. In another embodiment, IL-12 secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, IL-12 secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, IL-12 secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, IL-12 secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, IL-12 secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some

embodiments, IL-12 secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, IL-12 secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, IL-12 secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-12 secretion is inhibited relative to IL-12 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-12 secretion is inhibited relative to IL-12 secretion in a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0482] In some embodiments, provided herein are methods of inhibiting IL-22 secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0483] In one embodiment, IL-22 secretion is inhibited by at least about 5%. In some embodiments, IL-22 secretion is inhibited by at least about 10%. In another embodiment, IL-22 secretion is inhibited by at least about 15%. In other embodiments, IL-22 secretion is inhibited by at least about 20%. In one embodiment, IL-22 secretion is inhibited by at least about 25%. In another embodiment, IL-22 secretion is inhibited by at least about 30%. In some embodiments, IL-22 secretion is inhibited by at least about 35%. In one embodiment, IL-22 secretion is inhibited by at least about 40%. In another embodiment, IL-22 secretion is inhibited by at least about 45%. In other embodiments, IL-22 secretion is inhibited by at least about 50%. In some embodiments, IL-22 secretion is inhibited by at least about 55%. In another embodiment, IL-22 secretion is inhibited by at least about 60%. In one embodiment, IL-22 secretion is inhibited by at least about 65%. In one embodiment, IL-22 secretion is inhibited by at least about 70%. In another embodiment, IL-22 secretion is inhibited by at least about 75%. In some embodiments, IL-22 secretion is inhibited by at least about 80%. In other embodiments, IL-22 secretion is

inhibited by at least about 85%. In another embodiment, IL-22 secretion is inhibited by at least about 90%. In one embodiment, IL-22 secretion is inhibited by at least about 95%. In some embodiments, IL-22 secretion is inhibited by at least about 98%. In another embodiment, IL-22 secretion is inhibited by at least about 99%. In specific embodiments, IL-22 secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-22 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-22 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-22 secretion is inhibited relative to IL-22 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-22 secretion is inhibited relative to IL-22 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0484] In certain embodiments, IL-22 secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, IL-22 secretion is inhibited with an EC₅₀ of at most about 40 nM. In another embodiment, IL-22 secretion is inhibited with an EC₅₀ of at most about 30 nM. In some embodiments, IL-22 secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, IL-22 secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, IL-22 secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, IL-22 secretion is inhibited with an EC₅₀ of at most about 1 nM. In some embodiments, IL-22 secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, IL-22 secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other embodiments, IL-22 secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, IL-22 secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, IL-22 secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, IL-22 secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one embodiment, IL-22 secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, IL-22 secretion is inhibited with an EC₅₀ of at least about 50 nM. In other embodiments, IL-22 secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, IL-22 secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, IL-22 secretion is inhibited with an EC₅₀ of at least about 20 nM. In one embodiment, IL-22 secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, IL-22 secretion is inhibited with an EC₅₀ of at least about 5 nM. In another

embodiment, IL-22 secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, IL-22 secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, IL-22 secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, IL-22 secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, IL-22 secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some embodiments, IL-22 secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, IL-22 secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, IL-22 secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-22 secretion is inhibited relative to IL-22 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-22 secretion is inhibited relative to IL-22 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0485] In some embodiments, provided herein are methods of inhibiting IL-23 secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0486] In one embodiment, IL-23 secretion is inhibited by at least about 5%. In some embodiments, IL-23 secretion is inhibited by at least about 10%. In another embodiment, IL-23 secretion is inhibited by at least about 15%. In other embodiments, IL-23 secretion is inhibited by at least about 20%. In one embodiment, IL-23 secretion is inhibited by at least about 25%. In another embodiment, IL-23 secretion is inhibited by at least about 30%. In some embodiments, IL-23 secretion is inhibited by at least about 35%. In one embodiment, IL-23 secretion is inhibited by at least about 40%. In another embodiment, IL-23 secretion is inhibited by at least about 45%. In other embodiments, IL-23 secretion is inhibited by at least about 50%. In some

embodiments, IL-23 secretion is inhibited by at least about 55%. In another embodiment, IL-23 secretion is inhibited by at least about 60%. In one embodiment, IL-23 secretion is inhibited by at least about 65%. In one embodiment, IL-23 secretion is inhibited by at least about 70%. In another embodiment, IL-23 secretion is inhibited by at least about 75%. In some embodiments, IL-23 secretion is inhibited by at least about 80%. In other embodiments, IL-23 secretion is inhibited by at least about 85%. In another embodiment, IL-23 secretion is inhibited by at least about 90%. In one embodiment, IL-23 secretion is inhibited by at least about 95%. In some embodiments, IL-23 secretion is inhibited by at least about 98%. In another embodiment, IL-23 secretion is inhibited by at least about 99%. In specific embodiments, IL-23 secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of IL-23 secretion is assessed by methods described herein. In other embodiments, the inhibition of IL-23 secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-23 secretion is inhibited relative to IL-23 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-23 secretion is inhibited relative to IL-23 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0487] In certain embodiments, IL-23 secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, IL-23 secretion is inhibited with an EC₅₀ of at most about 40 nM. In another embodiment, IL-23 secretion is inhibited with an EC₅₀ of at most about 30 nM. In some embodiments, IL-23 secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, IL-23 secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, IL-23 secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, IL-23 secretion is inhibited with an EC₅₀ of at most about 1 nM. In some embodiments, IL-23 secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, IL-23 secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other embodiments, IL-23 secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, IL-23 secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, IL-23 secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, IL-23 secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one embodiment, IL-23 secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, IL-23 secretion is inhibited with an EC₅₀ of at least about 50 nM. In other

embodiments, IL-23 secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, IL-23 secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, IL-23 secretion is inhibited with an EC₅₀ of at least about 20 nM. In one embodiment, IL-23 secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, IL-23 secretion is inhibited with an EC₅₀ of at least about 5 nM. In another embodiment, IL-23 secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, IL-23 secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, IL-23 secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, IL-23 secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, IL-23 secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some embodiments, IL-23 secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, IL-23 secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, IL-23 secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the IL-23 secretion is inhibited relative to IL-23 secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-23 secretion is inhibited relative to IL-23 secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0488] In some embodiments, provided herein are methods of inhibiting GM-CSF secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0489] In one embodiment, GM-CSF secretion is inhibited by at least about 5%. In some embodiments, GM-CSF secretion is inhibited by at least about 10%. In another embodiment, GM-CSF secretion is inhibited by at least about 15%. In other embodiments, GM-CSF secretion

is inhibited by at least about 20%. In one embodiment, GM-CSF secretion is inhibited by at least about 25%. In another embodiment, GM-CSF secretion is inhibited by at least about 30%. In some embodiments, GM-CSF secretion is inhibited by at least about 35%. In one embodiment, GM-CSF secretion is inhibited by at least about 40%. In another embodiment, GM-CSF secretion is inhibited by at least about 45%. In other embodiments, GM-CSF secretion is inhibited by at least about 50%. In some embodiments, GM-CSF secretion is inhibited by at least about 55%. In another embodiment, GM-CSF secretion is inhibited by at least about 60%. In one embodiment, GM-CSF secretion is inhibited by at least about 65%. In one embodiment, GM-CSF secretion is inhibited by at least about 70%. In another embodiment, GM-CSF secretion is inhibited by at least about 75%. In some embodiments, GM-CSF secretion is inhibited by at least about 80%. In other embodiments, GM-CSF secretion is inhibited by at least about 85%. In another embodiment, GM-CSF secretion is inhibited by at least about 90%. In one embodiment, GM-CSF secretion is inhibited by at least about 95%. In some embodiments, GM-CSF secretion is inhibited by at least about 98%. In another embodiment, GM-CSF secretion is inhibited by at least about 99%. In specific embodiments, GM-CSF secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of GM-CSF secretion is assessed by methods described herein. In other embodiments, the inhibition of GM-CSF secretion is assessed by methods known to one of skill in the art (*e.g.*, MesoScale™ Discovery (MSD) multiplex assay). In a specific embodiment, the GM-CSF secretion is inhibited relative to GM-CSF secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-2 secretion is inhibited relative to GM-CSF secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0490] In certain embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at most about 40 nM. In another embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at most about 30 nM. In some embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at most about 1 nM. In some embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other

embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at least about 50 nM. In other embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at least about 20 nM. In one embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at least about 5 nM. In another embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some embodiments, GM-CSF secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, GM-CSF secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the GM-CSF secretion is inhibited relative to GM-CSF secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the IL-2 secretion is inhibited relative to GM-CSF secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0491] In some embodiments, provided herein are methods of inhibiting TNF- α secretion from a cell comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4,

PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0492] In one embodiment, TNF- α secretion is inhibited by at least about 5%. In some embodiments, TNF- α secretion is inhibited by at least about 10%. In another embodiment, TNF- α secretion is inhibited by at least about 15%. In other embodiments, TNF- α secretion is inhibited by at least about 20%. In one embodiment, TNF- α secretion is inhibited by at least about 25%. In another embodiment, TNF- α secretion is inhibited by at least about 30%. In some embodiments, TNF- α secretion is inhibited by at least about 35%. In one embodiment, TNF- α secretion is inhibited by at least about 40%. In another embodiment, TNF- α secretion is inhibited by at least about 45%. In other embodiments, TNF- α secretion is inhibited by at least about 50%. In some embodiments, TNF- α secretion is inhibited by at least about 55%. In another embodiment, TNF- α secretion is inhibited by at least about 60%. In one embodiment, TNF- α secretion is inhibited by at least about 65%. In one embodiment, TNF- α secretion is inhibited by at least about 70%. In another embodiment, TNF- α secretion is inhibited by at least about 75%. In some embodiments, TNF- α secretion is inhibited by at least about 80%. In other embodiments, TNF- α secretion is inhibited by at least about 85%. In another embodiment, TNF- α secretion is inhibited by at least about 90%. In one embodiment, TNF- α secretion is inhibited by at least about 95%. In some embodiments, TNF- α secretion is inhibited by at least about 98%. In another embodiment, TNF- α secretion is inhibited by at least about 99%. In specific embodiments, TNF- α secretion is inhibited by at least about 25% or 35%, optionally to about 75%. In some embodiments, the inhibition of TNF- α secretion is assessed by methods described herein. In other embodiments, the inhibition of TNF- α secretion is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the TNF- α secretion is inhibited relative to TNF- α secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the TNF- α secretion is inhibited relative to TNF- α secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0493] In certain embodiments, TNF- α secretion is inhibited with an EC₅₀ of at most about 50 nM. In other embodiments, TNF- α secretion is inhibited with an EC₅₀ of at most about 40 nM. In another embodiment, TNF- α secretion is inhibited with an EC₅₀ of at most about

30 nM. In some embodiments, TNF- α secretion is inhibited with an EC₅₀ of at most about 20 nM. In one embodiment, TNF- α secretion is inhibited with an EC₅₀ of at most about 10 nM. In another embodiment, TNF- α secretion is inhibited with an EC₅₀ of at most about 5 nM. In one embodiment, TNF- α secretion is inhibited with an EC₅₀ of at most about 1 nM. In some embodiments, TNF- α secretion is inhibited with an EC₅₀ of at most about 0.75 nM. In another embodiment, TNF- α secretion is inhibited with an EC₅₀ of at most about 0.5 nM. In other embodiments, TNF- α secretion is inhibited with an EC₅₀ of at most about 0.1 nM. In one embodiment, TNF- α secretion is inhibited with an EC₅₀ of at most about 0.05 nM. In another embodiment, TNF- α secretion is inhibited with an EC₅₀ of at most about 0.01 nM. In some embodiments, TNF- α secretion is inhibited with an EC₅₀ of at most about 0.005 nM. In one embodiment, TNF- α secretion is inhibited with an EC₅₀ of at most about 0.001 nM. In another embodiment, TNF- α secretion is inhibited with an EC₅₀ of at least about 50 nM. In other embodiments, TNF- α secretion is inhibited with an EC₅₀ of at least about 40 nM. In some embodiments, TNF- α secretion is inhibited with an EC₅₀ of at least about 30 nM. In another embodiment, TNF- α secretion is inhibited with an EC₅₀ of at least about 20 nM. In one embodiment, TNF- α secretion is inhibited with an EC₅₀ of at least about 10 nM. In one embodiment, TNF- α secretion is inhibited with an EC₅₀ of at least about 5 nM. In another embodiment, TNF- α secretion is inhibited with an EC₅₀ of at least about 1 nM. In some embodiments, TNF- α secretion is inhibited with an EC₅₀ of at least about 0.75 nM. In other embodiments, TNF- α secretion is inhibited with an EC₅₀ of at least about 0.5 nM. In another embodiment, TNF- α secretion is inhibited with an EC₅₀ of at least about 0.1 nM. In one embodiment, TNF- α secretion is inhibited with an EC₅₀ of at least about 0.05 nM. In some embodiments, TNF- α secretion is inhibited with an EC₅₀ of at least about 0.01 nM. In another embodiment, TNF- α secretion is inhibited with an EC₅₀ of at least about 0.005 nM. In one embodiment, TNF- α secretion is inhibited with an EC₅₀ of at least about 0.001 nM. In some embodiments, the EC₅₀ is assessed by methods described herein. In other embodiments, the EC₅₀ is assessed by methods known to one of skill in the art (*e.g.*, MSD multiplex assay). In a specific embodiment, the TNF- α secretion is inhibited relative to TNF- α secretion from a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the TNF- α secretion is inhibited relative to TNF- α secretion from a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0494] In some embodiments, provided herein are methods of downregulating PD-1 expression in a cell, comprising contacting the cell with an antibody that specifically binds to PD-1 (*e.g.*, an ECD of human PD-1 or an epitope of an ECD of human PD-1) as provided herein. In a specific embodiment, the cell is a T cell. In certain embodiments, the cell is contacted with an effective amount of an antibody or antigen binding fragment thereof described herein. In certain embodiments, the antibody is any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 or an antigen-binding fragment thereof, or an antibody comprising CDRs of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6.

[0495] In one embodiment, PD-1 expression is downregulated by at least about 5%. In one embodiment, PD-1 expression is downregulated by at least about 10%. In another embodiment, PD-1 expression is downregulated by at least about 15%. In some embodiments, PD-1 expression is downregulated by at least about 20%. In other embodiments, PD-1 expression is downregulated by at least about 25%. In another embodiment, PD-1 expression is downregulated by at least about 30%. In one embodiment, PD-1 expression is downregulated by at least about 35%. In some embodiments, PD-1 expression is downregulated by at least about 40%. In another embodiment, PD-1 expression is downregulated by at least about 45%. In one embodiment, PD-1 expression is downregulated by at least about 50%. In other embodiments, PD-1 expression is downregulated by at least about 55%. In another embodiment, PD-1 expression is downregulated by at least about 60%. In some embodiments, PD-1 expression is downregulated by at least about 65%. In one embodiment, PD-1 expression is downregulated by at least about 70%. In another embodiment, PD-1 expression is downregulated by at least about 75%. In one embodiment, PD-1 expression is downregulated by at least about 80%. In some embodiments, PD-1 expression is downregulated by at least about 85%. In another embodiment, PD-1 expression is downregulated by at least about 90%. In other embodiments, PD-1 expression is downregulated by at least about 95%. In one embodiment, PD-1 expression is downregulated by at least about 98%. In another embodiment, PD-1 expression is downregulated by at least about 99%. In specific embodiments, antibodies of a pharmaceutical formulation provided herein specifically bind to PD-1 and downregulates PD-1 expression by at least about 25% or 35%, optionally to about 75%. In some embodiments, the downregulation of PD-1 expression is assessed by methods described herein. In other embodiments, the downregulation of PD-1 expression is assessed by methods known to

one of skill in the art (*e.g.*, flow cytometry, Western blotting, Northern blotting, or RT-PCR). In a specific embodiment, the downregulation of PD-1 expression is assessed by flow cytometry. In another embodiment, the downregulation of PD-1 expression is assessed by Western blotting. In yet another embodiment, the downregulation of PD-1 expression is assessed by Northern blotting. In still another embodiment, the downregulation of PD-1 expression is assessed by RT-PCR. In a specific embodiment, the PD-1 expression is downregulated relative to PD-1 expression in a cell that is not contacted with an anti-PD-1 antibody. In other embodiments, the PD-1 expression is downregulated relative to PD-1 expression in a cell contacted with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[0496] In one embodiment, provided herein is a method of downregulating PD-1 expression on the surface of a T cell, comprising contacting the T cell with an effective amount of an antibody or antigen binding fragment thereof of a pharmaceutical formulation provided herein. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 10%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 20%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 30%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 40%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 45%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 50%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 55%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 60%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 65%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 70%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 75%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at

least about 80%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 85%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 90%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 95%. In one embodiment, the maximal percent downregulation of PD-1 expression by the antibody or antigen-binding fragment thereof is at least about 100%.

[0497] In certain embodiments, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours after the contact with the antibody or antigen-binding fragment thereof. In other embodiments, the downregulation of PD-1 expression on the surface of T cells occurs as early as 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, or 22 hours after the contact with the antibody or antigen-binding fragment thereof. In one embodiment, the downregulation occurs as early as 4 hours after the contact. In one embodiment, the downregulation occurs as early as 6 hours after the contact. In another embodiment, the downregulation occurs as early as 8 hours after the contact. In other embodiments, the downregulation occurs as early as 10 hours after the contact. In some embodiments, the downregulation occurs as early as 12 hours after the contact. In one embodiment, the downregulation occurs as early as 14 hours after the contact. In another embodiment, the downregulation occurs as early as 16 hours after the contact. In some embodiments, the downregulation occurs as early as 18 hours after the contact. In other embodiments, the downregulation occurs as early as 20 hours after the contact. In other embodiments, the downregulation occurs as early as 22 hours after the contact. In yet other embodiments, the downregulation of PD-1 expression on the surface of T cells occurs as early as 24 hours after the contact with the antibody or antigen-binding fragment thereof.

[0498] In one embodiment, the downregulation of PD-1 expression on the surface of the T cell precedes cytokine inhibition. In another embodiment, the downregulation of PD-1 expression on the surface of the T cell is concurrent with cytokine inhibition. In yet another embodiment, the downregulation of PD-1 expression on the surface of the T cell is preceded by cytokine inhibition. In certain embodiments, the cytokine is IL-2, IL-17, IFN- γ , or any combination thereof. In one embodiment, the cytokine is IL-2. In another embodiment, the cytokine is IL-17. In other embodiments, the cytokine is IFN- γ . In certain embodiments, the

cytokine is selected from the group consisting of IL-1, IL-2, IL-6, IL-12, IL-17, IL-22, IL-23, GM-CSF, IFN- γ , and TNF- α . In certain embodiments, the cytokine is IL-1. In other embodiments, the cytokine is IL-6. In yet other embodiments, the cytokine is IL-12. In still other embodiments, the cytokine is IL-22. In certain embodiments, the cytokine is IL-23. In some embodiments, the cytokine is GM-CSF. In other embodiments, the cytokine is TNF- α . Other combinations of two, three or more of the above-mentioned cytokines are also contemplated.

[0499] In other aspects, anti-PD-1 antibodies and fragments thereof of the present disclosure are useful for detecting the presence of PD-1 in a biological sample. Such anti-PD-1 antibodies may include those that bind to human and/or cynomolgus PD-1 but do not induce PD-1 signaling activity. The term “detecting” as used herein encompasses quantitative or qualitative detection. In certain embodiments, a biological sample comprises bodily fluid, a cell, or a tissue.

5.5 Pharmaceutical Compositions

[0500] In one aspect, the present disclosure further provides pharmaceutical compositions comprising at least one anti-PD-1 antibody of the present disclosure. In some embodiments, a pharmaceutical composition comprises 1) an anti-PD-1 antibody, and 2) a pharmaceutically acceptable carrier.

[0501] Pharmaceutical compositions comprising an antibody are prepared for storage by mixing the antibody having the desired degree of purity with optional physiologically acceptable carriers, excipients, or stabilizers (*see, e.g.,* Remington, Remington's Pharmaceutical Sciences (18th ed. 1980)) in the form of aqueous solutions or lyophilized or other dried forms.

[0502] The antibodies of the present disclosure may be formulated in any suitable form for delivery to a target cell/tissue, *e.g.,* as microcapsules or macroemulsions (Remington, *supra*; Park *et al.*, 2005, *Molecules* 10:146-61; Malik *et al.*, 2007, *Curr. Drug. Deliv.* 4:141-51), as sustained release formulations (Putney and Burke, 1998, *Nature Biotechnol.* 16:153-57), or in liposomes (Maclean *et al.*, 1997, *Int. J. Oncol.* 11:325-32; Kontermann, 2006, *Curr. Opin. Mol. Ther.* 8:39-45).

[0503] An antibody of a pharmaceutical formulation provided herein can also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacrylate) microcapsule, respectively, in colloidal drug delivery systems (for example,

liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed, for example, in Remington, *supra*.

[0504] Various compositions and delivery systems are known and can be used with an antibody that binds to PD-1 as described herein, including, but not limited to, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody, receptor-mediated endocytosis (*see, e.g.*, Wu and Wu, 1987, J. Biol. Chem. 262:4429-32), construction of a nucleic acid as part of a retroviral or other vector, *etc.* In another embodiment, a composition can be provided as a controlled release or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (*see, e.g.*, Langer, *supra*; Sefton, 1987, Crit. Ref. Biomed. Eng. 14:201-40; Buchwald *et al.*, 1980, Surgery 88:507-16; and Saudek *et al.*, 1989, N. Engl. J. Med. 321:569-74). In another embodiment, polymeric materials can be used to achieve controlled or sustained release of a prophylactic or therapeutic agent (*e.g.*, an antibody that binds to PD-1 as described herein) or a composition of the invention (*see, e.g.*, Medical Applications of Controlled Release (Langer and Wise eds., 1974); Controlled Drug Bioavailability, Drug Product Design and Performance (Smolen and Ball eds., 1984); Ranger and Peppas, 1983, J. Macromol. Sci. Rev. Macromol. Chem. 23:61-126; Levy *et al.*, 1985, Science 228:190-92; During *et al.*, 1989, Ann. Neurol. 25:351-56; Howard *et al.*, 1989, J. Neurosurg. 71:105-12; U.S. Pat. Nos. 5,679,377; 5,916,597; 5,912,015; 5,989,463; and 5,128,326; PCT Publication Nos. WO 99/15154 and WO 99/20253). Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In one embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable.

[0505] In yet another embodiment, a controlled or sustained release system can be placed in proximity of a particular target tissue, for example, the nasal passages or lungs, thus requiring only a fraction of the systemic dose (*see, e.g.*, Goodson, Medical Applications of Controlled Release Vol. 2, 115-38 (1984)). Controlled release systems are discussed, for example, by Langer, 1990, Science 249:1527-33. Any technique known to one of skill in the art can be used

to produce sustained release formulations comprising one or more antibodies that bind to PD-1 as described herein (*see, e.g.*, U.S. Pat. No. 4,526,938, PCT publication Nos. WO 91/05548 and WO 96/20698, Ning *et al.*, 1996, Radiotherapy & Oncology 39:179-89; Song *et al.*, 1995, PDA J. of Pharma. Sci. & Tech. 50:372-97; Cleek *et al.*, 1997, Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-54; and Lam *et al.*, 1997, Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-60).

[0506] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that binds to PD-1, including a PD-1 polypeptide, a PD-1 polypeptide fragment, a PD-1 peptide, or a PD-1 epitope. In certain embodiments, the various pharmaceutical formulations provided herein comprise antibodies that bind to human and/or cynomolgus PD-1. In other embodiments, the various pharmaceutical formulations provided herein comprise antibodies that do not bind to rodent PD-1 (*e.g.*, a mouse PD-1). In one embodiment, the various pharmaceutical formulations provided herein comprise antibodies that bind to human PD-1. In another embodiment, the various pharmaceutical formulations provided herein comprise antibodies that bind to cynomolgus PD-1. In another embodiment, the various pharmaceutical formulations provided herein comprise antibodies that bind to human PD-1 and cynomolgus PD-1. In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that bind to human PD-1 and do not bind to a rodent PD-1 (*e.g.*, a mouse PD-1). In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that bind to cynomolgus PD-1 and do not bind to a rodent PD-1 (*e.g.*, a mouse PD-1). In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that bind to human PD-1, bind to a cynomolgus PD-1, and do not bind to a rodent PD-1 (*e.g.*, a mouse PD-1). In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that do not block the binding of PD-L1 to a PD-1 polypeptide. In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that do not block the binding of PD-L2 to a PD-1 polypeptide. In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that do not block the binding of PD-L1 or PD-L2 to a PD-1 polypeptide. In other embodiments, the various pharmaceutical formulations provided herein comprise antibodies that are humanized antibodies (*e.g.*, comprising human constant regions) that bind PD-1, including a PD-1 polypeptide, a PD-1 polypeptide fragment, a PD-1 peptide, or a PD-1 epitope. In certain embodiments, the various

pharmaceutical formulations provided herein comprise antibodies that comprise a VH region, VL region, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of any one of the murine monoclonal antibodies of a pharmaceutical formulation provided herein, such as an amino acid sequence depicted in **Tables 1-6**. Accordingly, in some embodiments, the isolated antibody or functional fragment thereof of a pharmaceutical formulation provided herein comprises one, two, and/or three heavy chain CDRs and/or one, two, and/or three light chain CDRs from: (a) the antibody PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, or (f) the antibody PD1AB-6, as shown in **Tables 1-2**.

[0507] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises or consists of six CDRs, for example, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in **Tables 1-2**. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that can comprise fewer than six CDRs. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in **Tables 1-2**. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of the monoclonal antibody selected from the group consisting of: (a) the antibody PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, and (f) the antibody PD1AB-6, described herein. Accordingly, in some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises or consists of one, two, three, four, or five CDRs of anyone of the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 identified in **Tables 1-2**.

[0508] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising one or more (*e.g.*, one, two, or three) VH CDRs listed in **Table 2**. In other embodiments, the various pharmaceutical formulations provided herein comprise antibodies that comprise one or more (*e.g.*, one, two, or three) VL CDRs listed in **Table 1**. In yet other embodiments, the various pharmaceutical formulations provided herein comprise

antibodies that comprise one or more (*e.g.*, one, two, or three) VH CDRs listed in **Table 2** and one or more VL CDRs listed in **Table 1**. Accordingly, in some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that comprise a VH CDR1 having an amino acid sequence of SEQ ID NO:4. In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that comprise a VH CDR2 having an amino acid sequence of SEQ ID NO:5. In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that comprise a VH CDR3 having an amino acid sequence of SEQ ID NO:6. In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that comprise a VH CDR1 and/or a VH CDR2 and/or a VH CDR3 independently selected from any one of the VH CDR1, VH CDR2, VH CDR3 amino acid sequence(s) as depicted in **Table 2**. In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that comprise a VL CDR1 having an amino acid sequence of any one of SEQ ID NOS:1 and 7. In another embodiment, the various pharmaceutical formulations provided herein comprise antibodies that comprise a VL CDR2 having an amino acid sequence of SEQ ID NO:2. In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that comprise a VL CDR3 having an amino acid sequence of SEQ ID NO:3. In some embodiments, the various pharmaceutical formulations provided herein comprise antibodies that comprise a VL CDR1 and/or a VL CDR2 and/or a VL CDR3 independently selected from any one of the VL CDR1, VL CDR2, VL CDR3 amino acid sequences as depicted in **Table 1**.

[0509] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region comprising: (1) a VH CDR1 having an amino acid sequence of SEQ ID NO:4; (2) a VH CDR2 having an amino acid sequence of SEQ ID NO:5; and (3) a VH CDR3 having an amino acid sequence of SEQ ID NO:6; and a VL region comprising: (1) a VL CDR1 having an amino acid sequence of SEQ ID NO:1; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3. In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH region comprising: (1) a VH CDR1 having an amino acid sequence of SEQ ID NO:4; (2) a VH CDR2 having an amino acid sequence of SEQ ID NO:5; and (3) a VH CDR3 having an amino acid sequence of SEQ ID NO:6; and a VL region comprising: (1) a VL CDR1 having an amino acid of SEQ ID NOS:7; (2)

a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH region comprising: (1) a VH CDR1 having an amino acid sequence of SEQ ID NO:4; (2) a VH CDR2 having an amino acid sequence of SEQ ID NO:5; and (3) a VH CDR3 having an amino acid sequence of SEQ ID NO:6. In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VL region comprising: (1) a VL CDR1 having an amino acid sequence of SEQ ID NO:1; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VL region comprising: (1) a VL CDR1 having an amino acid sequence of SEQ ID NO:7; (2) a VL CDR2 having an amino acid sequence of SEQ ID NO:2; and (3) a VL CDR3 having an amino acid sequence of SEQ ID NO:3.

[0510] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising one or more (*e.g.*, one, two, or three) VH CDRs and one or more (*e.g.*, one, two, or three) VL CDRs listed in **Tables 1-2**. In particular embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4) and a VL CDR1 (SEQ ID NOS:1 or 7). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4) and a VL CDR2 (SEQ ID NO:2). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4) and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5) and a VL CDR1 (SEQ ID NOS:1 or 7). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5) and a VL CDR2 (SEQ ID NO:2). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5) and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR3 (SEQ ID NO:6) and a VL CDR1 (SEQ ID NOS:1 or 7). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR3

(SEQ ID NO:6) and a VL CDR2 (SEQ ID NO:2). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR3 (SEQ ID NO:6) and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), and a VL CDR1 (SEQ ID NOS:1 or 7). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), and a VL CDR2 (SEQ ID NO:2). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR1 (SEQ ID NOS:1 or 7). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR2 (SEQ ID NO:2). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), and a VL CDR1 (SEQ ID NOS:1 or 7). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), and a VL CDR2 (SEQ ID NO:2). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that

comprises a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR3 (SEQ ID NO:6), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR1 (SEQ ID NOS:1 or 7). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR2 (SEQ ID NO:2). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In other embodiments, the various

pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR2 (SEQ ID NO:2). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), and a VL CDR3 (SEQ ID NO:3). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR1 (SEQ ID NO:4), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an

antibody that comprises a VH CDR1 (SEQ ID NO:4), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In one embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR2 (SEQ ID NO:5), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody that comprises a VH CDR3 (SEQ ID NO:6), a VL CDR1 (SEQ ID NOS:1 or 7), a VL CDR2 (SEQ ID NO:2), and a VL CDR3 (SEQ ID NO:3). In another embodiment, the various pharmaceutical formulations provided herein comprise an antibody that comprises any combination thereof of the VH CDRs and VL CDRs listed in **Tables 1-2**.

[0511] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising CDRs disclosed herein that include consensus sequences derived from groups of related antibodies (*see, e.g.*, **Tables 1-2**).

[0512] In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody (or functional fragment thereof) that further comprises one, two, three, and/or four heavy chain FRs and/or one, two, three, and/or four light chain FRs from: (a) the antibody PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, or (f) the antibody PD1AB-6, as shown in **Tables 3-4**.

[0513] In certain embodiments, the various pharmaceutical formulations provided herein comprise an antibody (or functional fragment thereof) that further comprises one, two, three, and/or four heavy chain FRs from: (a) the antibody PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, or (f) the antibody PD1AB-6, as shown in **Table 4**. In some embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-1. In some embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-2. In other embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-3. In certain embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-4. In other embodiments, the antibody heavy chain FR(s) is from the antibody PD1AB-5. In another embodiment, the antibody heavy chain FR(s) is from the antibody PD1AB-6.

[0514] In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody (or functional fragment thereof) that further comprises one, two, three, and/or four light chain FRs from: (a) the antibody PD1AB-1, (b) the antibody PD1AB-2, (c) the antibody PD1AB-3, (d) the antibody PD1AB-4, (e) the antibody PD1AB-5, or (f) the antibody

PD1AB-6, as shown in **Table 3**. In some embodiments, the antibody light chain FR(s) is from the antibody PD1AB-1. In some embodiments, the antibody light chain FR(s) is from the antibody PD1AB-2. In other embodiments, the antibody light chain FR(s) is from the antibody PD1AB-3. In certain embodiments, the antibody light chain FR(s) is from the antibody PD1AB-4. In other embodiments, the antibody light chain FR(s) is from the antibody PD1AB-5. In another embodiment, the antibody light chain FR(s) is from the antibody PD1AB-6.

[0515] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region that comprises: (1) a VH FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS:19 and 24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:21 and 23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In certain embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region that comprises: (1) a VH FR1 having an amino acid of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In certain embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region that comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO: 23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In certain embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region that comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO: 24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In certain embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region that comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO: 23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22. In specific embodiments, the various pharmaceutical formulations provided herein comprise an antibody

comprising a VH region that comprises all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4.

[0516] Accordingly, in some embodiments, the various pharmaceutical formulations provided herein comprise a humanized antibody comprising a VH region that includes a VH FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS:19 and 24. In one embodiment, the various pharmaceutical formulations provided herein comprise a humanized antibody comprising a VH region that includes a VH FR1 having an amino acid sequence of SEQ ID NO:19. In one embodiment, the various pharmaceutical formulations provided herein comprise a humanized antibody comprising a VH region that includes a VH FR1 having an amino acid sequence of SEQ ID NO:24. In some embodiments, the various pharmaceutical formulations provided herein comprise a humanized antibody comprising a VH region that includes a VH FR2 having an amino acid sequence of SEQ ID NO: 20. In some embodiments, the various pharmaceutical formulations provided herein comprise a humanized antibody comprising a VH region that includes a VH FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:21 and 23. In one embodiment, the various pharmaceutical formulations provided herein comprise a humanized antibody comprising a VH region that includes a VH FR3 having an amino acid sequence of SEQ ID NO:21. In one embodiment, the various pharmaceutical formulations provided herein comprise a humanized antibody comprising a VH region that includes a VH FR3 having an amino acid sequence of SEQ ID NO:23. In other embodiments, the various pharmaceutical formulations provided herein comprise a humanized antibody comprising a VH region that includes a VH FR4 having an amino acid sequence of SEQ ID NO:22.

[0517] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VL region that comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:16 and 18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VL region that comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NOS:16; and/or (4) a VL FR4 having an amino

acid sequence of SEQ ID NO:17. In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VL region that comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO: 18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17.

[0518] Accordingly, in some embodiments, the various pharmaceutical formulations provided herein comprise a humanized antibody that comprises a VL region that includes a VL FR1 having an amino acid sequence of SEQ ID NO:14. In certain embodiments, the various pharmaceutical formulations provided herein comprise a humanized antibody that comprises a VL region that includes a VL FR2 having an amino acid sequence of SEQ ID NO:15. In other embodiments, the various pharmaceutical formulations provided herein comprise a humanized antibody that comprises a VL region that includes a VL FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:16 and 18. In one embodiment, the various pharmaceutical formulations provided herein comprise a humanized antibody that comprises a VL region that includes a VL FR3 having an amino acid sequence of SEQ ID NOS:16. In other embodiments, the various pharmaceutical formulations provided herein comprise a humanized antibody that comprises a VL region that includes a VL FR3 having an amino acid sequence of SEQ ID NO: 18. In yet other embodiments, the various pharmaceutical formulations provided herein comprise a humanized antibody that comprises a VL region that includes a VL FR4 having an amino acid sequence of SEQ ID NO:17.

[0519] In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence selected from the group consisting of SEQ ID NOS:19 and 24; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:21 and 23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence selected from the group consisting of SEQ ID NOS:16 and 18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region

comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0520] In certain embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:16; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0521] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:21; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having

an amino acid sequence of SEQ ID NO:18; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0522] In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence of SEQ ID NO:23; and/or (4) a VH FR4 having an amino acid sequence of SEQ ID NO:22; and wherein the VL region comprises: (1) a VL FR1 having an amino acid sequence of SEQ ID NO:14; (2) a VL FR2 having an amino acid sequence of SEQ ID NO:15; (3) a VL FR3 having an amino acid sequence of SEQ ID NO:16; and/or (4) a VL FR4 having an amino acid sequence of SEQ ID NO:17. In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4. In other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4. In yet other embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region comprising all four of the above-referenced VH FR1, VH FR2, VH FR3, and VH FR4, and a VL region comprising all four of the above-referenced VL FR1, VL FR2, VL FR3, and VL FR4.

[0523] In some embodiments, the various pharmaceutical formulations provided herein comprise an antibody comprising a VH region and a VL region, wherein the VH region comprises: (1) a VH FR1 having an amino acid sequence of SEQ ID NO:19; (2) a VH FR2 having an amino acid sequence of SEQ ID NO:20; (3) a VH FR3 having an amino acid sequence

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WHAT IS CLAIMED:

1. A pharmaceutical formulation comprising an antibody or antigen-binding fragment thereof that
 - (a) binds to an epitope of human PD-1 recognized by an antibody comprising a light chain variable region having an amino acid sequence of SEQ ID NO:8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO:13; or
 - (b) competes for the binding to human PD-1 with an antibody comprising a light chain variable region having an amino acid sequence of SEQ ID NO:8 and a heavy chain variable region having an amino acid sequence of SEQ ID NO:13.
2. A pharmaceutical formulation comprising an antibody or antigen-binding fragment thereof that binds to PD-1, wherein the antibody or antigen-binding fragment thereof comprises:
 - (a) a light chain variable region (VL) comprising VL complementarity determining region 1 (CDR1), VL CDR2, and VL CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in Table 1; and/or
 - (b) a heavy chain variable region (VH) comprising VH complementarity determining region 1 (CDR1), VH CDR2, and VH CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in Table 2.
3. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
 - (a) a light chain variable region (VL) further comprising VL framework 1 (FR1), VL FR2, VL FR3, and VL FR4 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in Table 3; and/or

- (b) a heavy chain variable region (VH) further comprising VH framework 1 (FR1), VH FR2, VH FR3, and VH FR4 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in Table 4.
4. The pharmaceutical formulation of claim 2, wherein the VL CDR1, VL CDR2, and VL CDR3 comprise amino acid sequences of SEQ ID NOS:1, 2, and 3, respectively, and the VH CDR1, VH CDR2, and VH CDR3 comprise amino acid sequences of SEQ ID NOS:4, 5, and 6, respectively.
 5. The pharmaceutical formulation of claim 2, wherein the VL CDR1, VL CDR2, and VL CDR3 comprise amino acid sequences of SEQ ID NOS:7, 2, and 3, respectively, and the VH CDR1, VH CDR2, and VH CDR3 comprise amino acid sequences of SEQ ID NOS:4, 5, and 6, respectively.
 6. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises a VL comprising an amino acid sequence of SEQ ID NO:8.
 7. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises a VL comprising an amino acid sequence of SEQ ID NO:9.
 8. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises a VL comprising an amino acid sequence of SEQ ID NO:10.
 9. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises a VH comprising an amino acid sequence of SEQ ID NO:11.
 10. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises a VH comprising an amino acid sequence of SEQ ID NO:12.
 11. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises a VH comprising an amino acid sequence of SEQ ID NO:13.
 12. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:

- (a) a VL comprising an amino acid sequence of SEQ ID NO:8; and
 - (b) a VH comprising an amino acid sequence of SEQ ID NO:11.
13. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a VL comprising an amino acid sequence of SEQ ID NO:9; and
 - (b) a VH comprising an amino acid sequence of SEQ ID NO:11.
14. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a VL comprising an amino acid sequence of SEQ ID NO:10; and
 - (b) a VH comprising an amino acid sequence of SEQ ID NO:11.
15. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a VL comprising an amino acid sequence of SEQ ID NO:8; and
 - (b) a VH comprising an amino acid sequence of SEQ ID NO:12.
16. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a VL comprising an amino acid sequence of SEQ ID NO:9; and
 - (b) a VH comprising an amino acid sequence of SEQ ID NO:12.
17. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a VL comprising an amino acid sequence of SEQ ID NO:10; and
 - (b) a VH comprising an amino acid sequence of SEQ ID NO:12.

18. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
 - (a) a VL comprising an amino acid sequence of SEQ ID NO:8; and
 - (b) a VH comprising an amino acid sequence of SEQ ID NO:13.
19. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
 - (a) a VL comprising an amino acid sequence of SEQ ID NO:9; and
 - (b) a VH comprising an amino acid sequence of SEQ ID NO:13.
20. The pharmaceutical formulation of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
 - (a) a VL comprising an amino acid sequence of SEQ ID NO:10; and
 - (b) a VH comprising an amino acid sequence of SEQ ID NO:13.
21. The pharmaceutical formulation of any one of claims 1-20, wherein the antibody or antigen-binding fragment thereof comprises a human IgG1 Fc region or a mutant thereof.
22. The pharmaceutical formulation of any one of claims 1-20, wherein the antibody or antigen-binding fragment thereof comprises a human IgG1-K322A Fc region.
23. The pharmaceutical formulation of any one of claims 1-20, wherein the antibody or antigen-binding fragment thereof comprises a human IgG4 Fc region or a mutant thereof.
24. The pharmaceutical formulation of any one of claims 1-20, wherein the antibody or antigen-binding fragment thereof comprises a human IgG4P Fc region.
25. The pharmaceutical formulation of any one of claims 1-20, wherein the antibody or antigen-binding fragment thereof comprises a human IgG4PE Fc region.

26. The pharmaceutical formulation of any one of claims 1-20, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain Fc region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:36-40.
27. The pharmaceutical formulation of claim 26, wherein the antibody or antigen-binding fragment thereof further comprises a light chain constant region comprising an amino acid sequence of SEQ ID NO:41.
28. The pharmaceutical formulation of any one of claims 1-20, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a light chain constant region comprising an amino acid sequence of SEQ ID NO:41; and
 - (b) a heavy chain Fc region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:36-40.
29. The pharmaceutical formulation of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence of SEQ ID NO:31.
30. The pharmaceutical formulation of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:32.
31. The pharmaceutical formulation of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a light chain comprising an amino acid sequence of SEQ ID NO:31; and
 - (b) a heavy chain comprising an amino acid sequence of SEQ ID NO:32.
32. The pharmaceutical formulation of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:33.

33. The pharmaceutical formulation of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a light chain comprising an amino acid sequence of SEQ ID NO:31; and
 - (b) a heavy chain comprising an amino acid sequence of SEQ ID NO:33.
34. The pharmaceutical formulation of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:34.
35. The pharmaceutical formulation of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a light chain comprising an amino acid sequence of SEQ ID NO:31; and
 - (b) a heavy chain comprising an amino acid sequence of SEQ ID NO:34.
36. The pharmaceutical formulation of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence of SEQ ID NO:35.
37. The pharmaceutical formulation of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof comprises:
- (a) a light chain comprising an amino acid sequence of SEQ ID NO:31; and
 - (b) a heavy chain comprising an amino acid sequence of SEQ ID NO:35.
38. The pharmaceutical formulation of any one of claims 1-37, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to at least one of residues 100-109 within an amino acid sequence of SEQ ID NO:42.
39. The pharmaceutical formulation of claim 38, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to at least one of residues 100-105 within an amino acid sequence of SEQ ID NO:42.

40. The pharmaceutical formulation of any one of claims 1-37, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to at least one residue selected from the group consisting of N33, T51, S57, L100, N102, G103, R104, D105, H107, and S109 within an amino acid sequence of SEQ ID NO:42.
41. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to N33 within an amino acid sequence of SEQ ID NO:42.
42. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to T51 within an amino acid sequence of SEQ ID NO:42.
43. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to S57 within an amino acid sequence of SEQ ID NO:42.
44. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to L100 within an amino acid sequence of SEQ ID NO:42.
45. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to N102 within an amino acid sequence of SEQ ID NO:42.
46. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to G103 within an amino acid sequence of SEQ ID NO:42.
47. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to R104 within an amino acid sequence of SEQ ID NO:42.

48. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to D105 within an amino acid sequence of SEQ ID NO:42.
49. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to H107 within an amino acid sequence of SEQ ID NO:42.
50. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to S109 within an amino acid sequence of SEQ ID NO:42.
51. The pharmaceutical formulation of claim 40, wherein, when bound to PD-1, the antibody or antigen-binding fragment binds to G103 and R104 within an amino acid sequence of SEQ ID NO:42.
52. The pharmaceutical formulation of any one of claims 1-51, wherein the antibody or antigen-binding fragment thereof:
- (a) attenuates T cell activity; and/or
 - (b) downregulates PD-1 expression on the surface of T cells.
53. The pharmaceutical formulation of any one of claims 1-52, wherein the antibody or antigen-binding fragment thereof specifically binds to human PD-1 and/or monkey PD-1, but not rodent PD-1.
54. The pharmaceutical formulation of any one of claims 1-53, wherein the antibody or antigen-binding fragment thereof has attenuated ADCC activity and/or attenuated CDC activity.
55. The pharmaceutical formulation of claim 52, wherein the attenuation of T cell activity occurs in human PBMC or whole blood samples.

56. The pharmaceutical formulation of claim 52 or 55, wherein the attenuation of T cell activity is measured by inhibition of cytokine production.
57. The pharmaceutical formulation of claim 56, wherein the cytokine that is inhibited by the antibody or antigen-binding fragment thereof comprises IL-1, IL-2, IL-6, IL-12, IL-17, IL-22, IL-23, GM-CSF, TNF- α , and/or IFN- γ .
58. The pharmaceutical formulation of claim 52, wherein the downregulation of PD-1 expression on the surface of T cells:
- (a) occurs as early as 4 hours after the treatment with the antibody or antigen-binding fragment thereof; and/or
 - (b) is concurrent with or precedes cytokine inhibition.
59. The pharmaceutical formulation of claim 53, wherein the K_D for binding to purified human PD-1 is from about 100 pM to about 10 nM, and the K_D for binding to human PD-1 expressed on cell surface and monkey PD-1 expressed on cell surface is from about 100 pM to about 10 nM.
60. The pharmaceutical formulation of claim 56, wherein the EC_{50} for attenuating T cell activity is from about 1 pM to about 10 pM, from about 10 pM to about 100 pM, from about 100 pM to about 1 nM, from about 1 nM to about 10 nM, or from about 10 nM to about 100 nM.
61. The pharmaceutical formulation of claim 56, wherein the maximal percent attenuation of T cell activity is at least about 10%, 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.
62. The pharmaceutical formulation of claim 52 or 58, wherein the maximal percent downregulation of PD-1 expression is at least about 10%, 20%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.
63. The pharmaceutical formulation of any one of claims 1-62, wherein the antibody is a monoclonal antibody.

64. The pharmaceutical formulation of any one of claims 1-63, wherein the antibody is a humanized, human, or chimeric antibody.
65. The pharmaceutical formulation of claim 64, wherein the humanized antibody is a deimmunized antibody or a composite human antibody.
66. The pharmaceutical formulation of any one of claims 1-65, wherein the antibody or antigen-binding fragment thereof is a Fab, a Fab', a F(ab')₂, a Fv, a scFv, a dsFv, a diabody, a triabody, a tetrabody, or a multispecific antibody formed from antibody fragments.
67. The pharmaceutical formulation of any one of claims 1-66, wherein the antibody or antigen-binding fragment thereof is conjugated to an agent.
68. The pharmaceutical formulation of claim 67, wherein the agent is selected from the group consisting of a radioisotope, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound, and a chemiluminescent compound.
69. The pharmaceutical formulation of any one of claims 1-68, further comprising a buffer system.
70. The pharmaceutical formulation of claim 69, wherein the buffer system is selected from the group consisting of acetate buffer, succinate buffer, histidine buffer, and citrate buffer.
71. The pharmaceutical formulation of claim 70, wherein the buffer system is acetate buffer.
72. The pharmaceutical formulation of claim 70, wherein the buffer system is succinate buffer.
73. The pharmaceutical formulation of claim 70, wherein the buffer system is histidine buffer.
74. The pharmaceutical formulation of claim 70, wherein the buffer system is citrate buffer.

75. The pharmaceutical formulation of any one of claims 1-69, wherein the concentration of the buffer system is within the range of 0.1 mM to 1 M.
76. The pharmaceutical formulation of claim 75, wherein the concentration of the buffer system is within the range of 1 mM to 100 mM.
77. The pharmaceutical formulation of claim 76, wherein the concentration of the buffer system is 10 mM.
78. The pharmaceutical formulation of any one of claims 1-77, wherein the pH of the buffer system is within the range of pH 4-6.5.
79. The pharmaceutical formulation of claim 78, wherein the pH of the buffer system is within the range of pH 4.7-5.7.
80. The pharmaceutical formulation of claim 79, wherein the pH of the buffer system is pH 5.2.
81. The pharmaceutical formulation of any one of claims 1-80, further comprising a polyol.
82. The pharmaceutical formulation of claim 81, wherein the polyol is selected from the group consisting of sugar, sugar alcohol, and sugar acid.
83. The pharmaceutical formulation of claim 82, wherein the polyol is sugar.
84. The pharmaceutical formulation of claim 83, wherein the sugar is sucrose.
85. The pharmaceutical formulation of claim 84, wherein the concentration of the sucrose is within the range of 5-10% (w/v).
86. The pharmaceutical formulation of claim 85, wherein the concentration of the sucrose is 8.5% (w/v).
87. The pharmaceutical formulation of any one of claims 1-86, further comprising a surfactant.

88. The pharmaceutical formulation of claim 87, wherein the surfactant is polysorbate-20.
89. The pharmaceutical formulation of claim 87, wherein the surfactant is polysorbate-80.
90. The pharmaceutical formulation of claim 89, wherein the concentration of the polysorbate-80 is within the range of 0.001-0.1% (w/v).
91. The pharmaceutical formulation of claim 90, wherein the concentration of the polysorbate-80 is 0.005% (w/v).
92. A pharmaceutical formulation comprising an antibody or antigen-binding fragment thereof that binds to PD-1, 10 mM sodium acetate buffer (pH 5.2), 8.5% (w/v) sucrose, and 0.005% (w/v) polysorbate-80.
93. The pharmaceutical formulation of claim 92, wherein the antibody or antigen-binding fragment thereof comprises:
 - (a) a light chain variable region (VL) comprising VL complementarity determining region 1 (CDR1), VL CDR2, and VL CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in Table 1; and/or
 - (b) a heavy chain variable region (VH) comprising VH complementarity determining region 1 (CDR1), VH CDR2, and VH CDR3 of any one of antibodies PD1AB-1, PD1AB-2, PD1AB-3, PD1AB-4, PD1AB-5, or PD1AB-6 as set forth in Table 2.
94. The pharmaceutical formulation of any one of claims 1-93, wherein the pharmaceutical formulation is stable for at least 12 months when stored at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$.
95. The pharmaceutical formulation of any one of claims 1-93, wherein the pharmaceutical formulation is stable for at least 6 months when stored at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.
96. A method of making the pharmaceutical formulation of any one of claims 1-95, comprising:

- (a) culturing a cell in a medium, wherein the cell comprises one or more polynucleotides comprising nucleotide sequences encoding a heavy chain, a light chain, or both a heavy chain and a light chain of the antibody or antigen-binding fragment thereof;
 - (b) harvesting the medium;
 - (c) subjecting the medium to a series of purification steps.
97. The method of claim 96, wherein the purification steps comprise:
- (a) an affinity chromatography;
 - (b) a viral inactivation;
 - (c) an ion exchange chromatography;
 - (d) a viral filtration; and
 - (e) an ultrafiltration/diafiltration.
98. The method of claim 97, wherein the affinity chromatography is a protein A affinity chromatography.
99. The method of claim 97, wherein the ion exchange chromatography is an anion exchange chromatography.
100. The method of claim 97, wherein the viral inactivation step is a low-pH viral inactivation step.
101. The method of any one of claims 96-100, further comprising a formulation step.

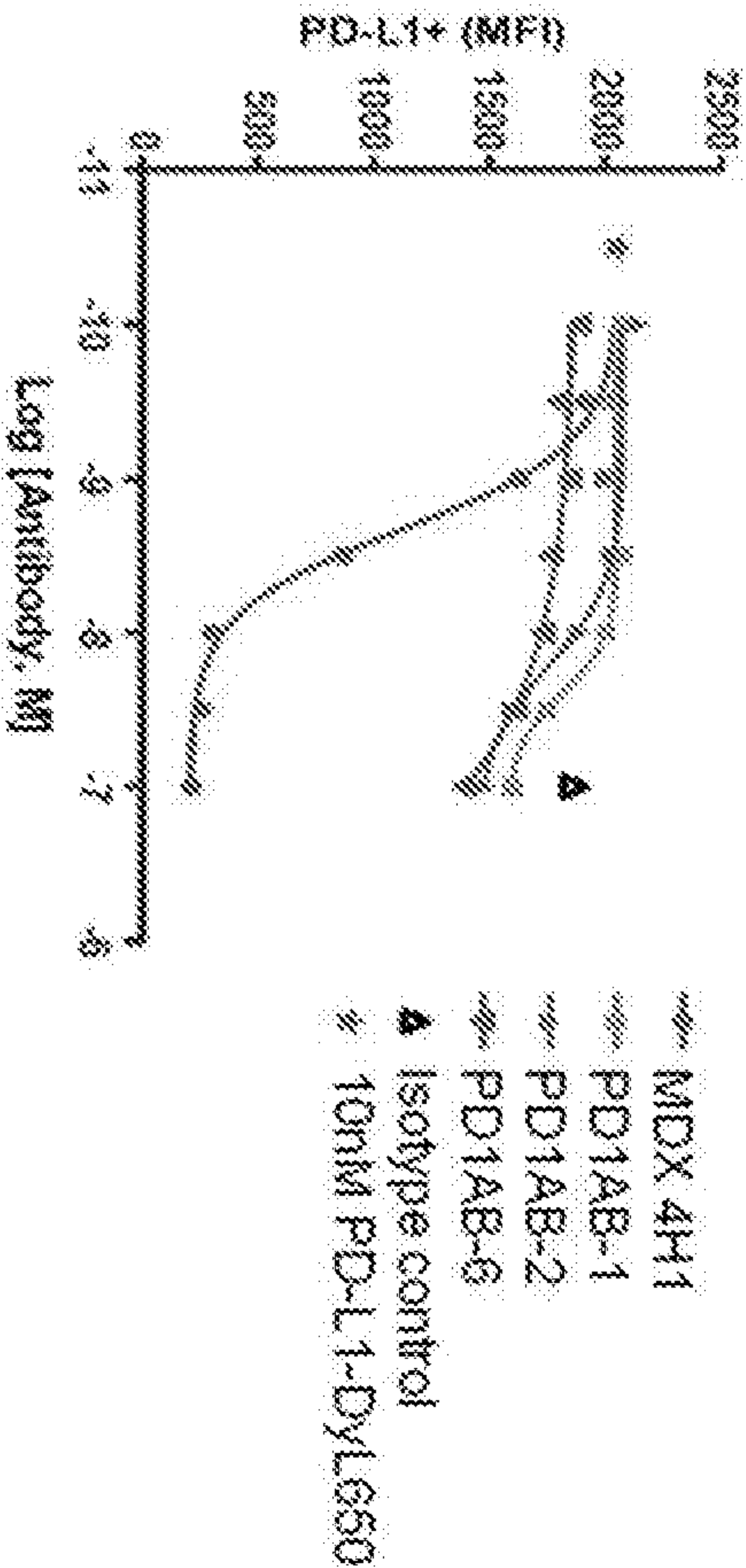


FIG. 1A

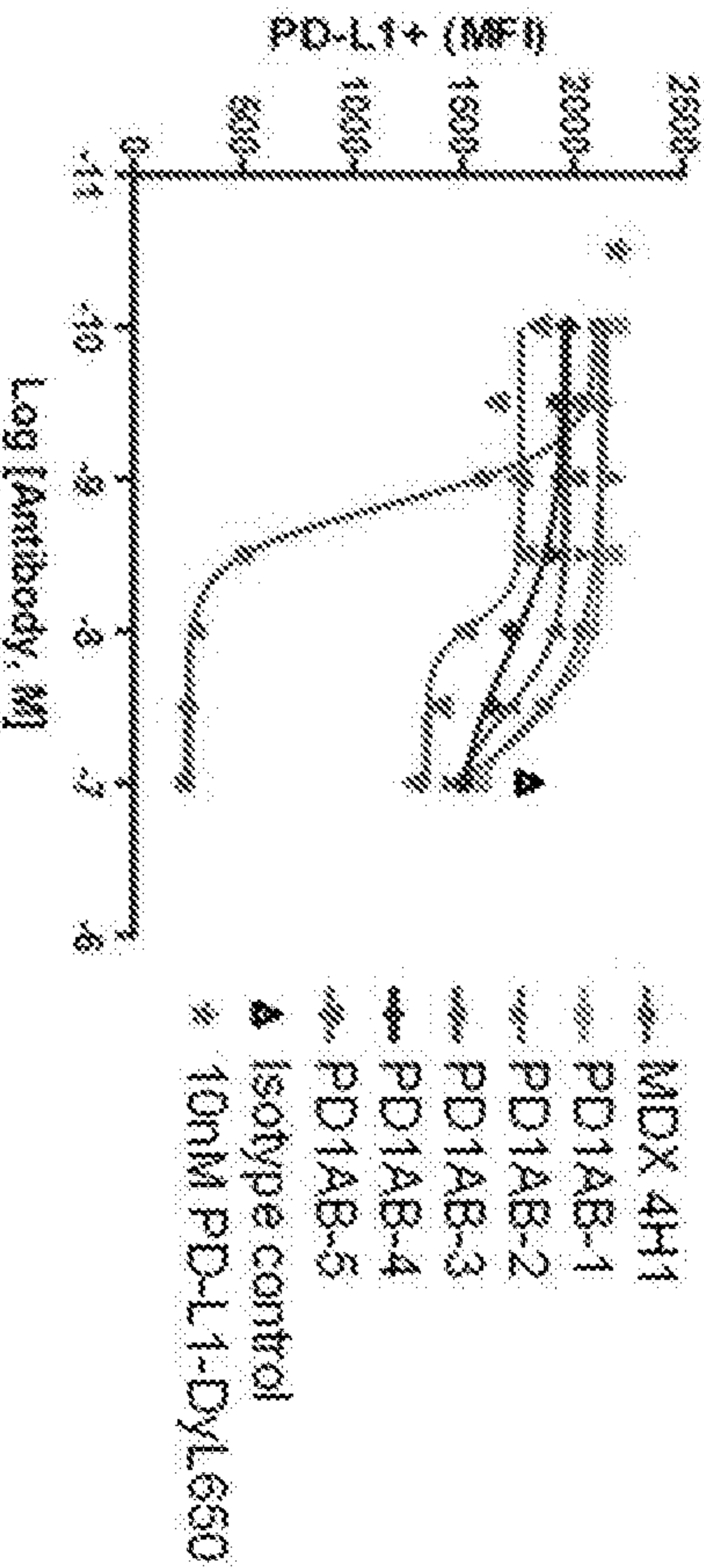
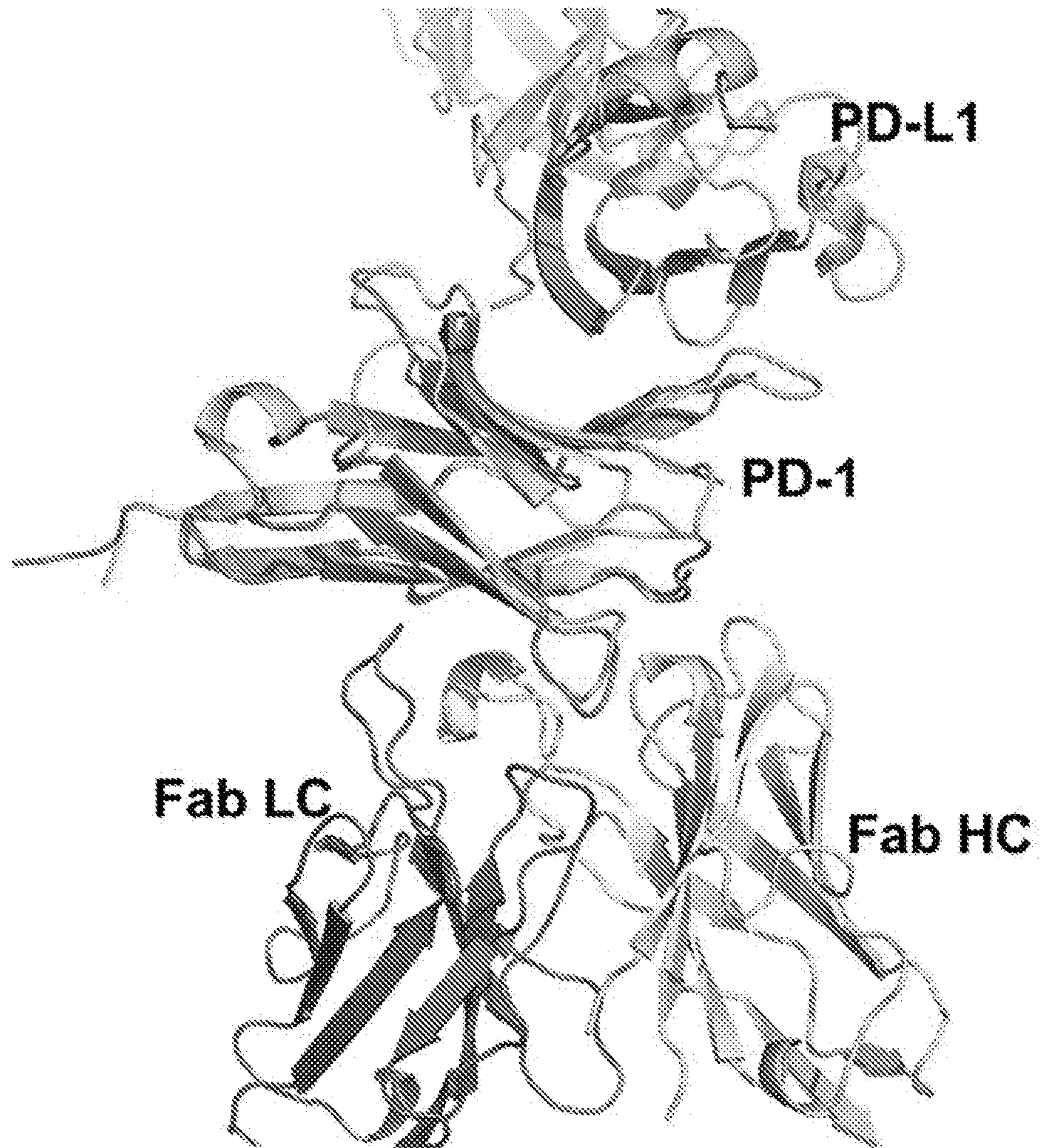
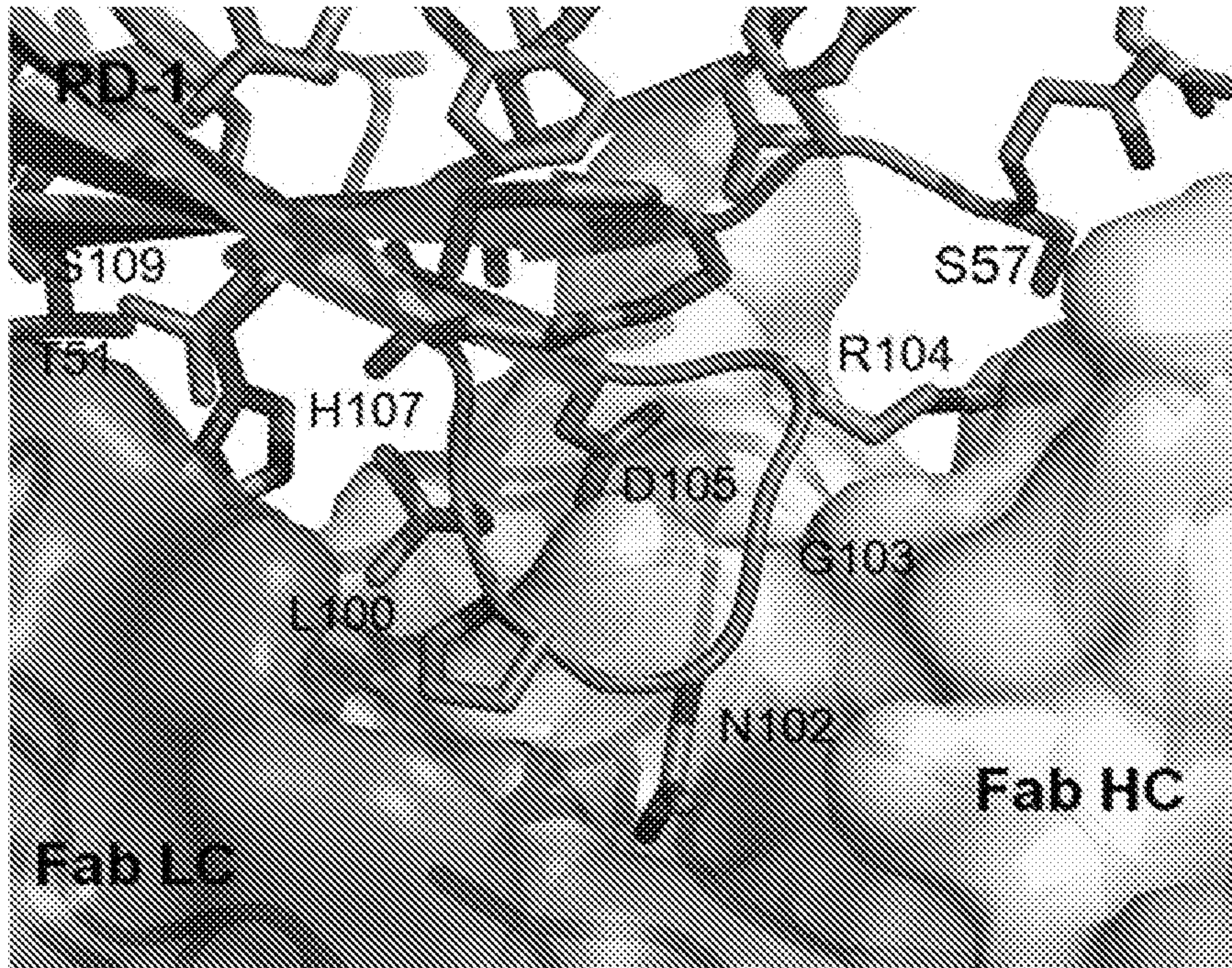


FIG. 1B

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**FIG. 2**

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**FIG. 3**

>LC_PDIAB-6-IgG1
DIVMTQSPDSLAVSLGERATINCKSGQSVLTSSNQKNLAWYQQKPGQPKLITYWASTLESGVPDRFSGSGGTDFITLTISSLAQAE
DVAVYYCHQYTLSSVTFGQGTKELEIKRIVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSITYSLSSHLILSKADYEEKIKVYACEVTHQGLSPVTKSFNRGEC

>HC_PDIAB-6-IgG1
EVQLVQSGAEVKKPGATVKISCKASQENNIKDTYIQLTWYQQAAPGKGLEWMGRIDDAKNDKKYTDKKIQGRVTITADISTDIAYMEIS
SLRSEDIAYYYCARSGPVYYTQSSYVMDYWGQGTITVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALISGVHITPAPLQSSGLYSLSVTVPPSSSLGTQTYICNVNHKPSNTKVDKVEPKSCDKHTHTCPPAPAEILGPPSVFLPPPKPD
TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLIHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSRDELIKNQVSLICLVKGFYPSDIAVEWESNGQPENNYKITTPVILDSGSEFLYSKLTVDKSRWQ
QGNVFSCSVMEALHNHYTQKSLSPGK

>HC_PDIAB-6-IgG1-K322A
EVQLVQSGAEVKKPGATVKISCKASQENNIKDTYIQLTWYQQAAPGKGLEWMGRIDDAKNDKKYTDKKIQGRVTITADISTDIAYMEIS
SLRSEDIAYYYCARSGPVYYTQSSYVMDYWGQGTITVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG
ALISGVHITPAPLQSSGLYSLSVTVPPSSSLGTQTYICNVNHKPSNTKVDKVEPKSCDKHTHTCPPAPAEILGPPSVFLPPPKPD
TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLIHQDWLNGKEYKCAVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSRDELIKNQVSLICLVKGFYPSDIAVEWESNGQPENNYKITTPVILDSGSEFLYSKLTVDKSRWQ
QGNVFSCSVMEALHNHYTQKSLSPGK

>HC_PDIAB-6-IgG4P
EVQLVQSGAEVKKPGATVKISCKASQENNIKDTYIQLTWYQQAAPGKGLEWMGRIDDAKNDKKYTDKKIQGRVTITADISTDIAYMEIS
SLRSEDIAYYYCARSGPVYYTQSSYVMDYWGQGTITVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALIS
GVHITPAPLQSSGLYSLSVTVPPSSSLGTQTYICNVNHKPSNTKVDKVEPKSCDKHTHTCPPAPAEILGPPSVFLPPPKPDITLMISRTPEV
CTVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLIHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQV
TLPPSOEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKITTPVILDSGSEFLYSKLTVDKSRWQEGNVFSCSVMEALHNHYTQ
KSLSPGK

FIG. 4

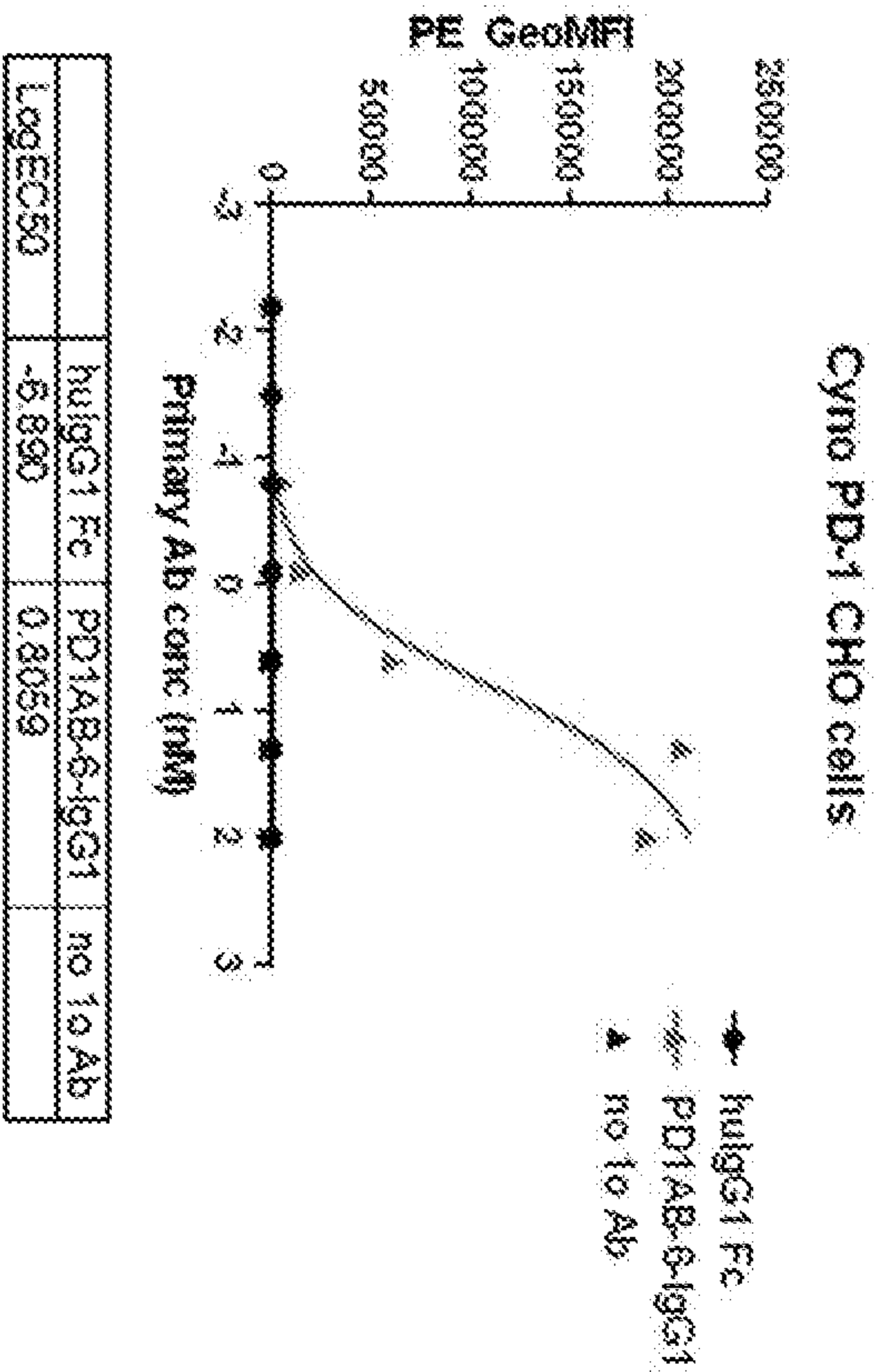


FIG. 5A

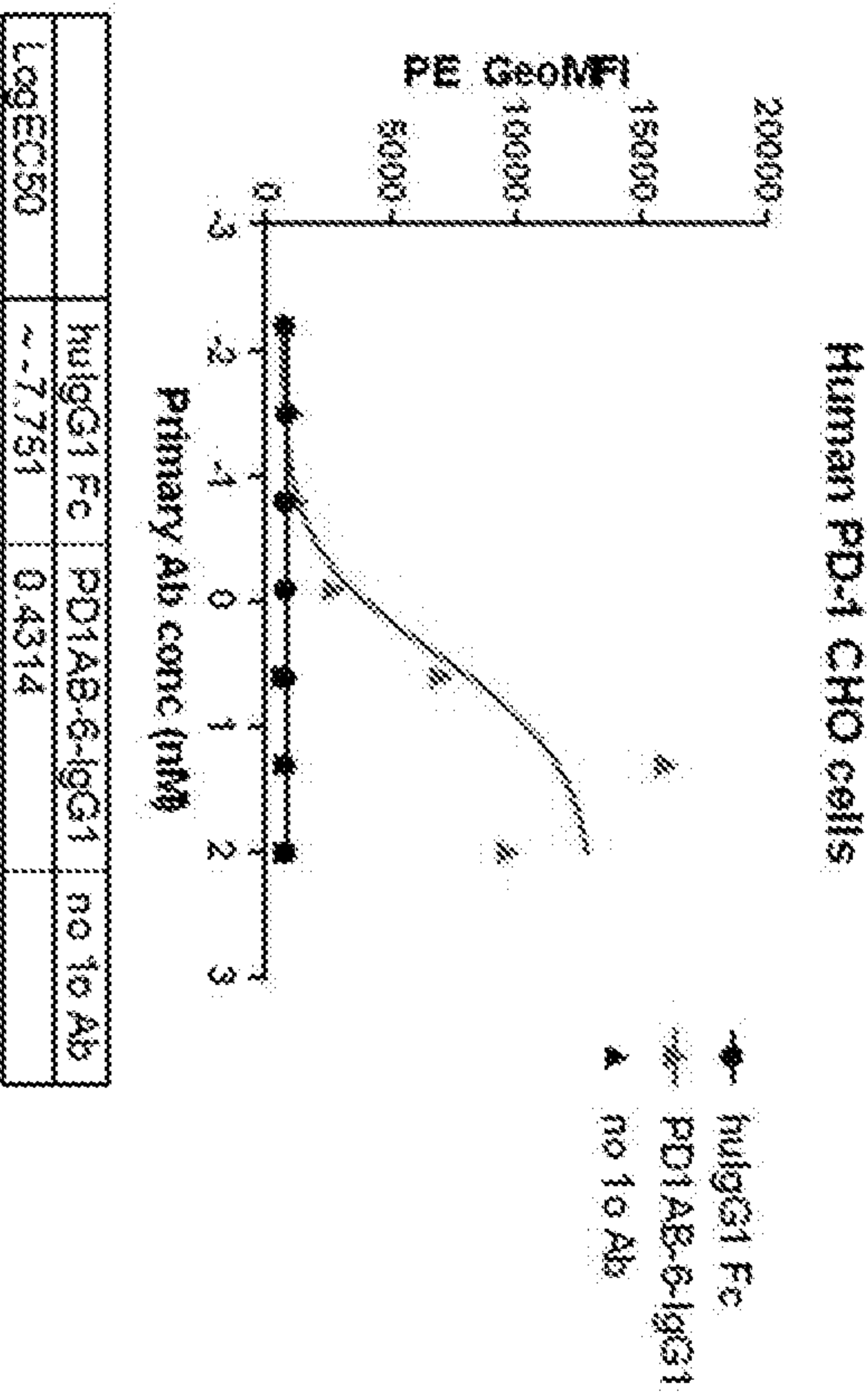


FIG. 5B

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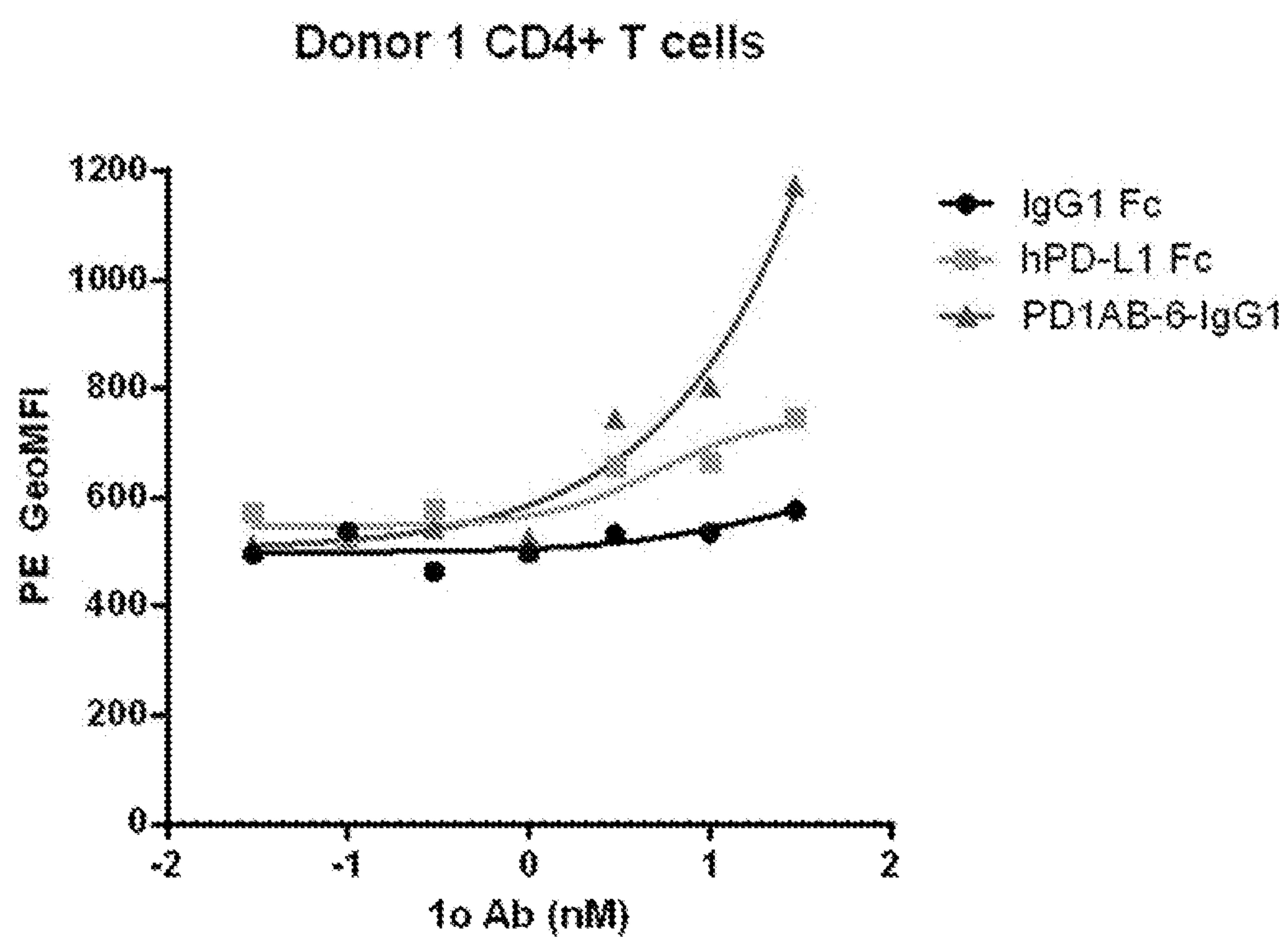
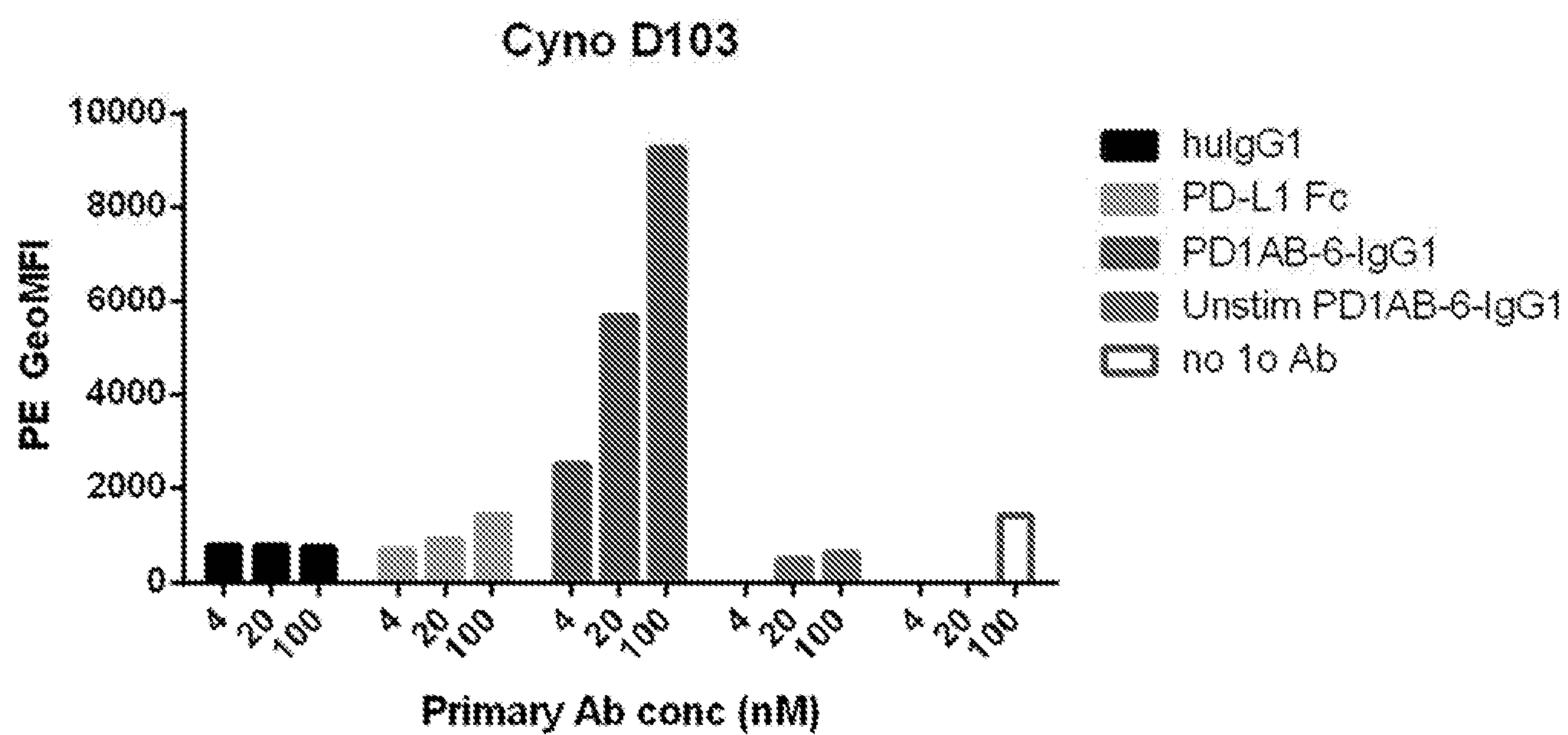


FIG. 6

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**FIG. 7**

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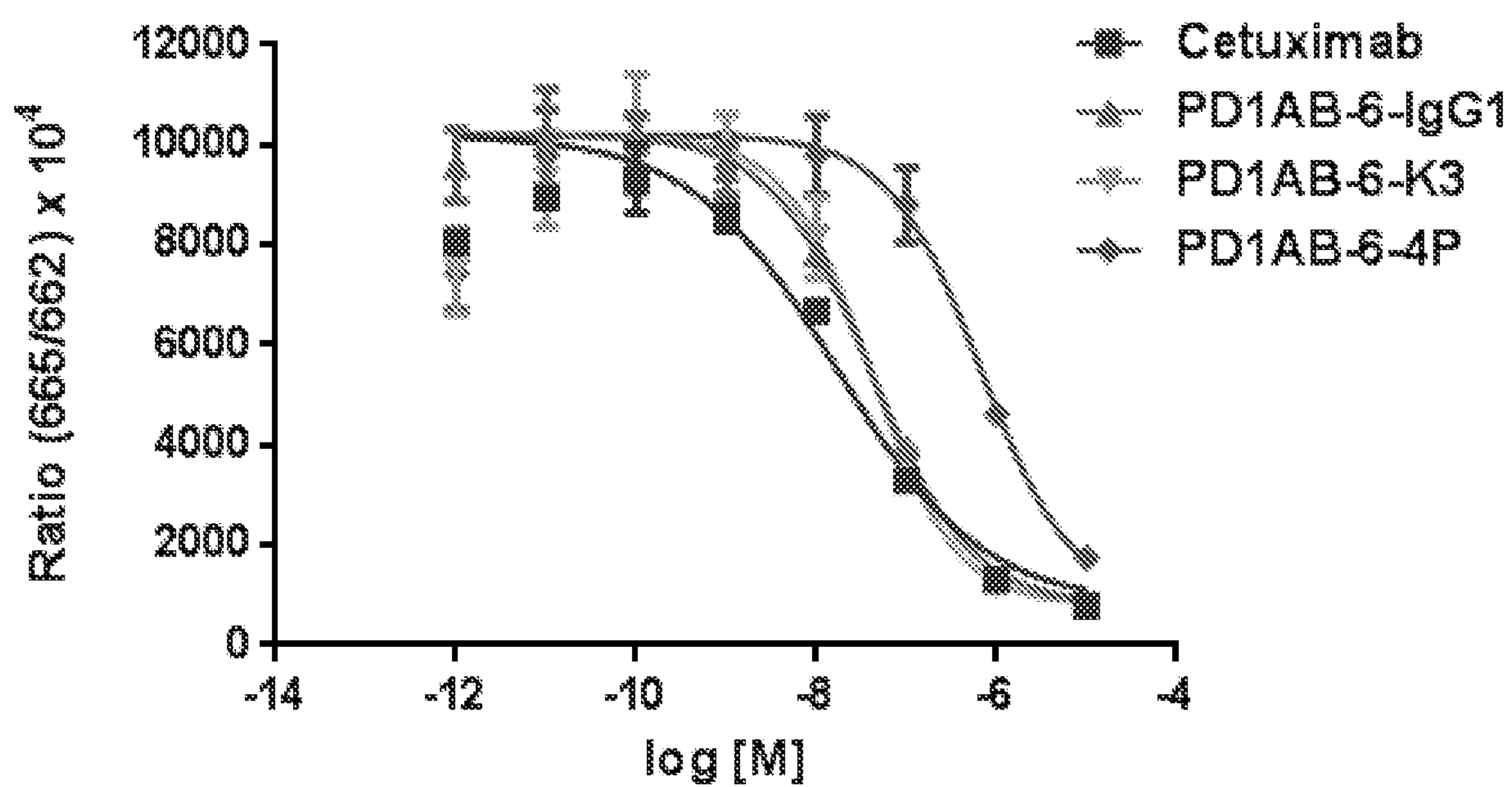


FIG. 8A

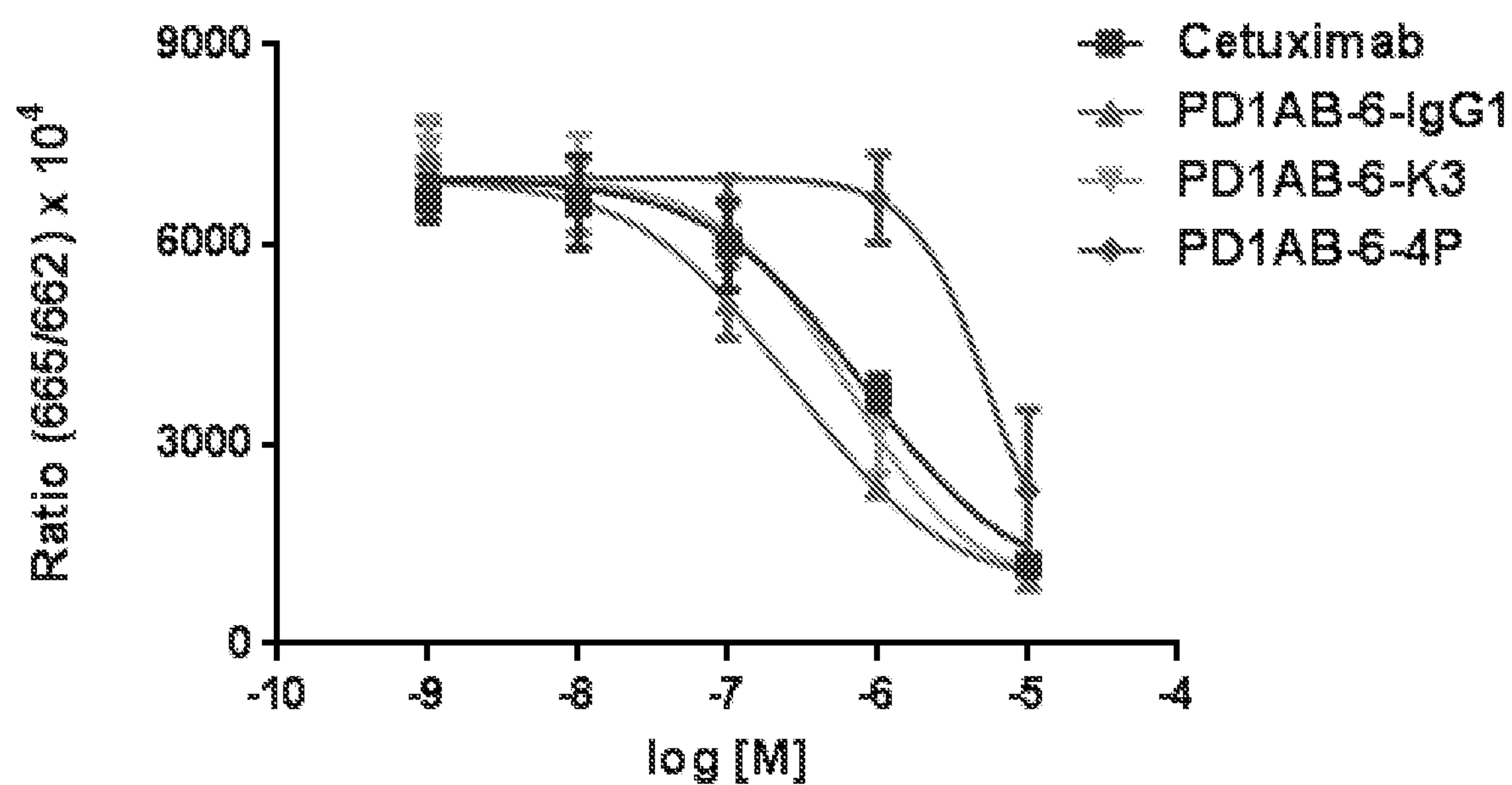


FIG. 8B

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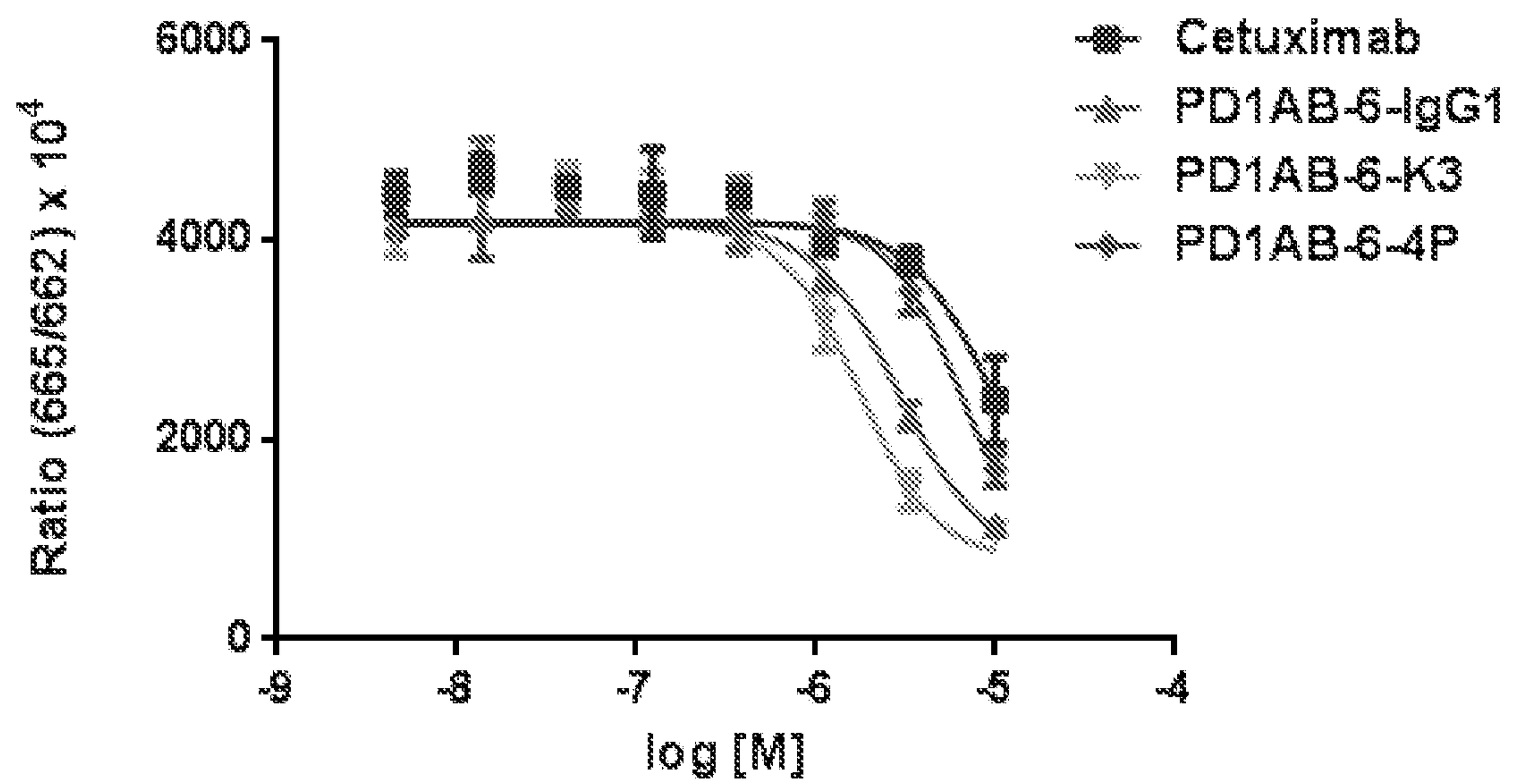


FIG. 8C

EC ₅₀ nM	FcγRI	FcγRIIIa (V158)	FcγRIIb
Cetuximab	33.1	915.7	9749.7
PD1AB-6-IgG1	54.7	293.9	2804.5
PD1AB-6-K3	56.0	622.6	1652.9
PD1AB-6-4P	868.9	6325.8	7179.1

FIG. 8D

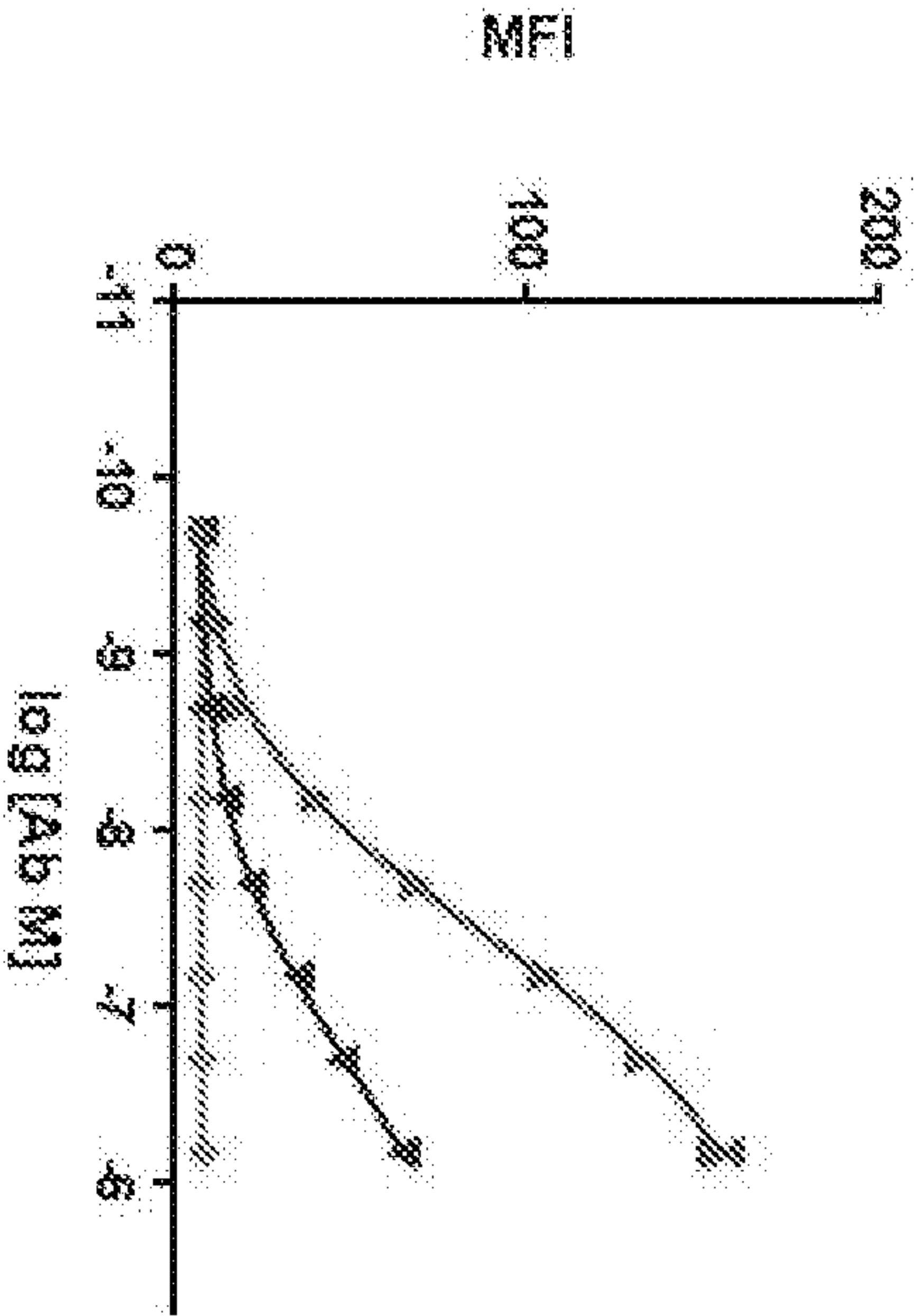


FIG. 9A

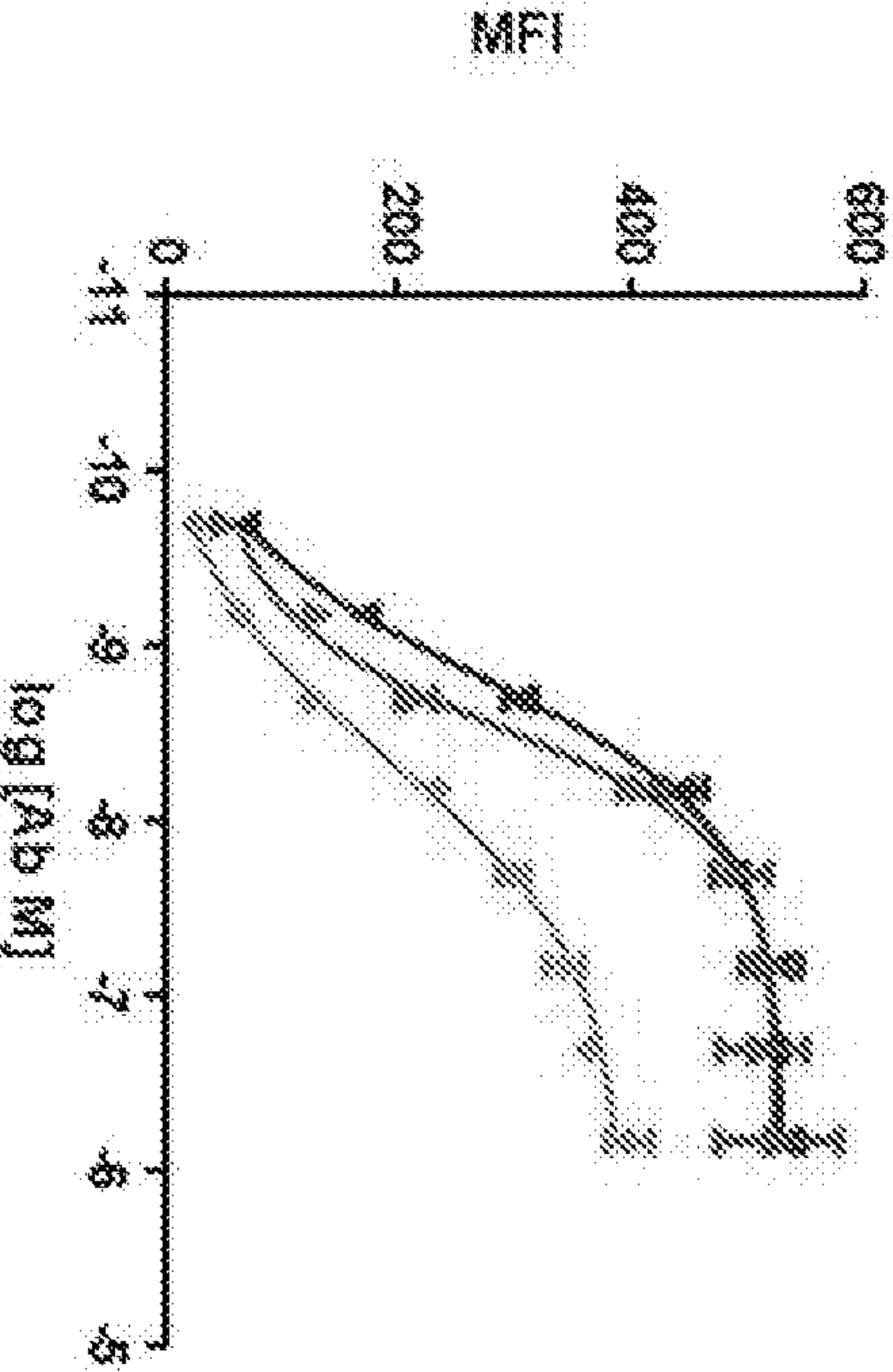


FIG. 9B

PD1AB-6-IgG1
PD1AB-6-K3
PD1AB-6-4P

EC ₅₀ (nM)	PD1AB-6-IgG1	PD1AB-6-K3	PD1AB-6-4P
FcγRI	2.6	1.5	12.4
FcγRIII	31.4	>666	NB

FIG. 9C

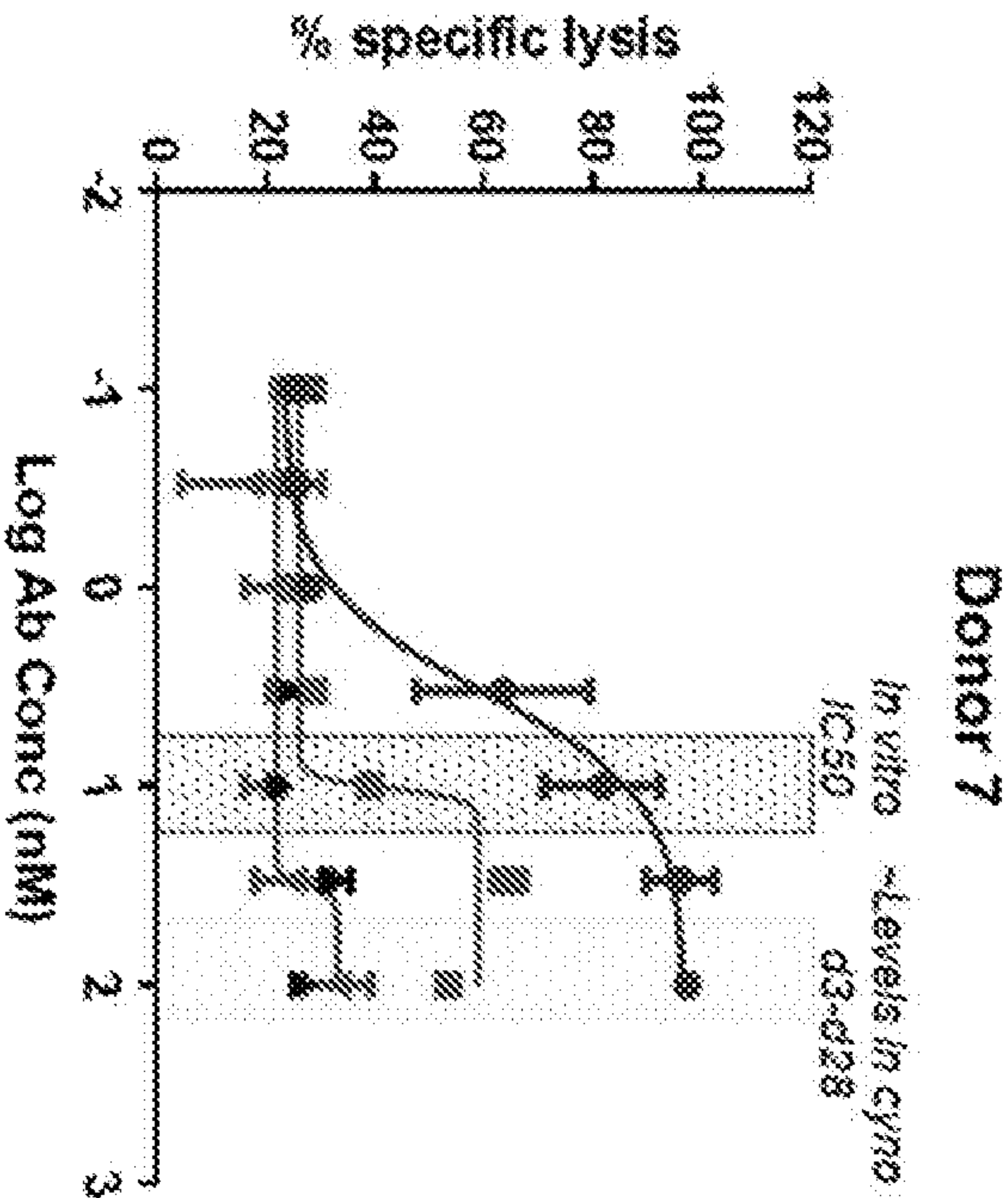


FIG. 10A

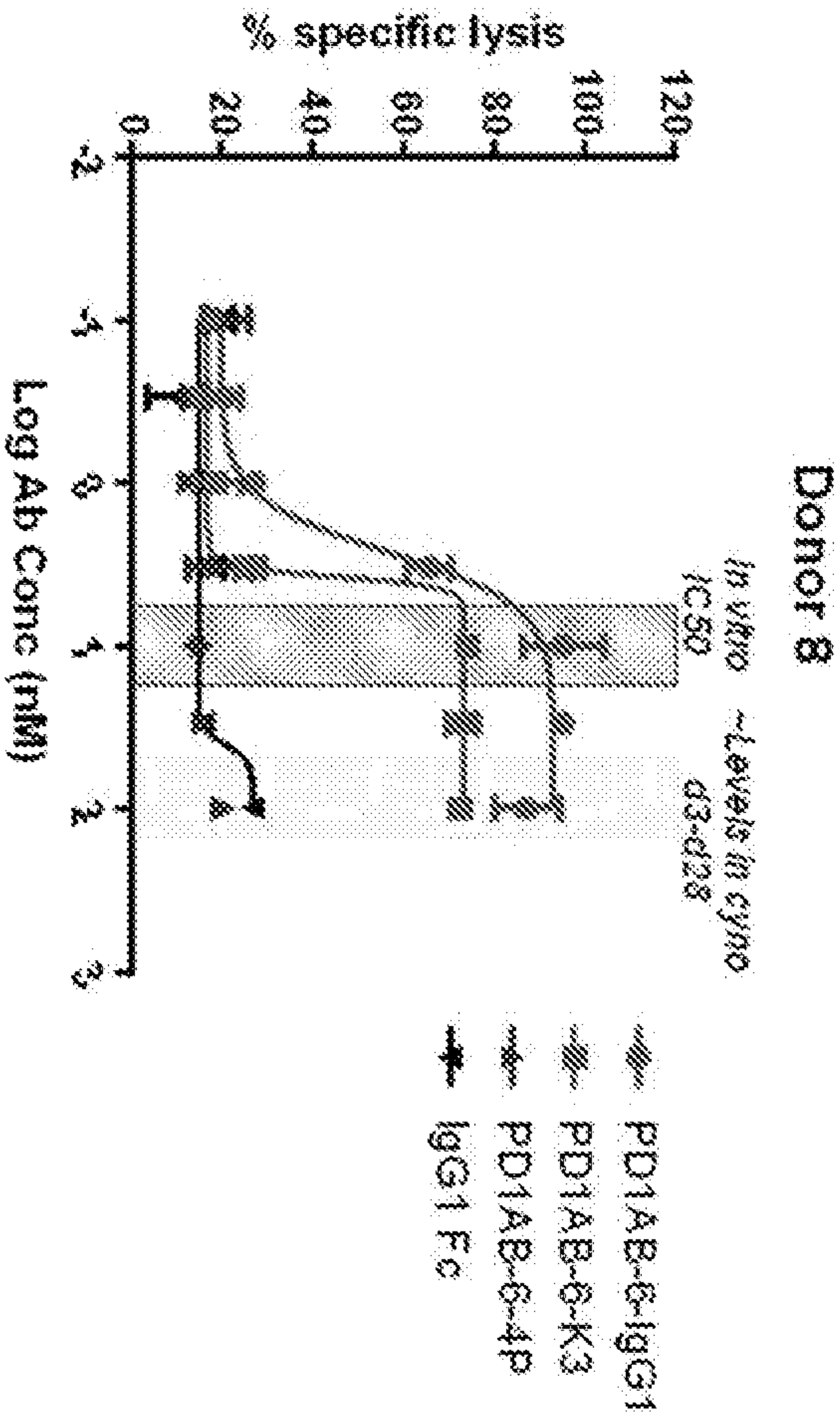


FIG. 10B

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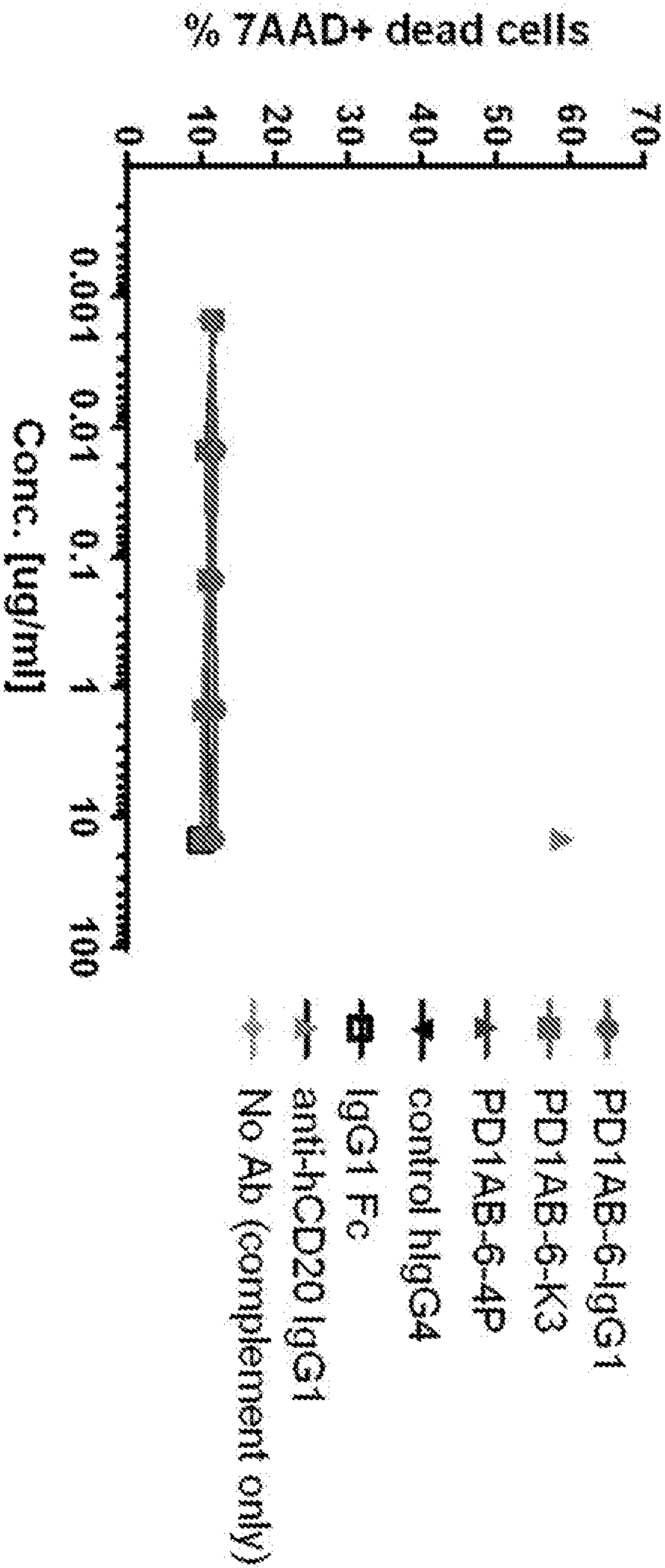
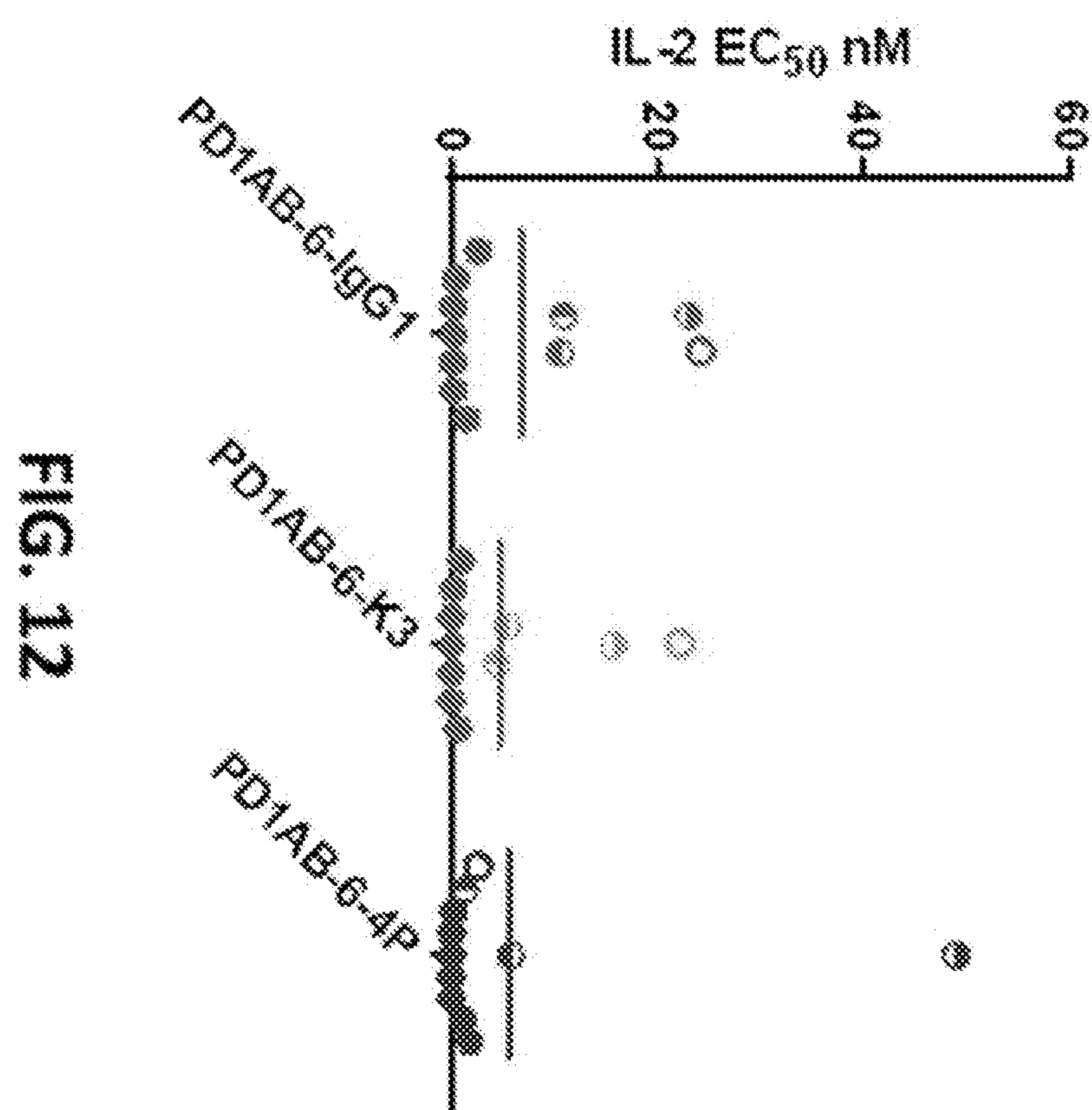
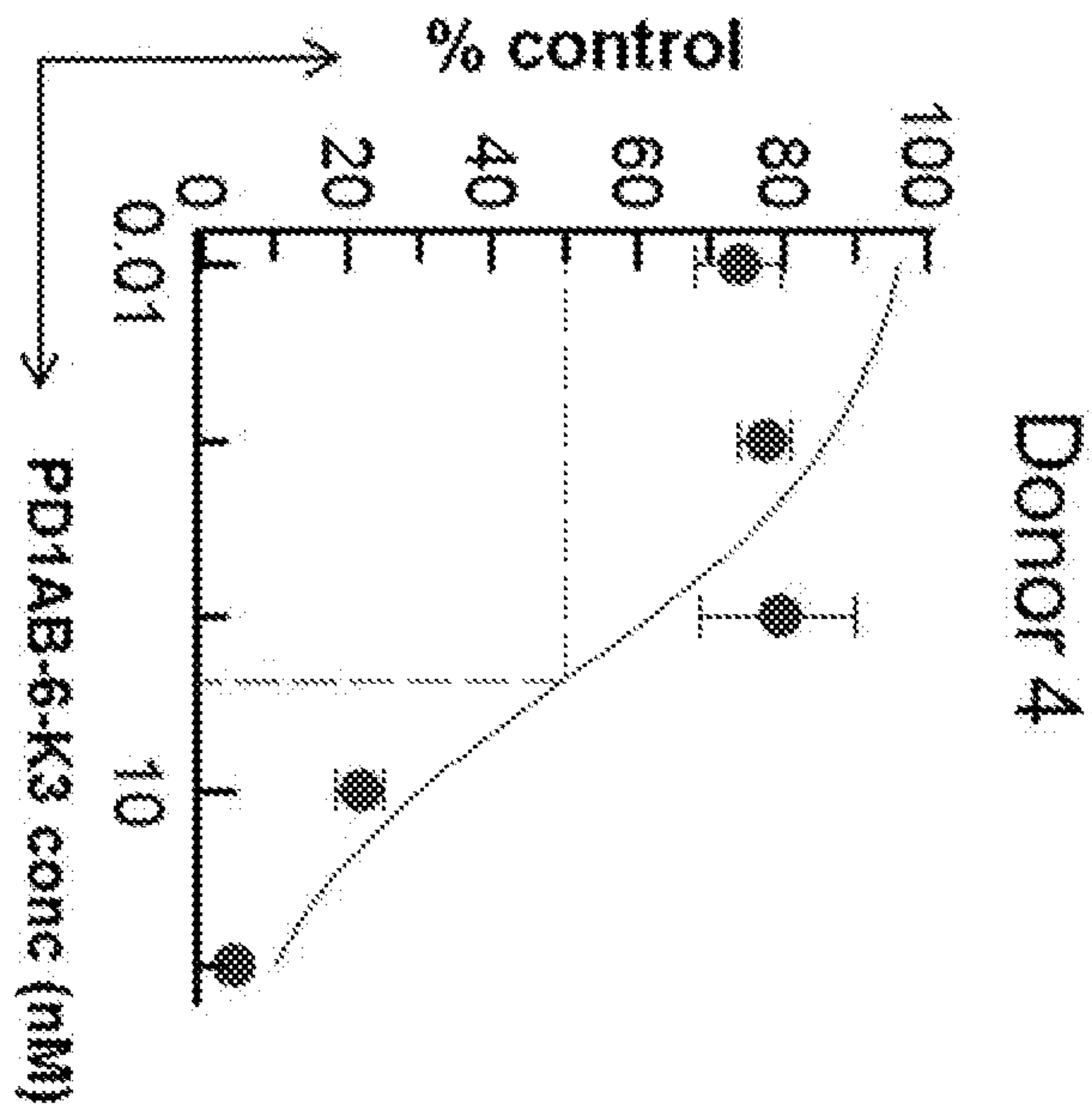


FIG. 11

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	PD1AB-6-K3	PD1AB-6-4P	CTLA4i8
	IFN- γ EC50 (nM)		
Donor 1	<0.01	<0.01	0.02
Donor 2	<0.01	0.02	<0.01
Donor 3	22.4	51	81
Donor 4	2.3	>100	9

FIG. 13

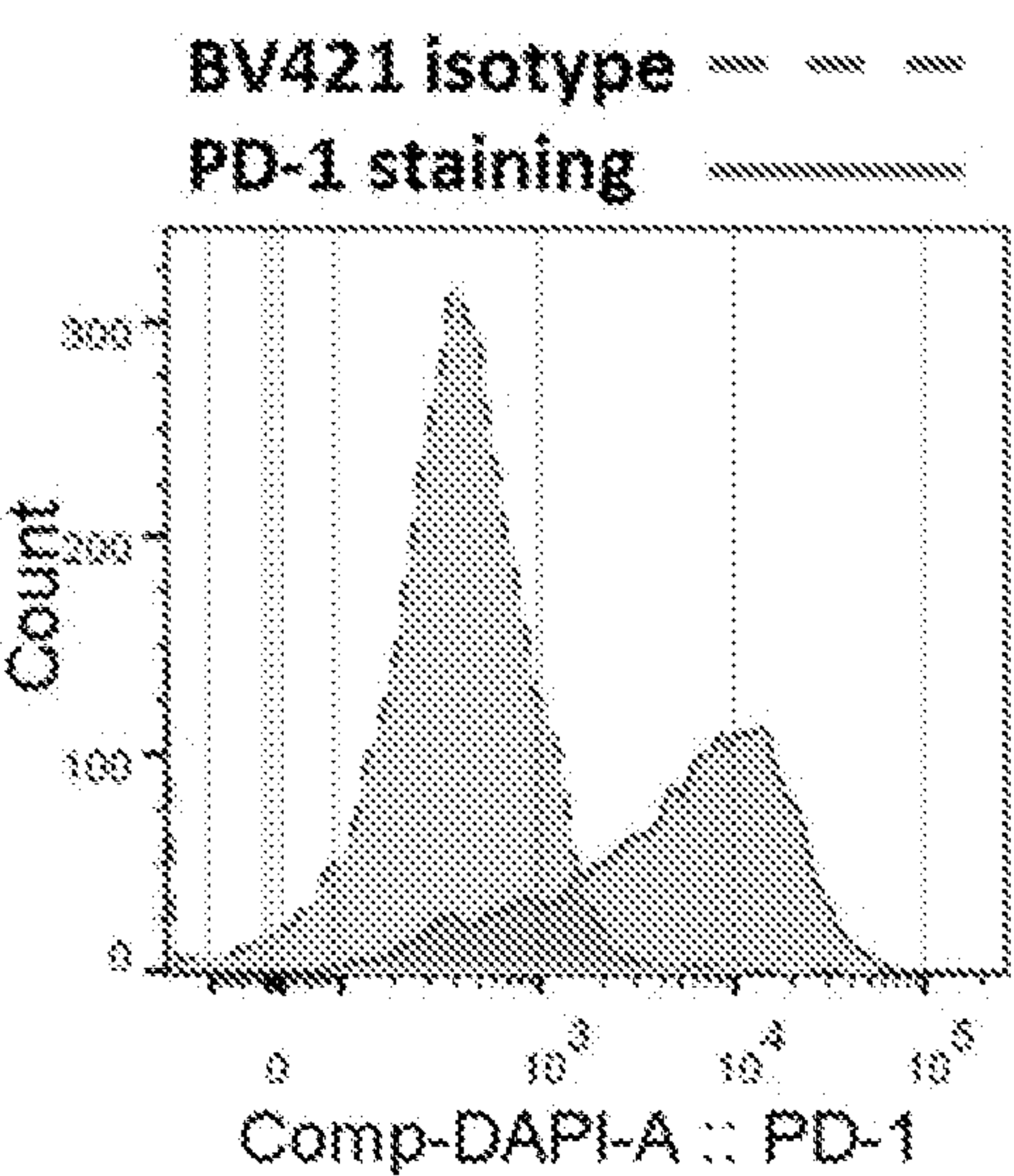


FIG. 14A

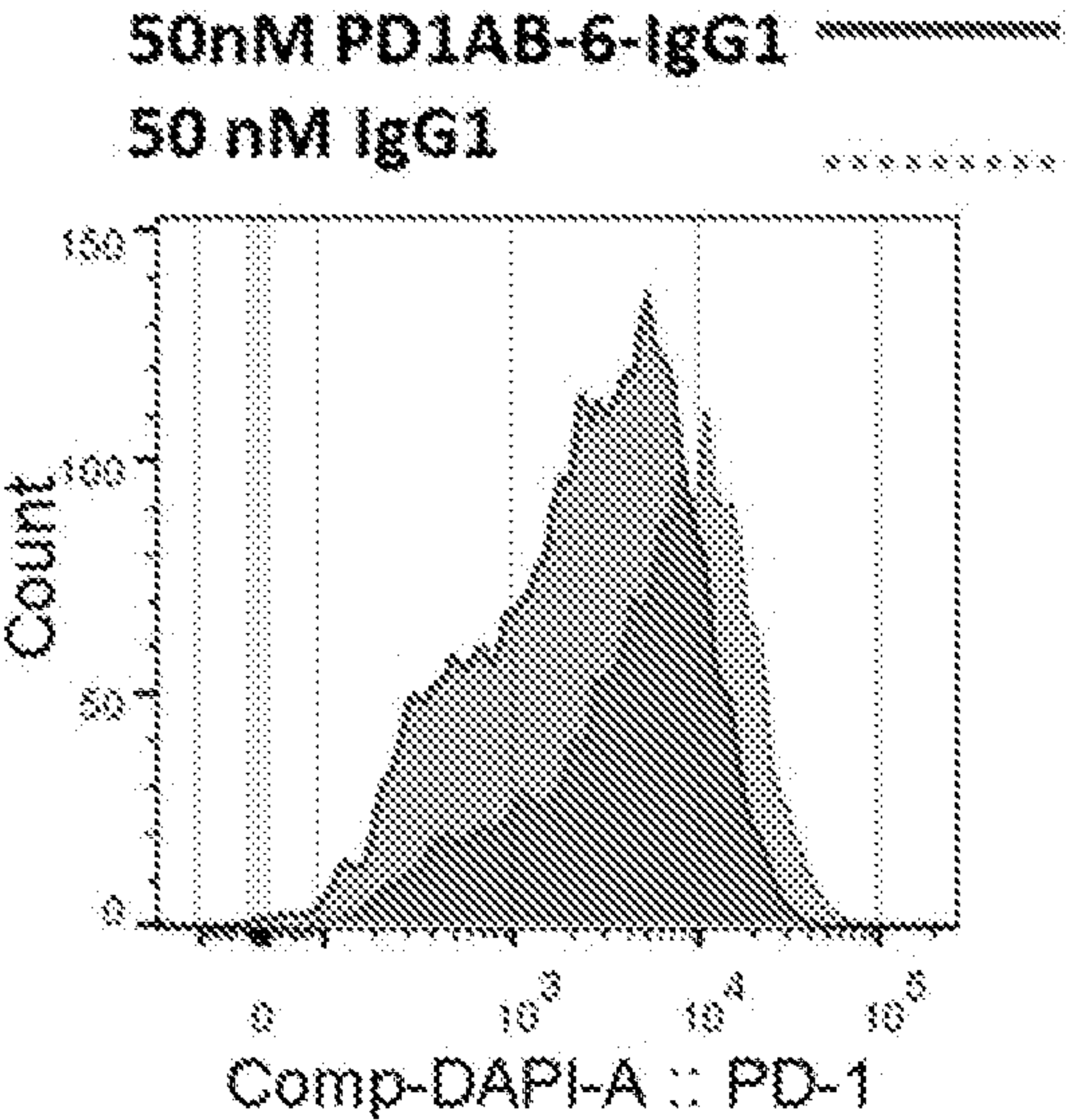


FIG. 14B

Gated on CD3+ T cells

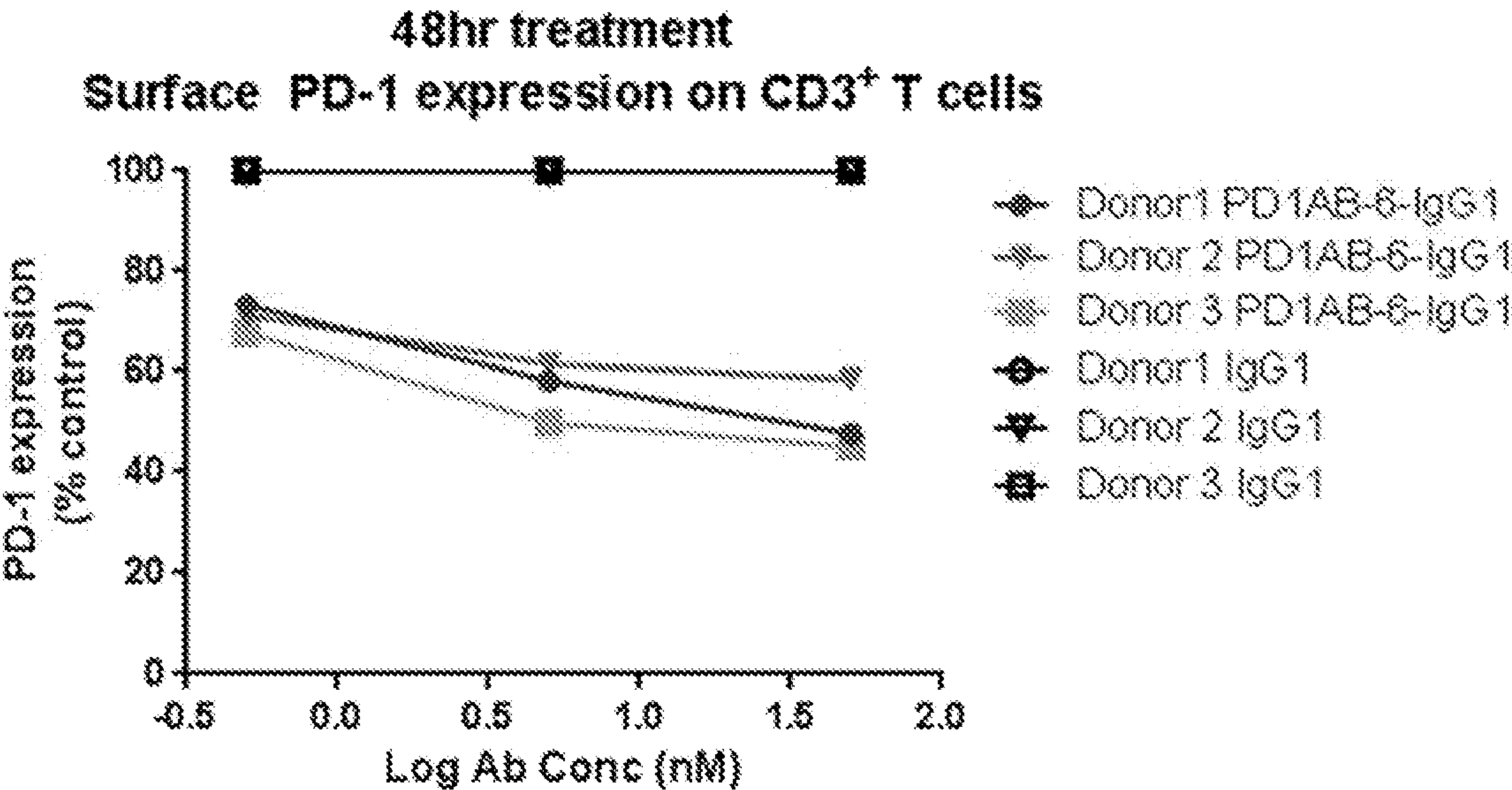


FIG. 14C

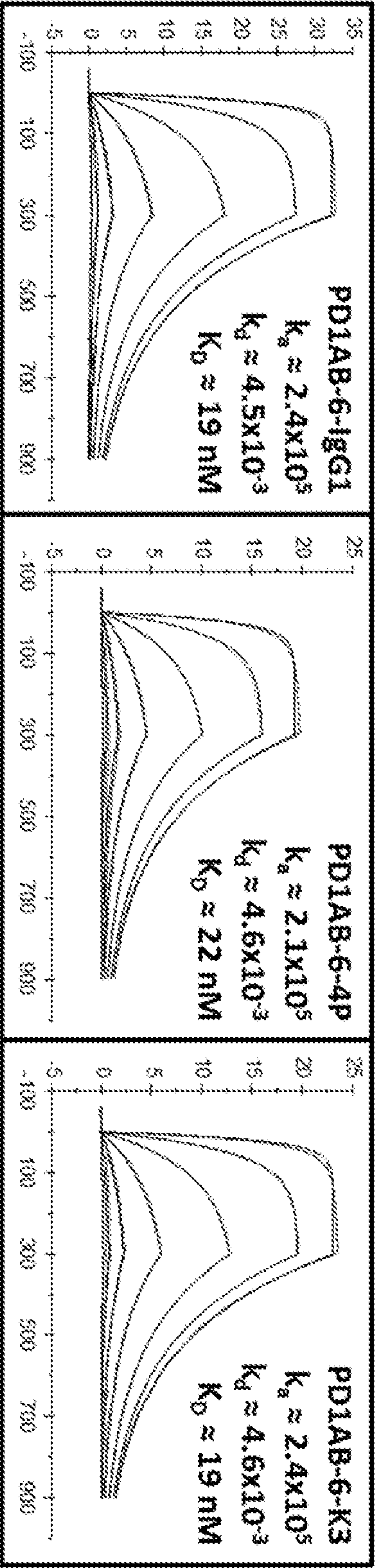
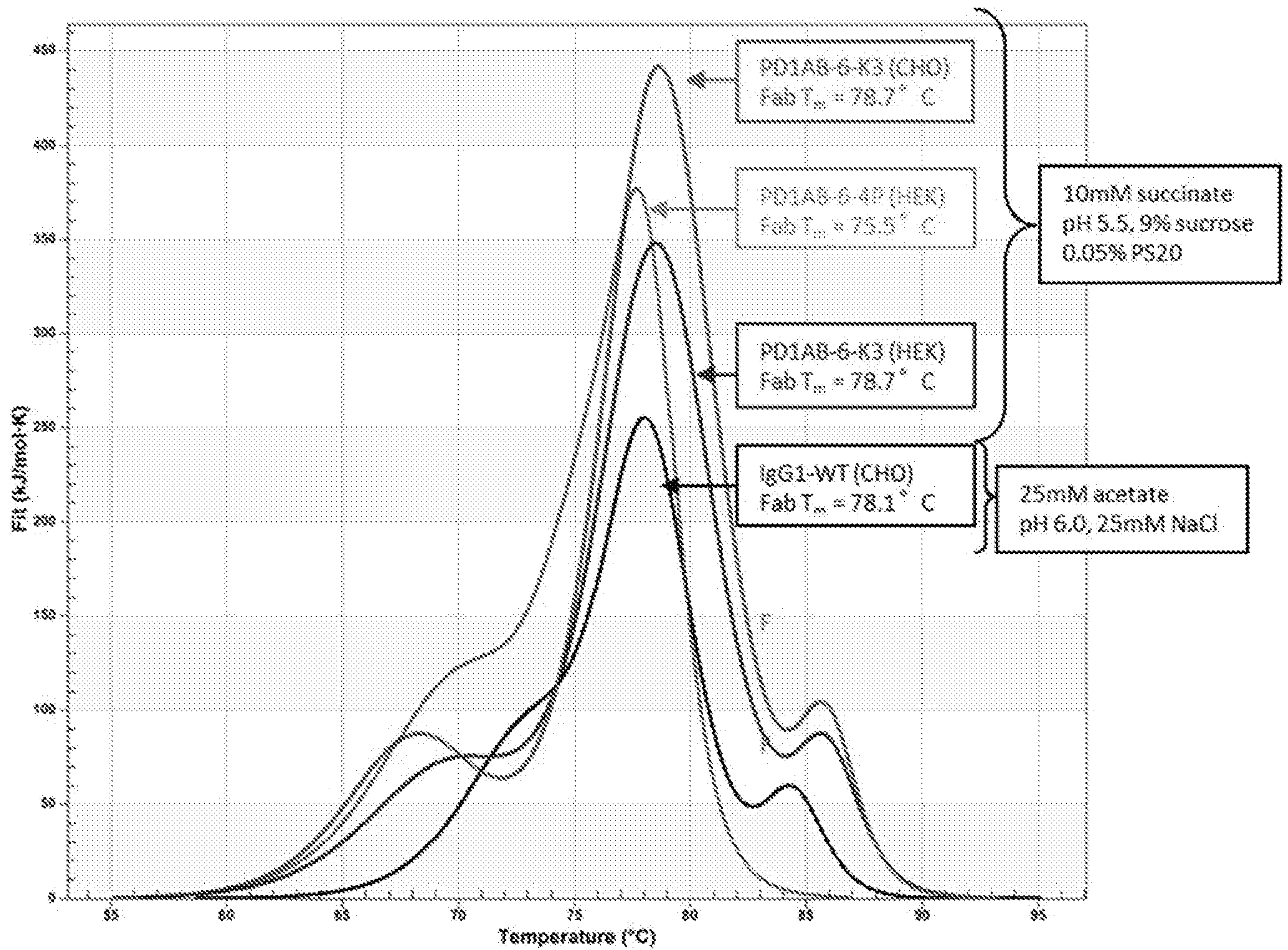


FIG. 15A

FIG. 15B

FIG. 15C

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**FIG. 16**

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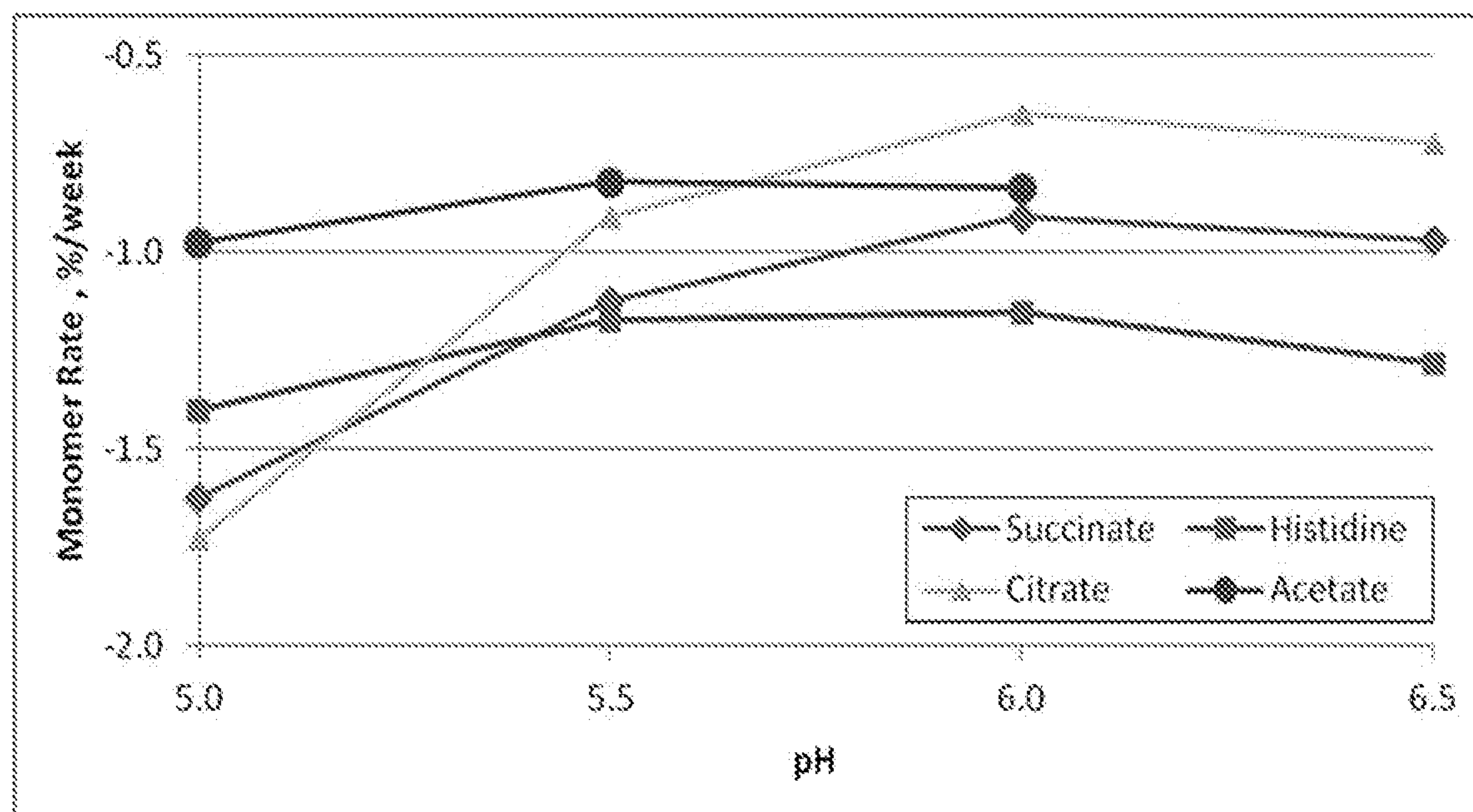


FIG. 17

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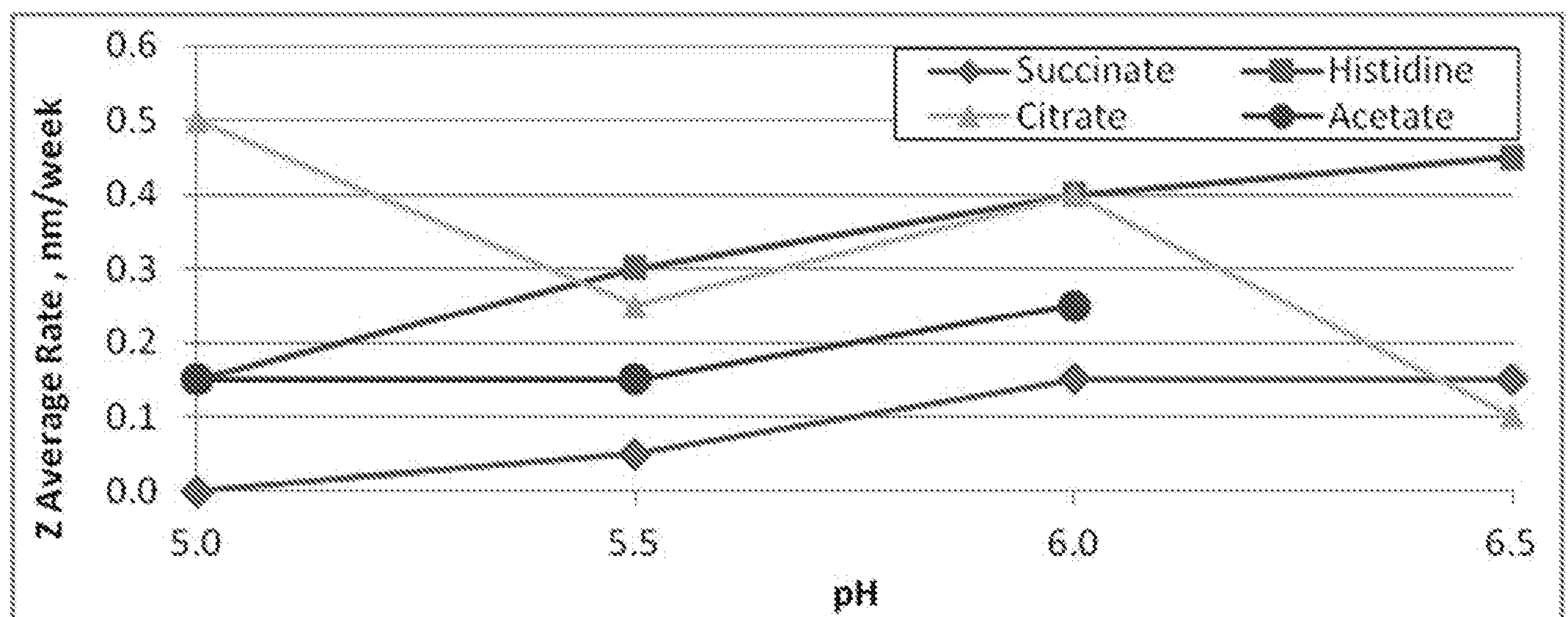


FIG. 18

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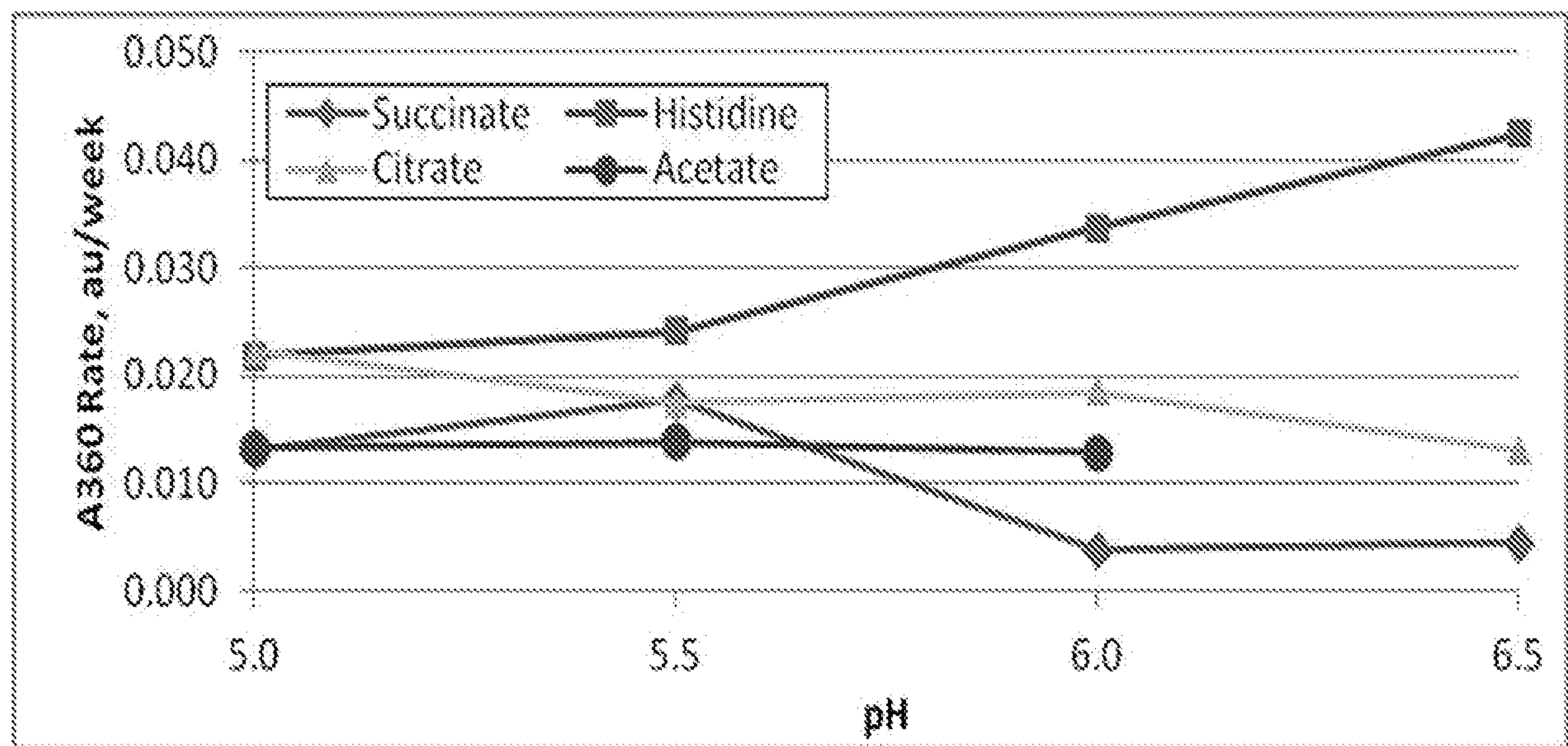


FIG. 19

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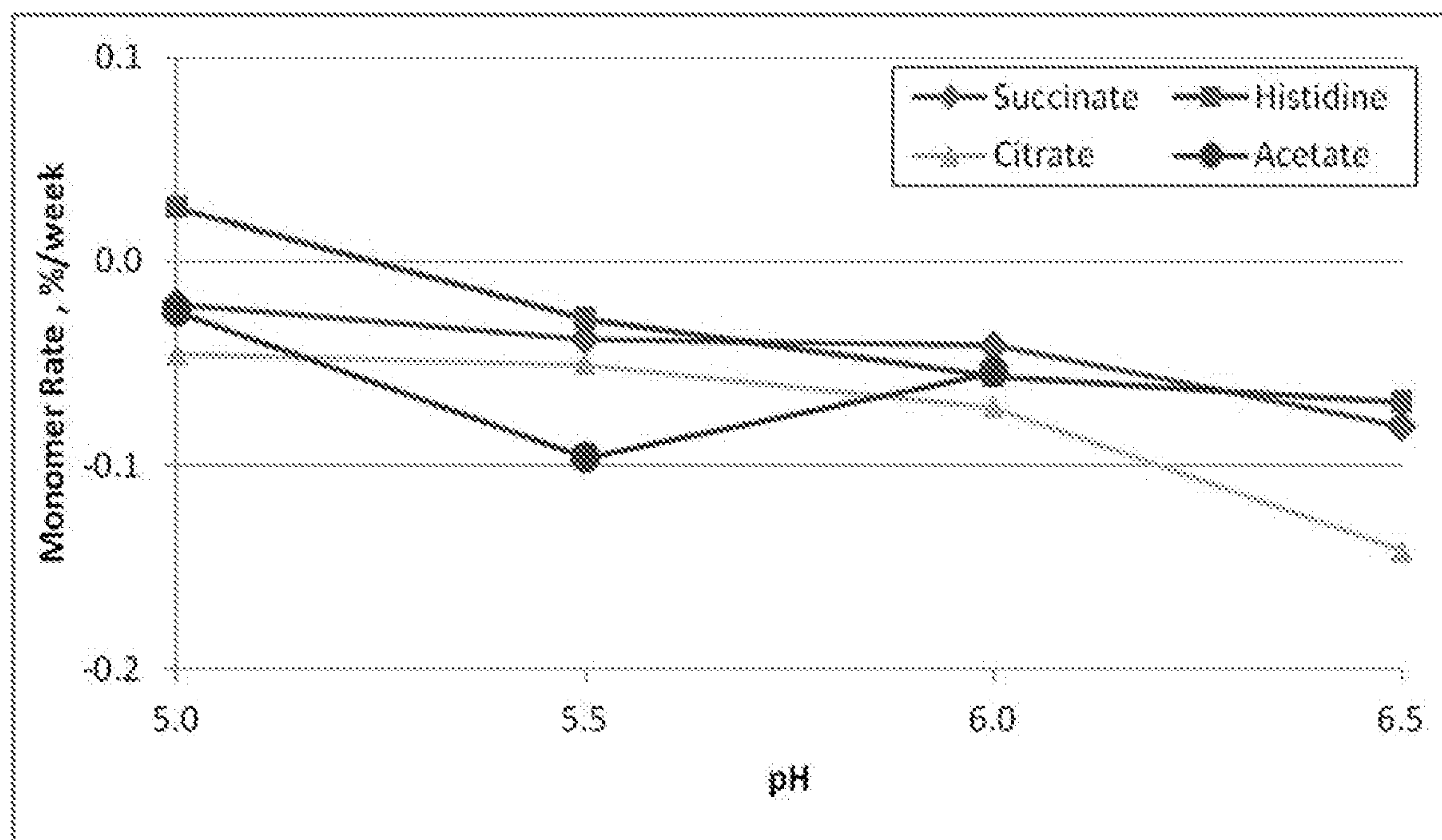
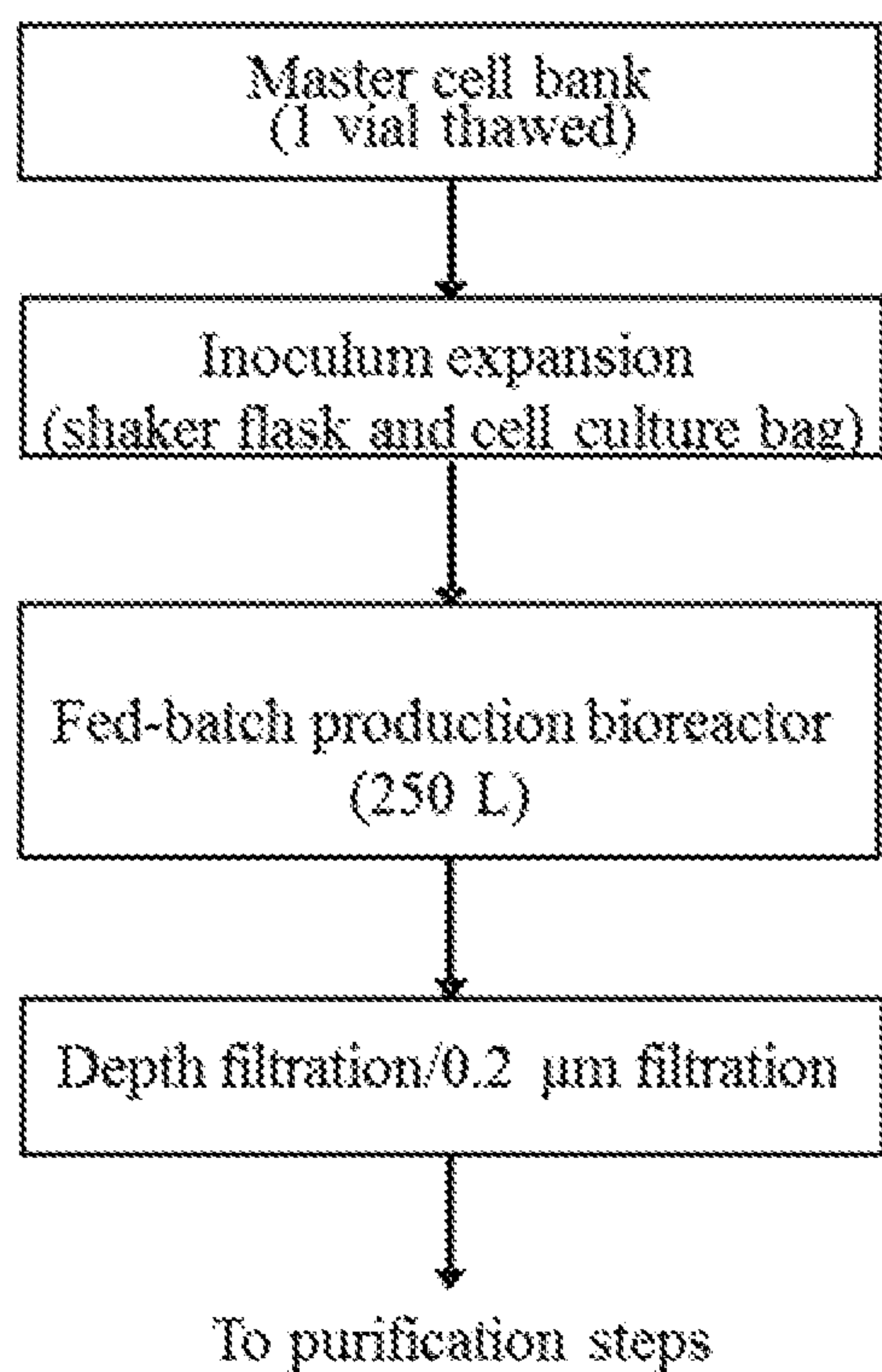
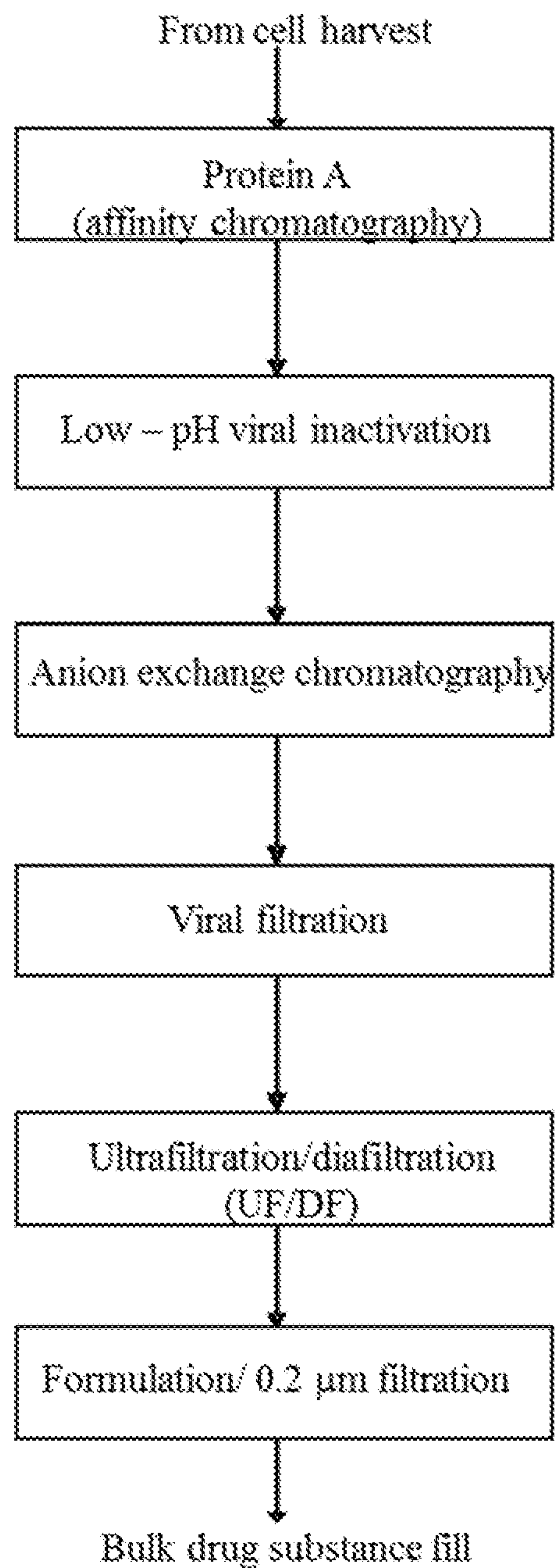


FIG. 20

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**FIG. 21A****FIG. 21B**

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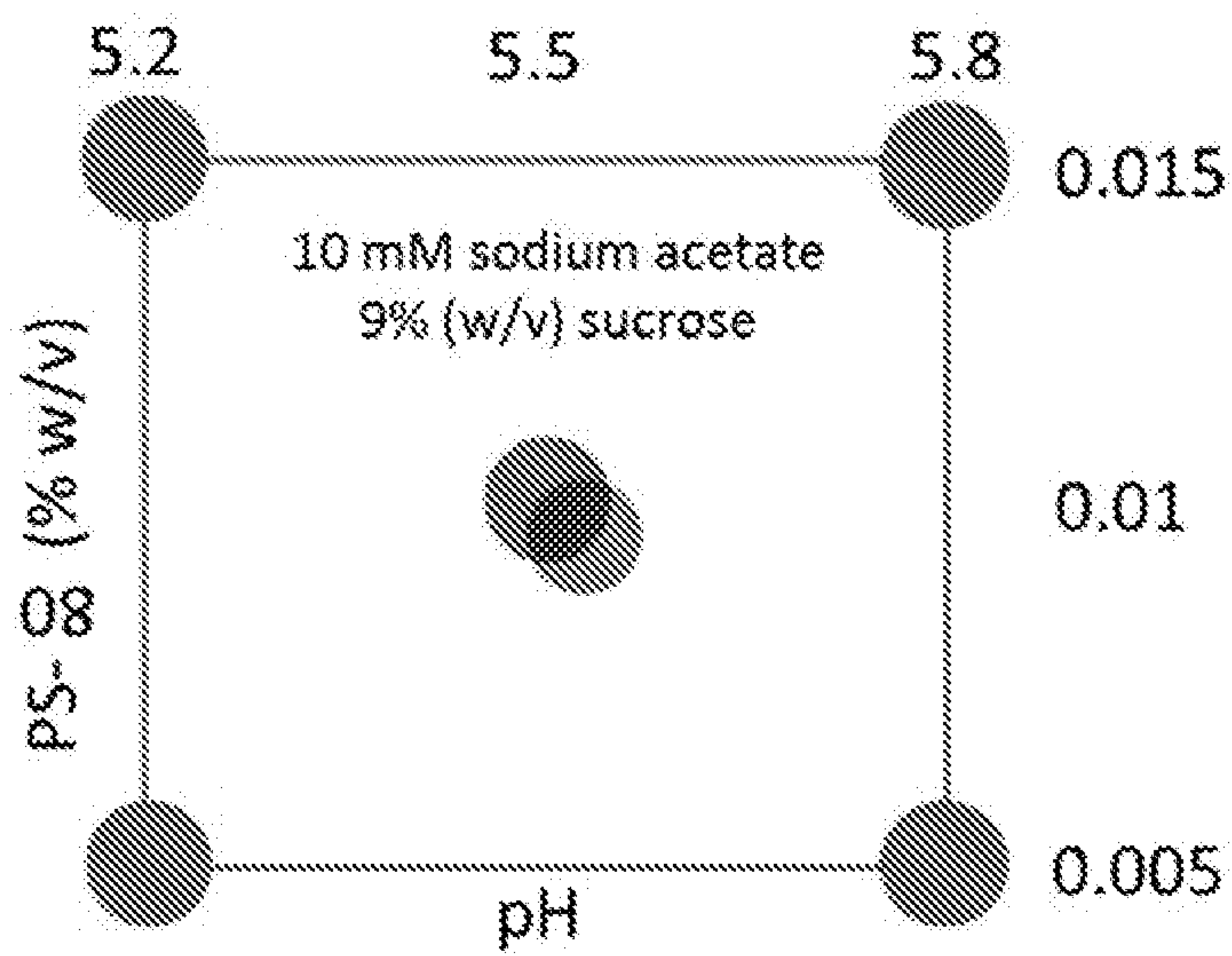


FIG. 22

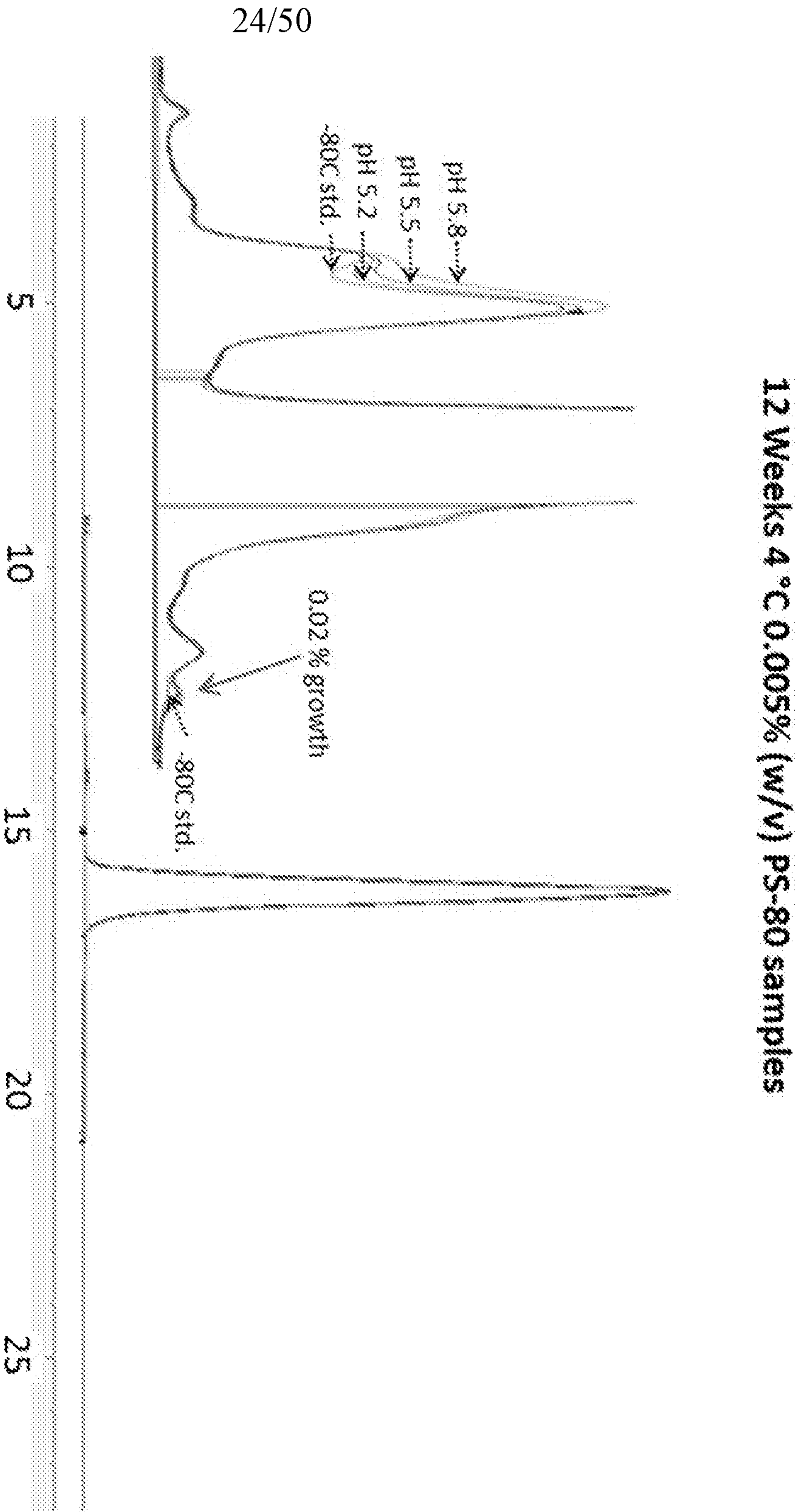
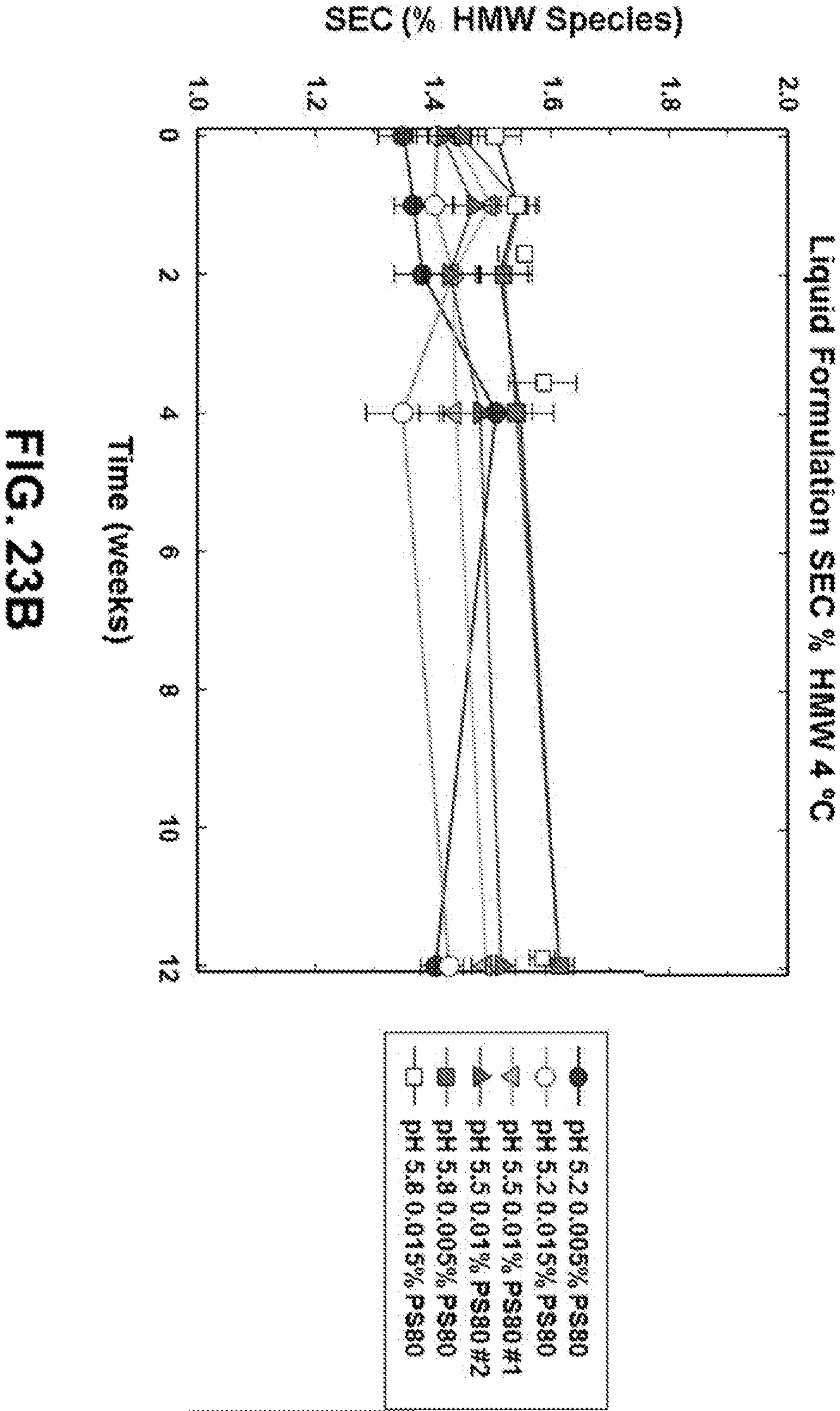
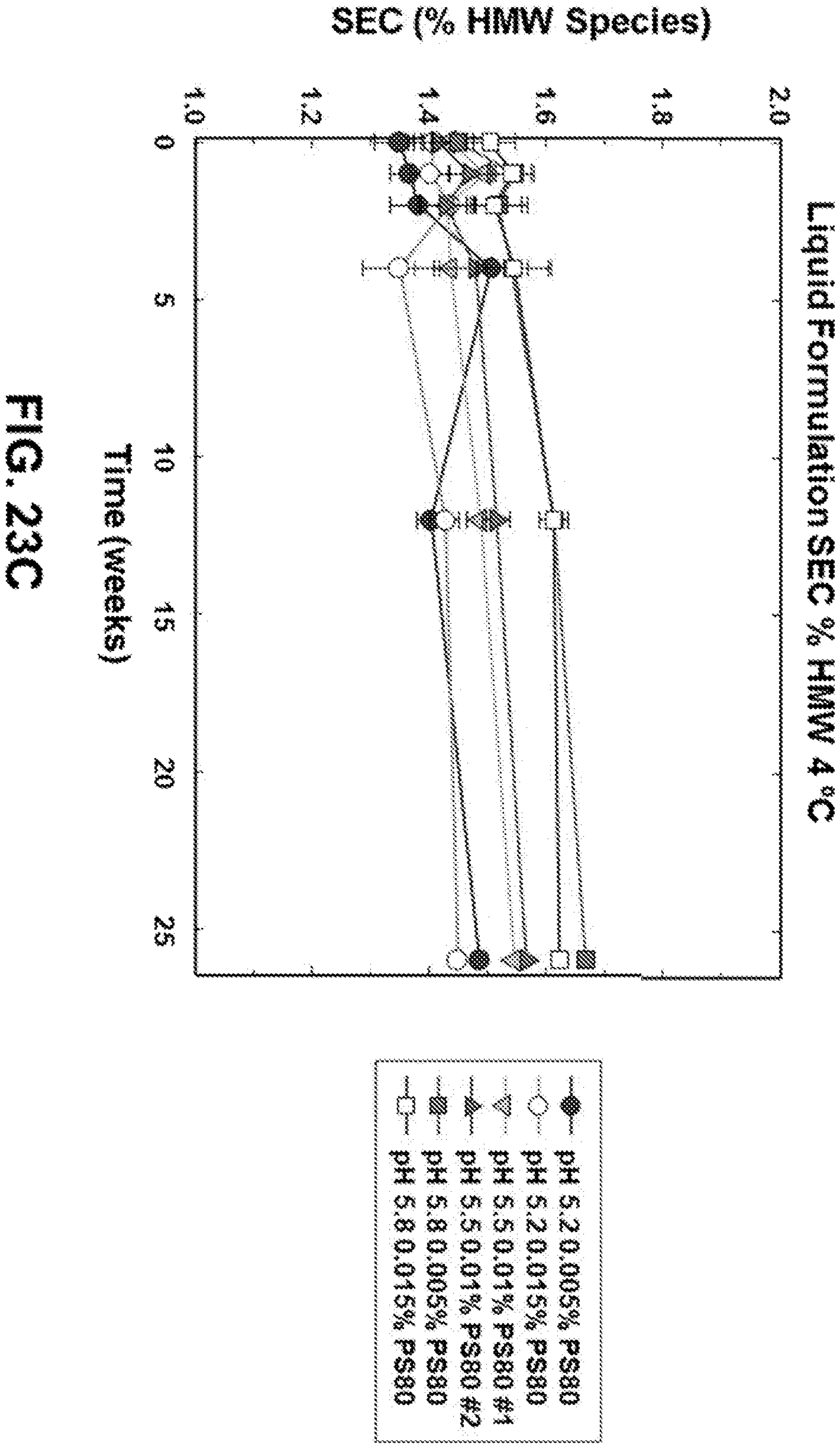
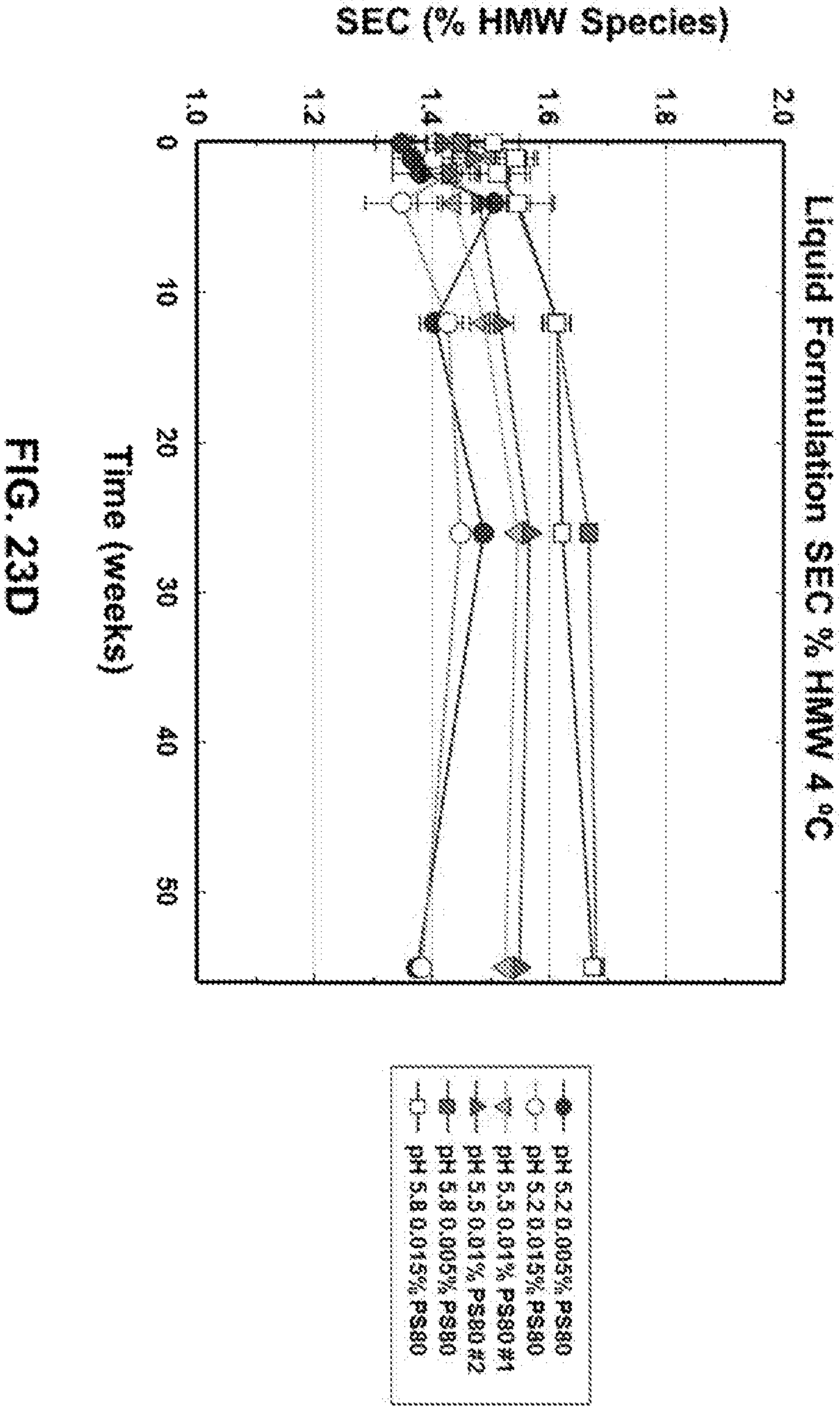


FIG. 23A







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12 Weeks 25 °C 0.005% (w/v) PS-80 samples

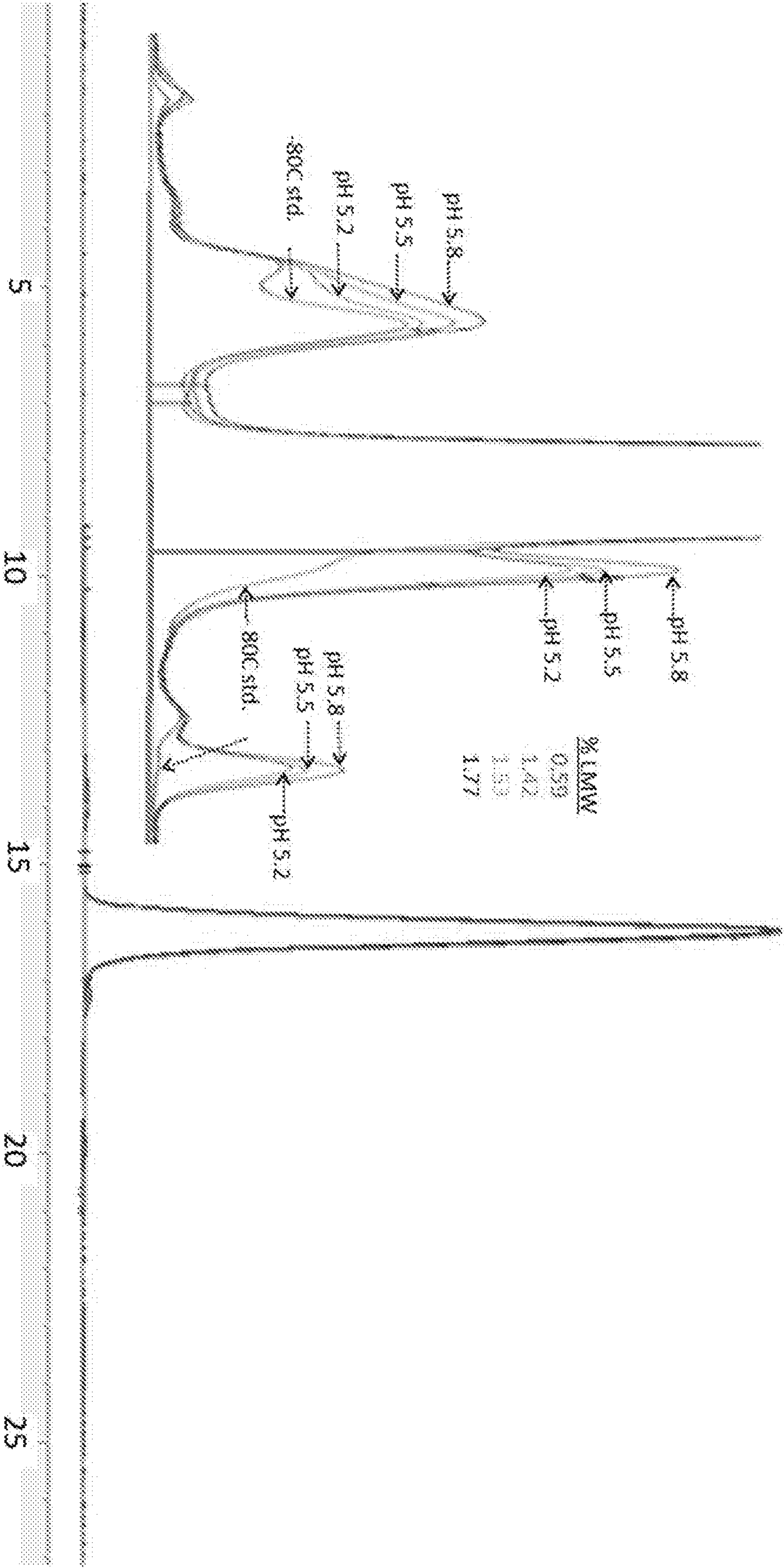


FIG. 24A

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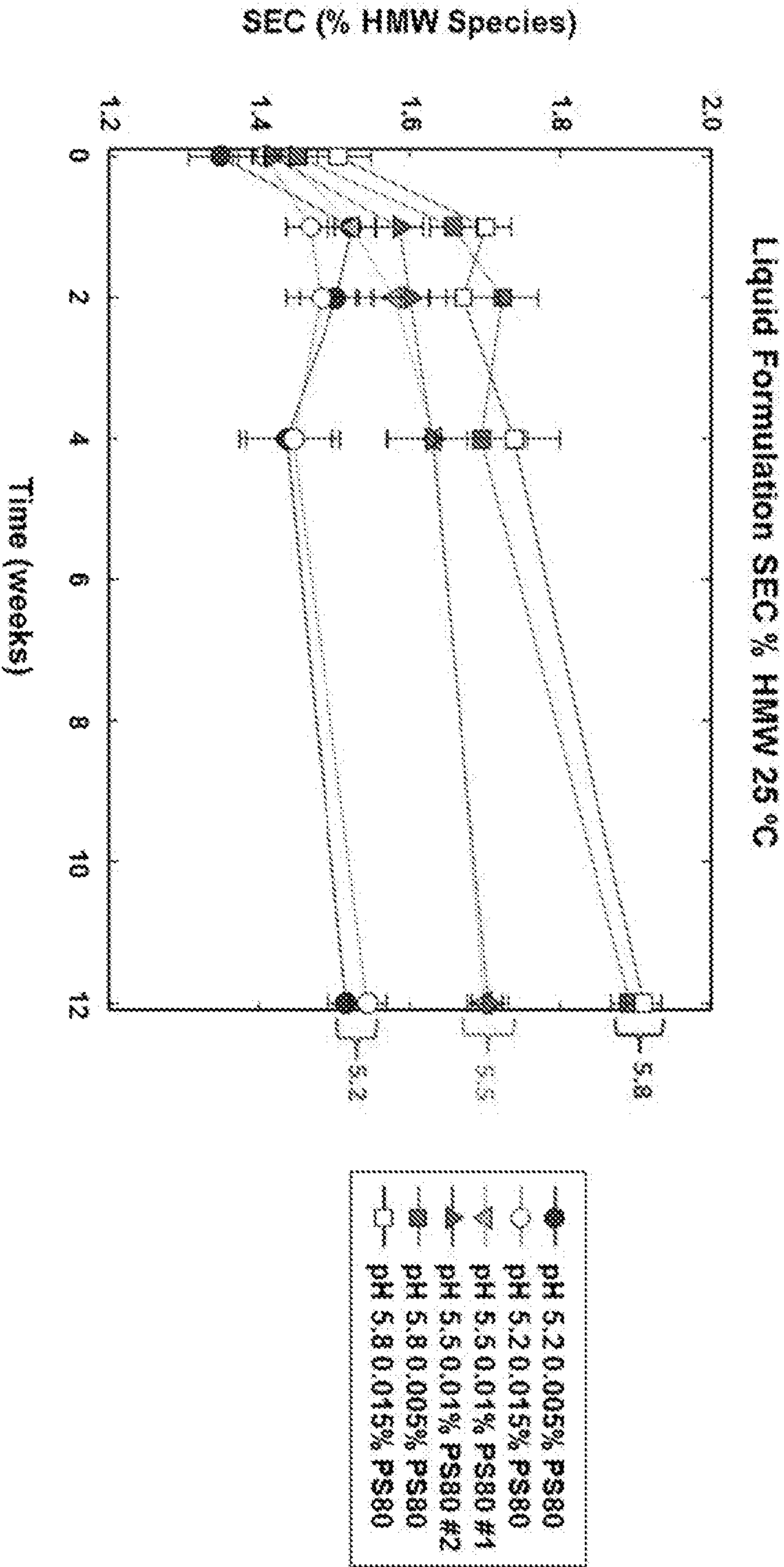


FIG. 24B

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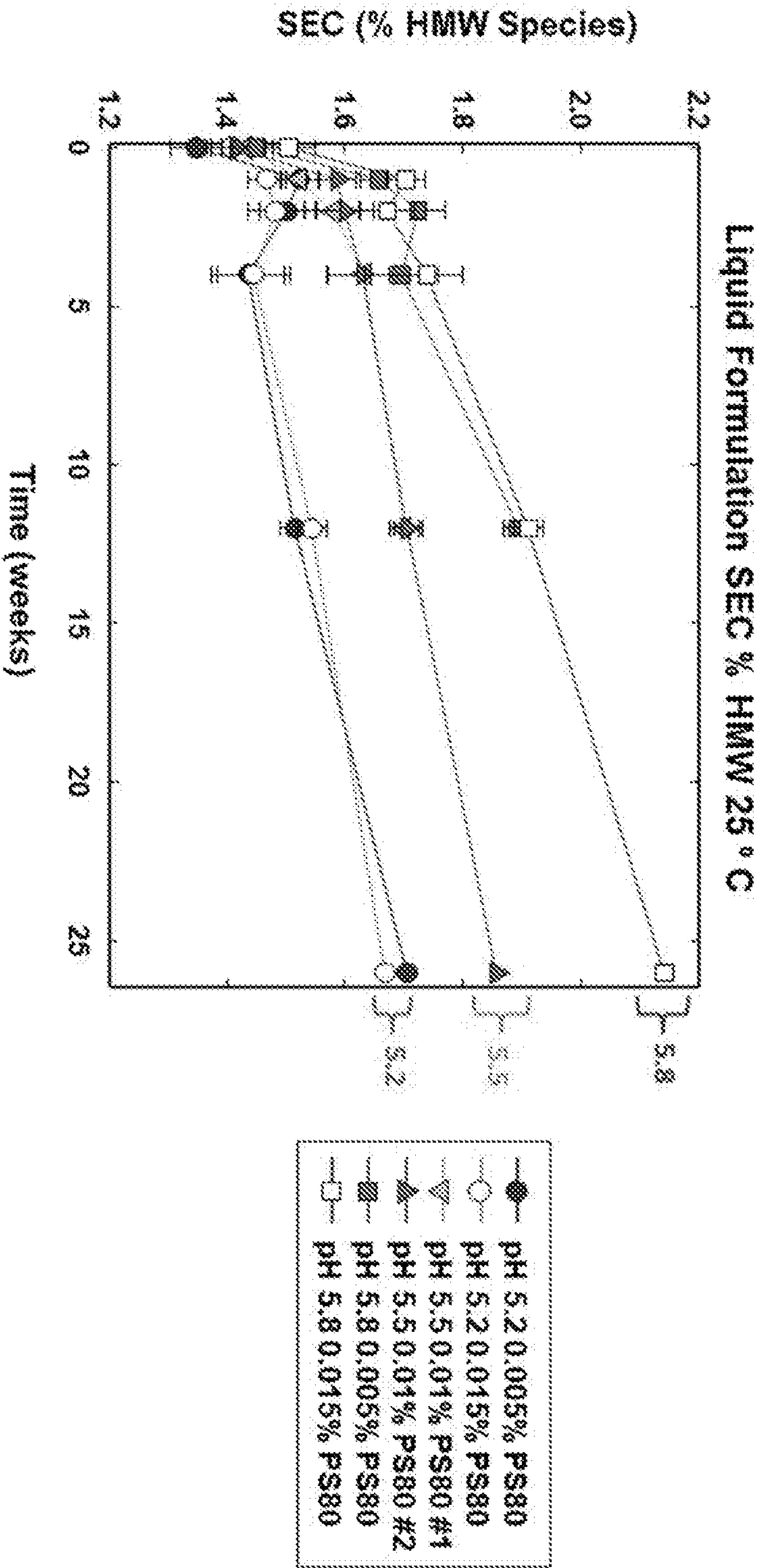


FIG. 24C

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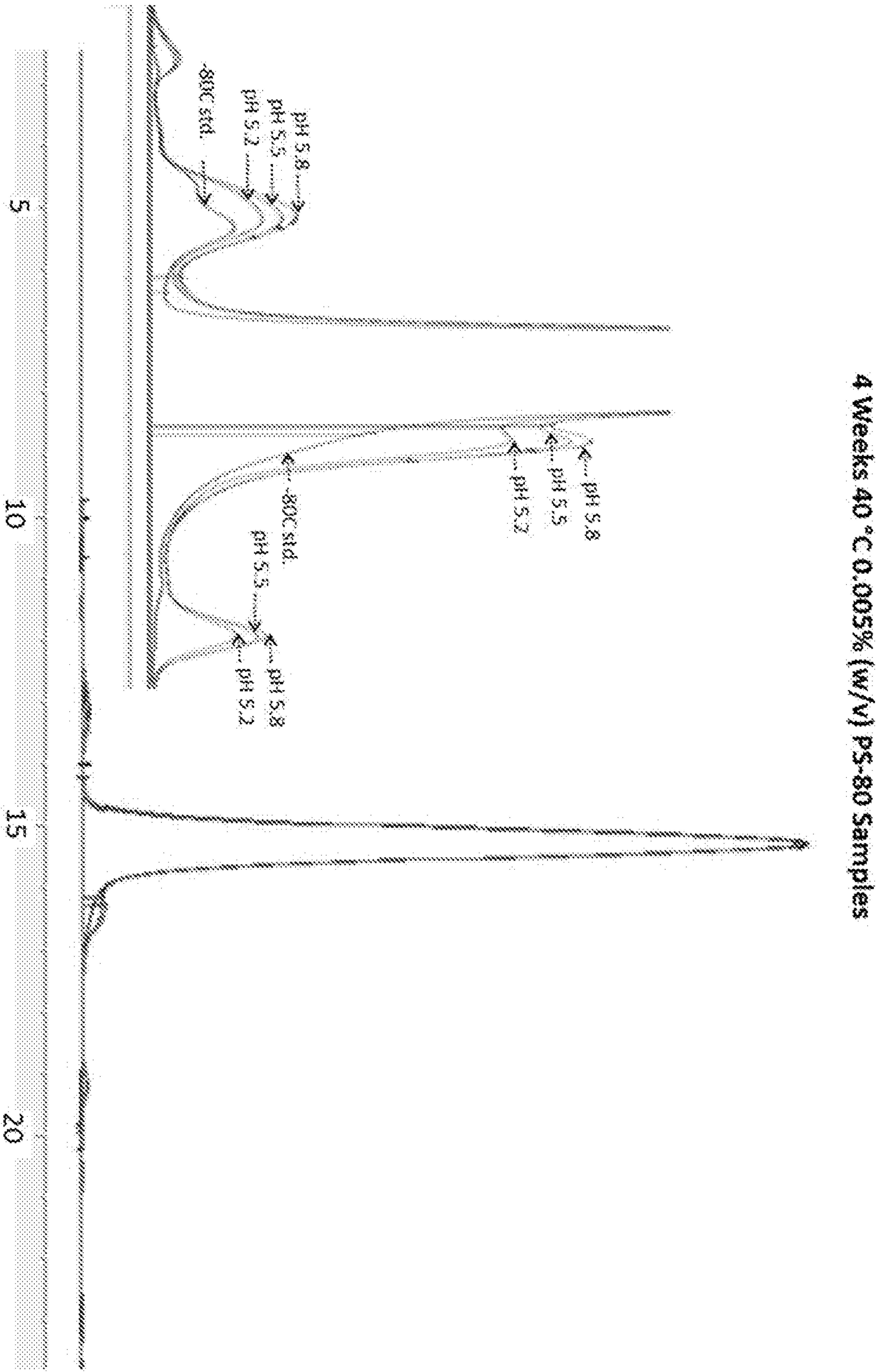


FIG. 25A

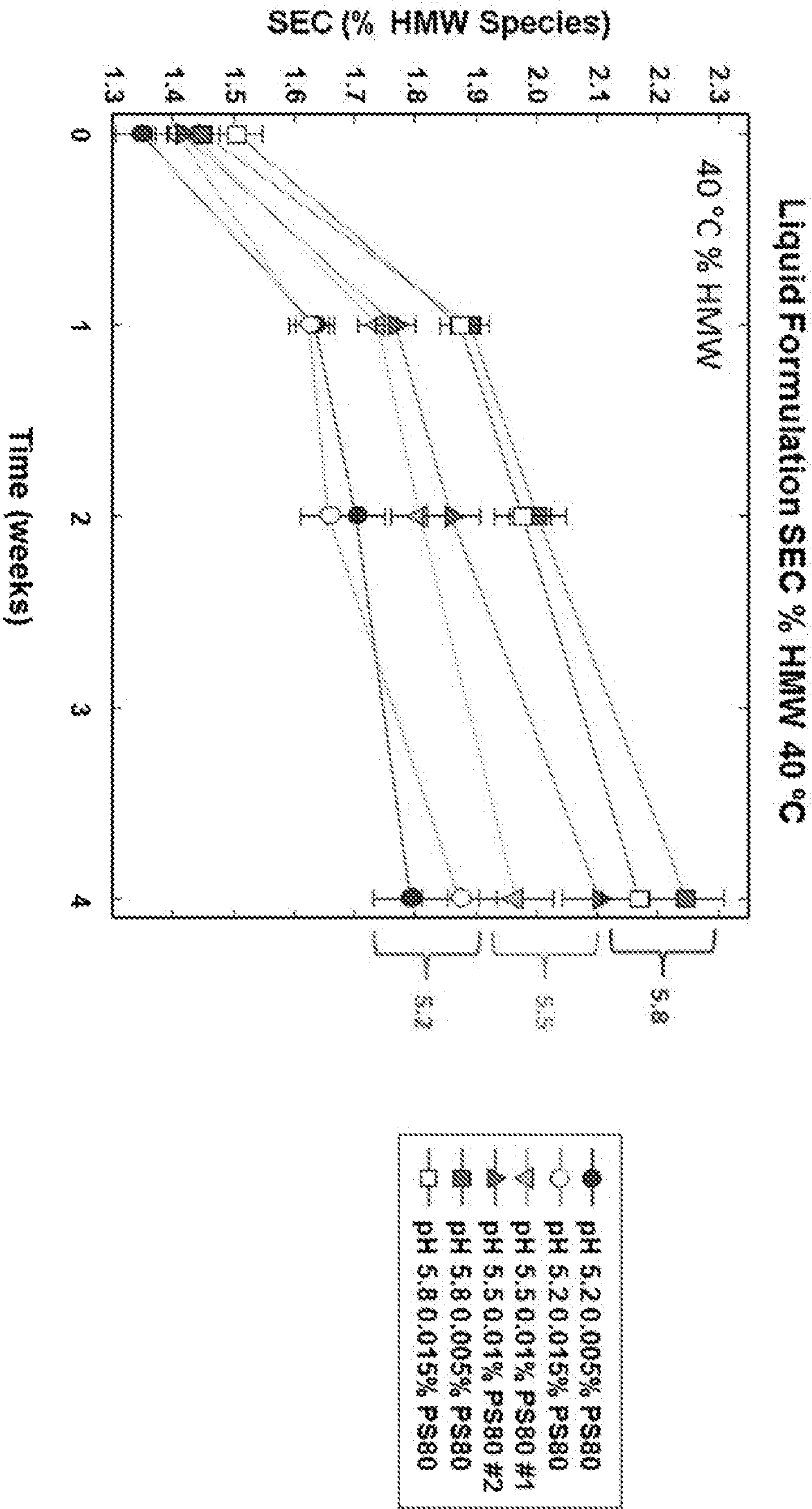


FIG. 25B

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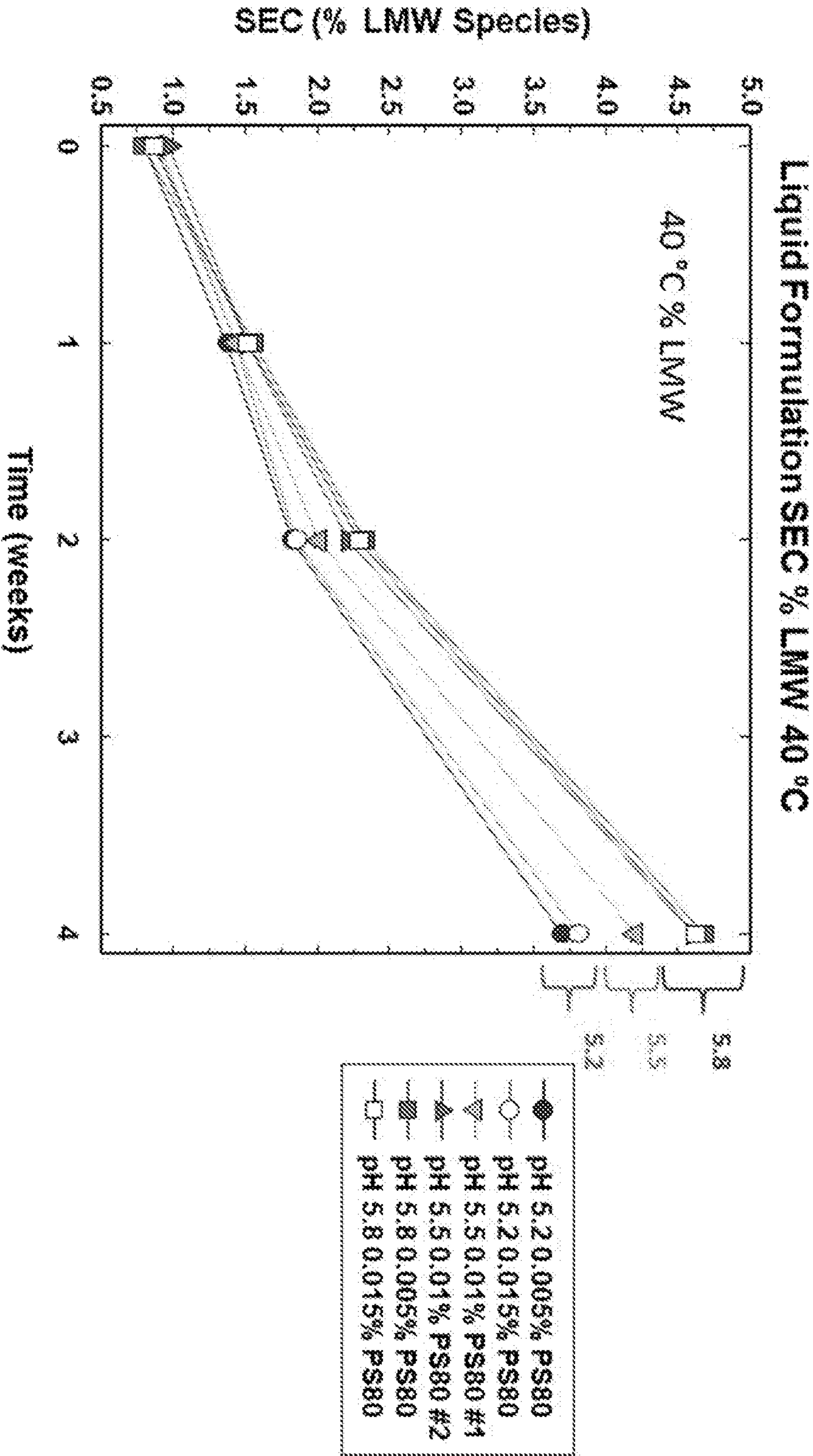


FIG. 25C

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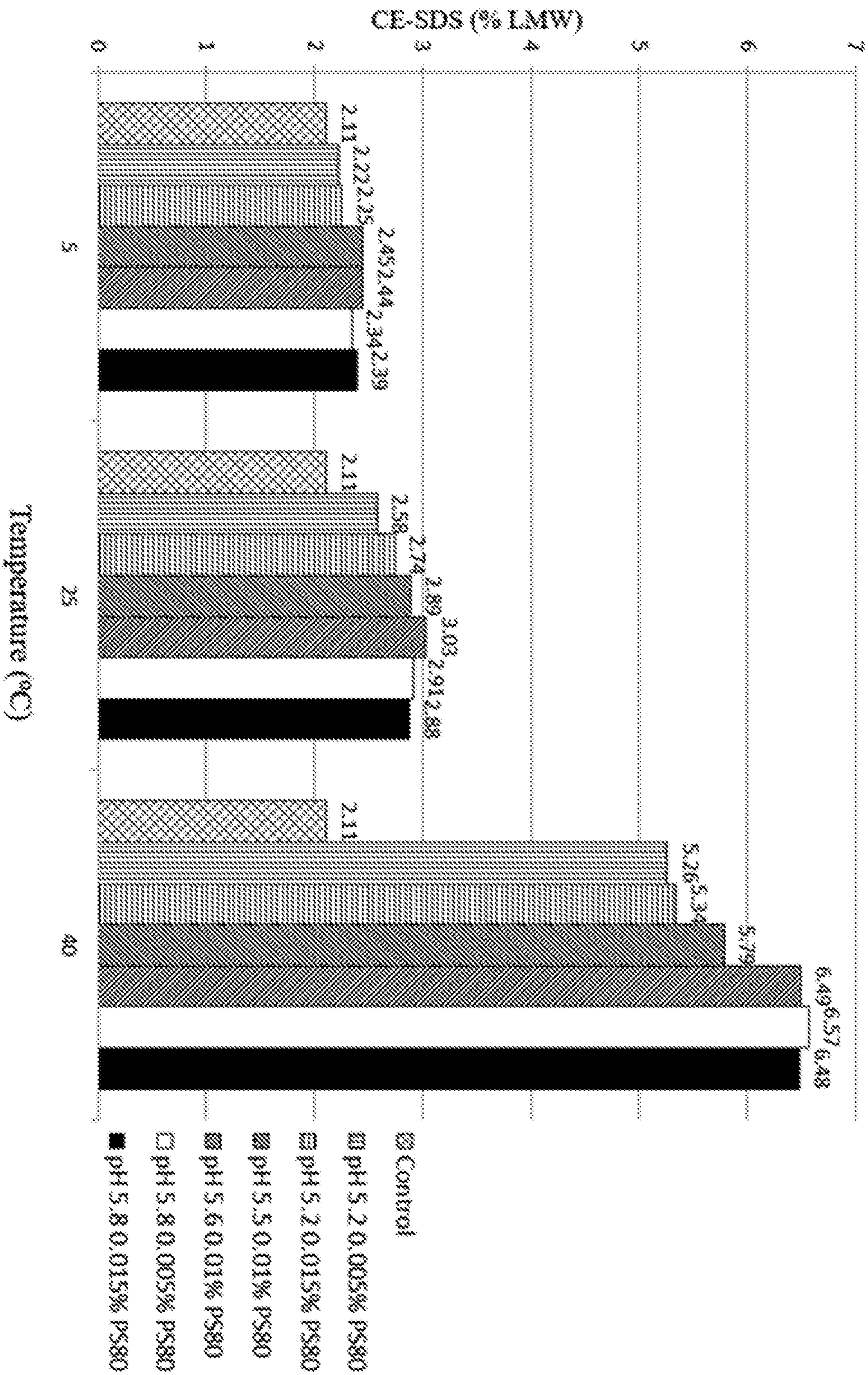


FIG. 26

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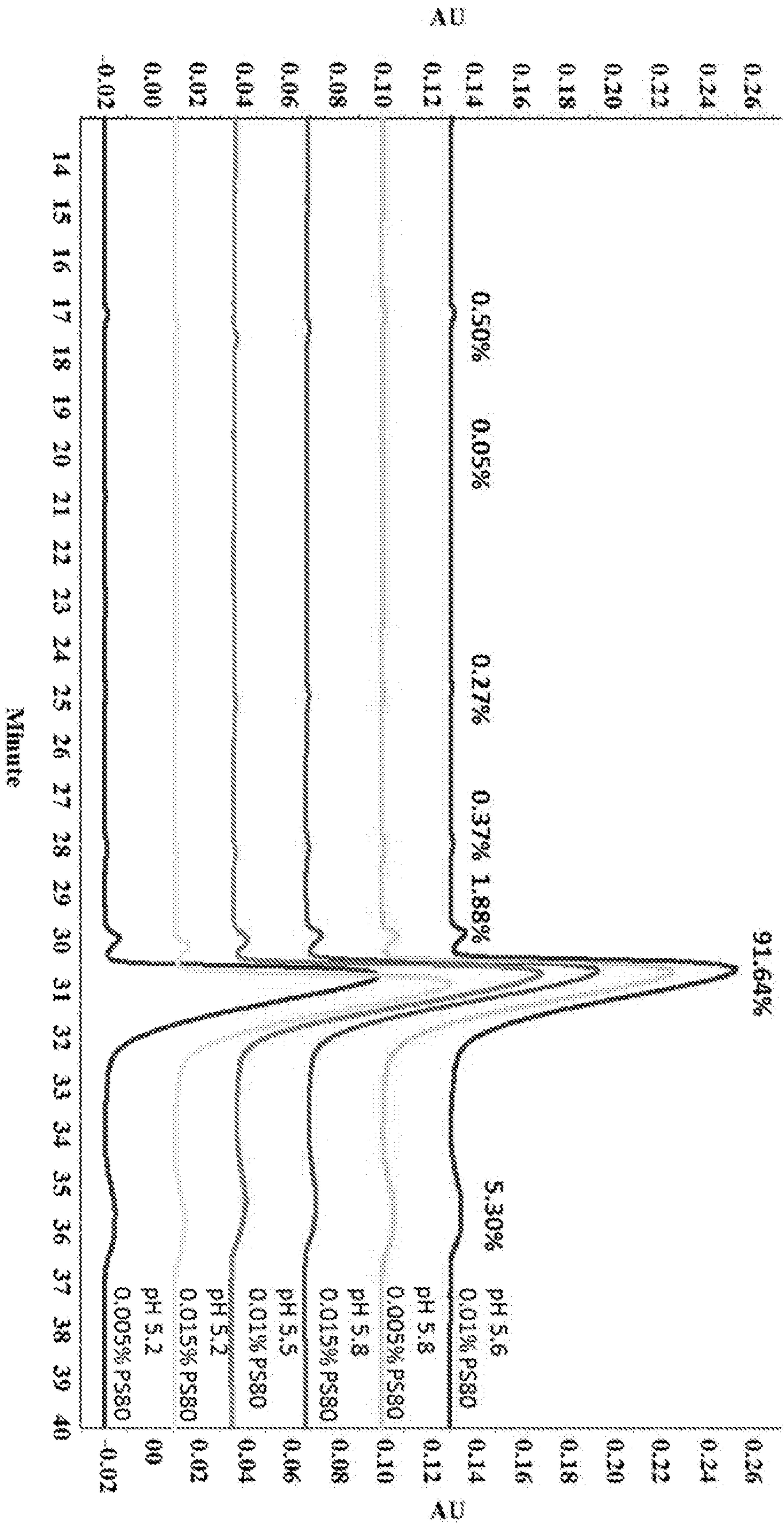


FIG. 27

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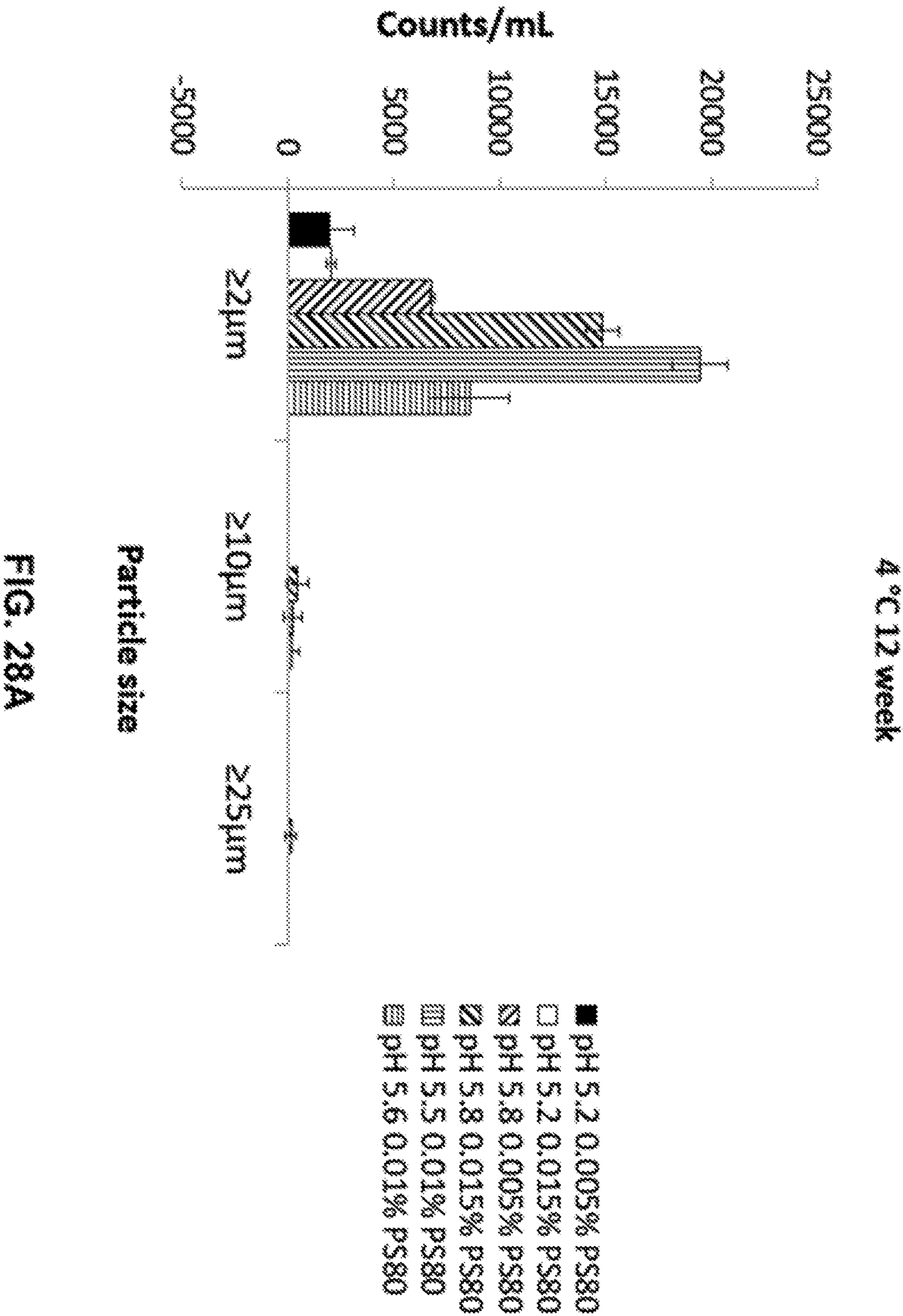
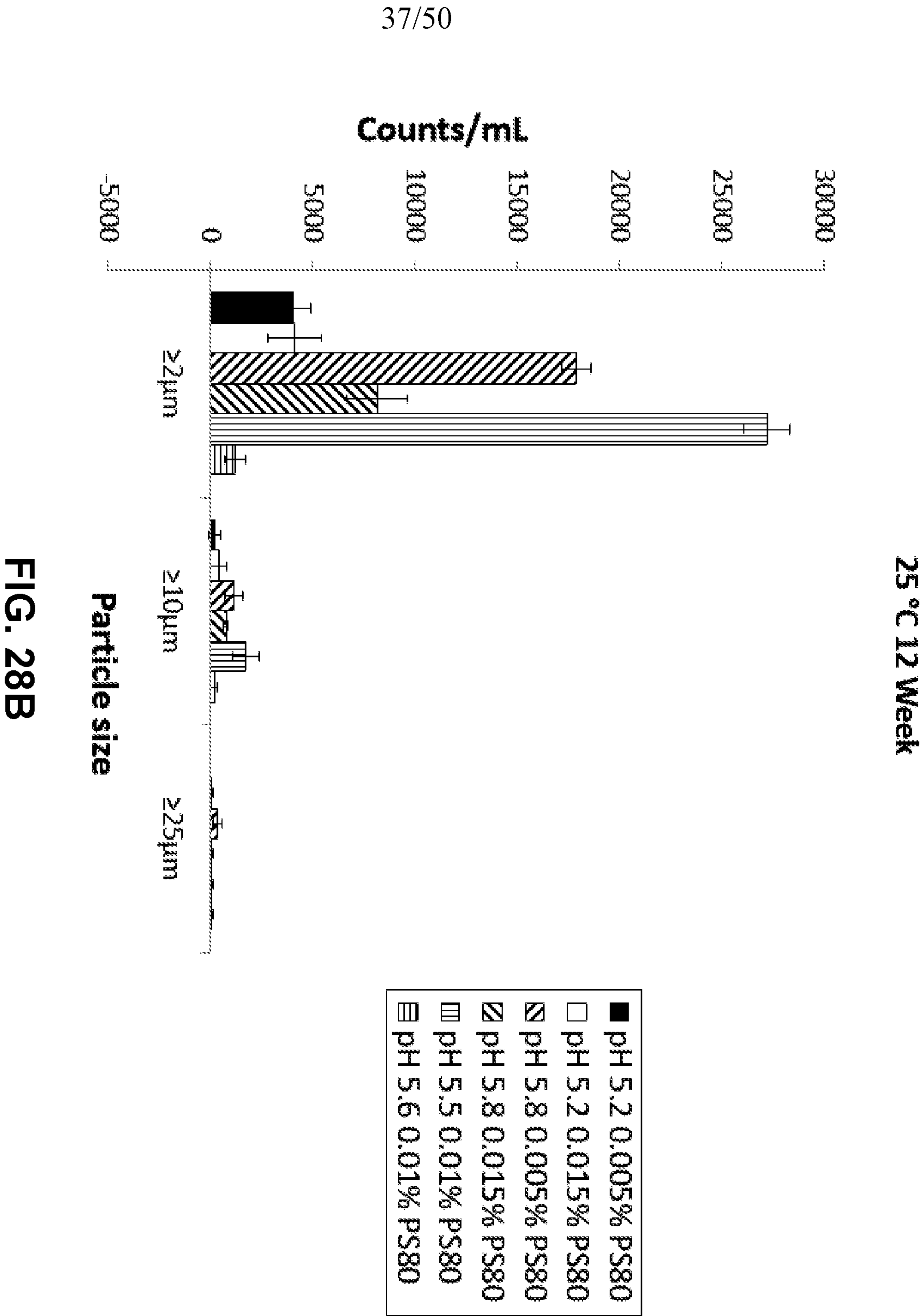


FIG. 28A



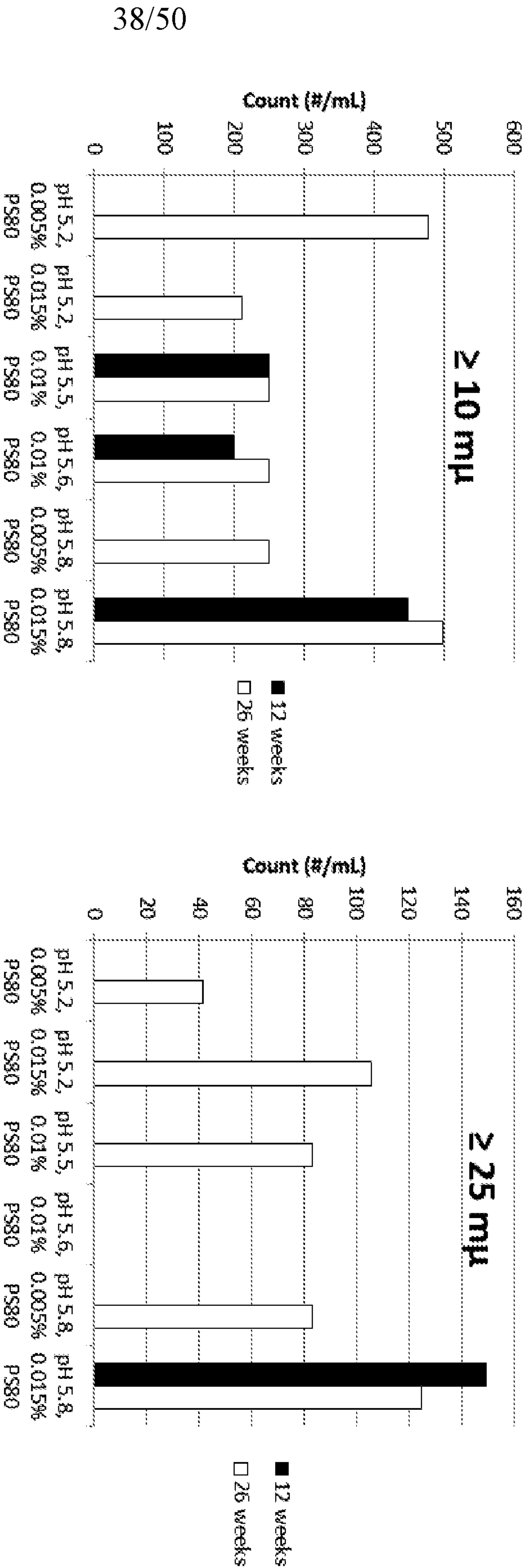


FIG. 29

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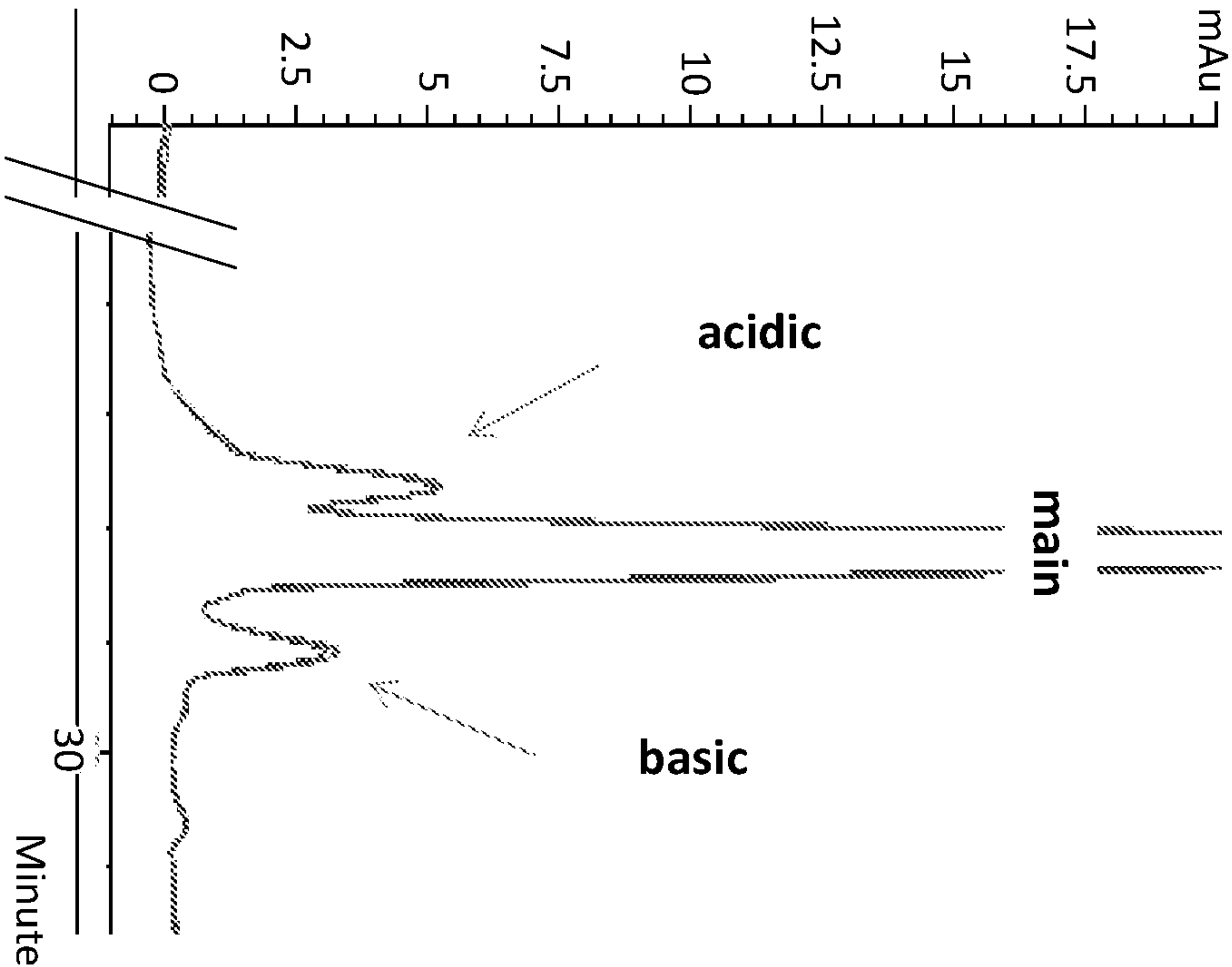
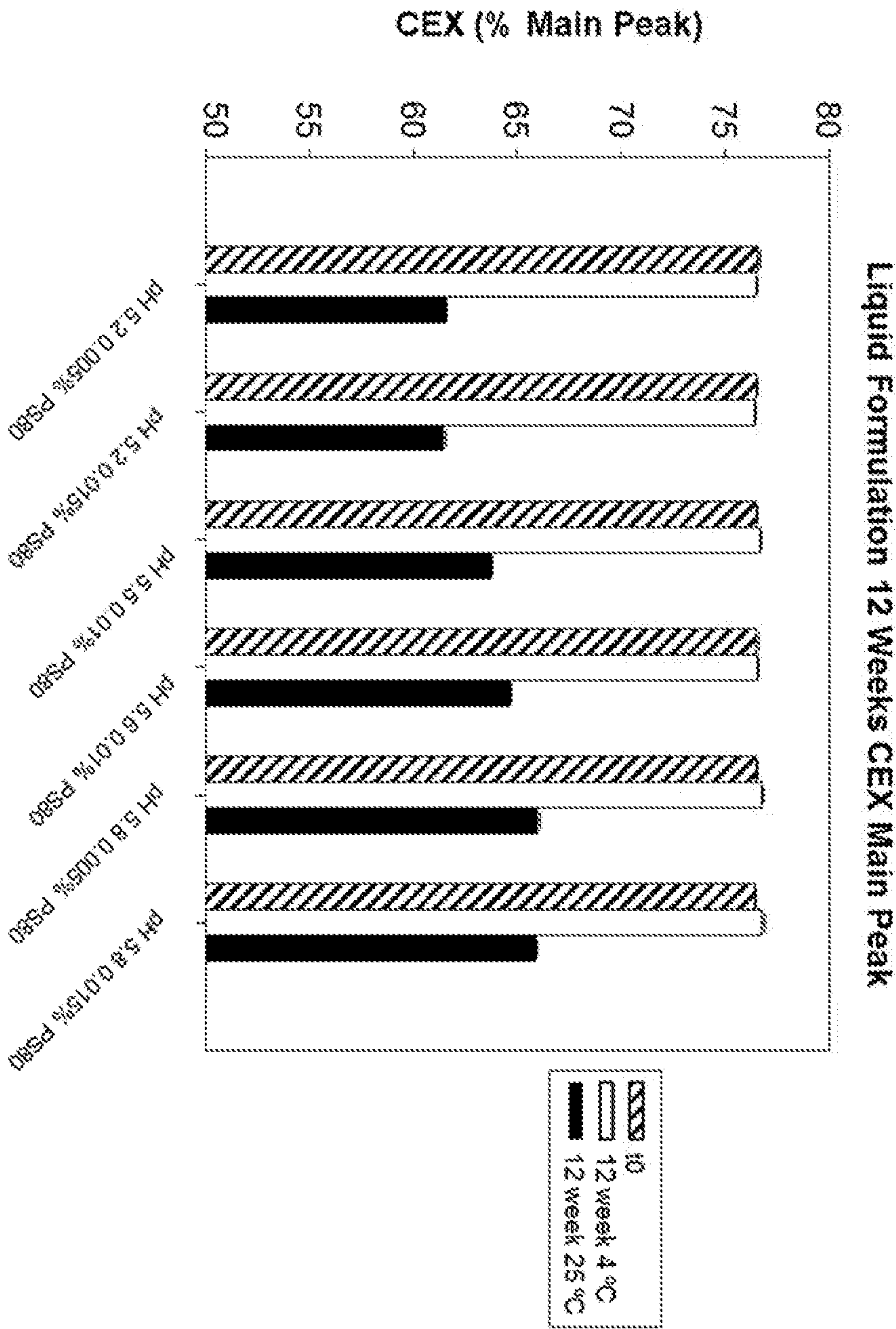


FIG. 30A

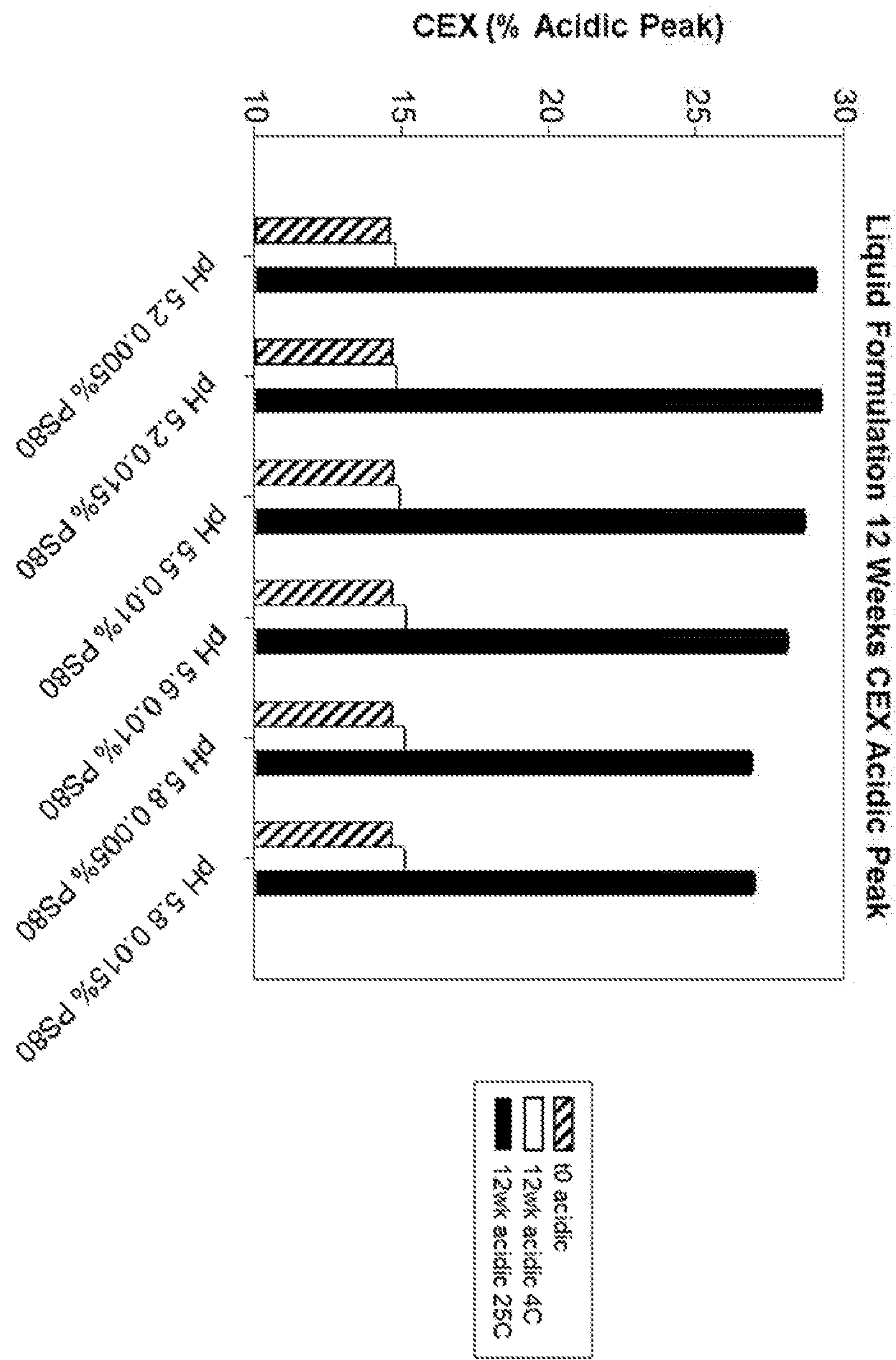
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FIG. 30B



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FIG. 30C



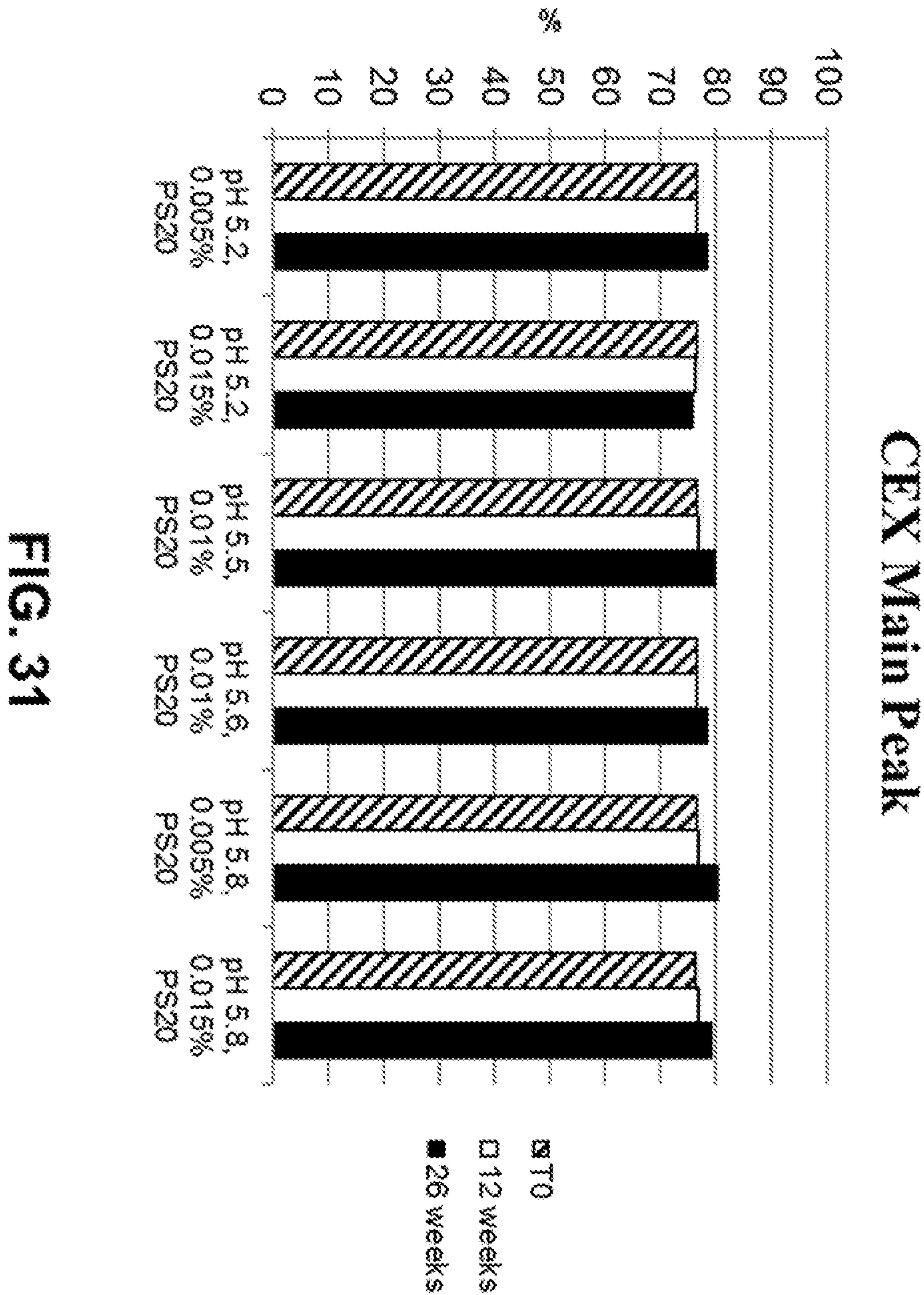


FIG. 31

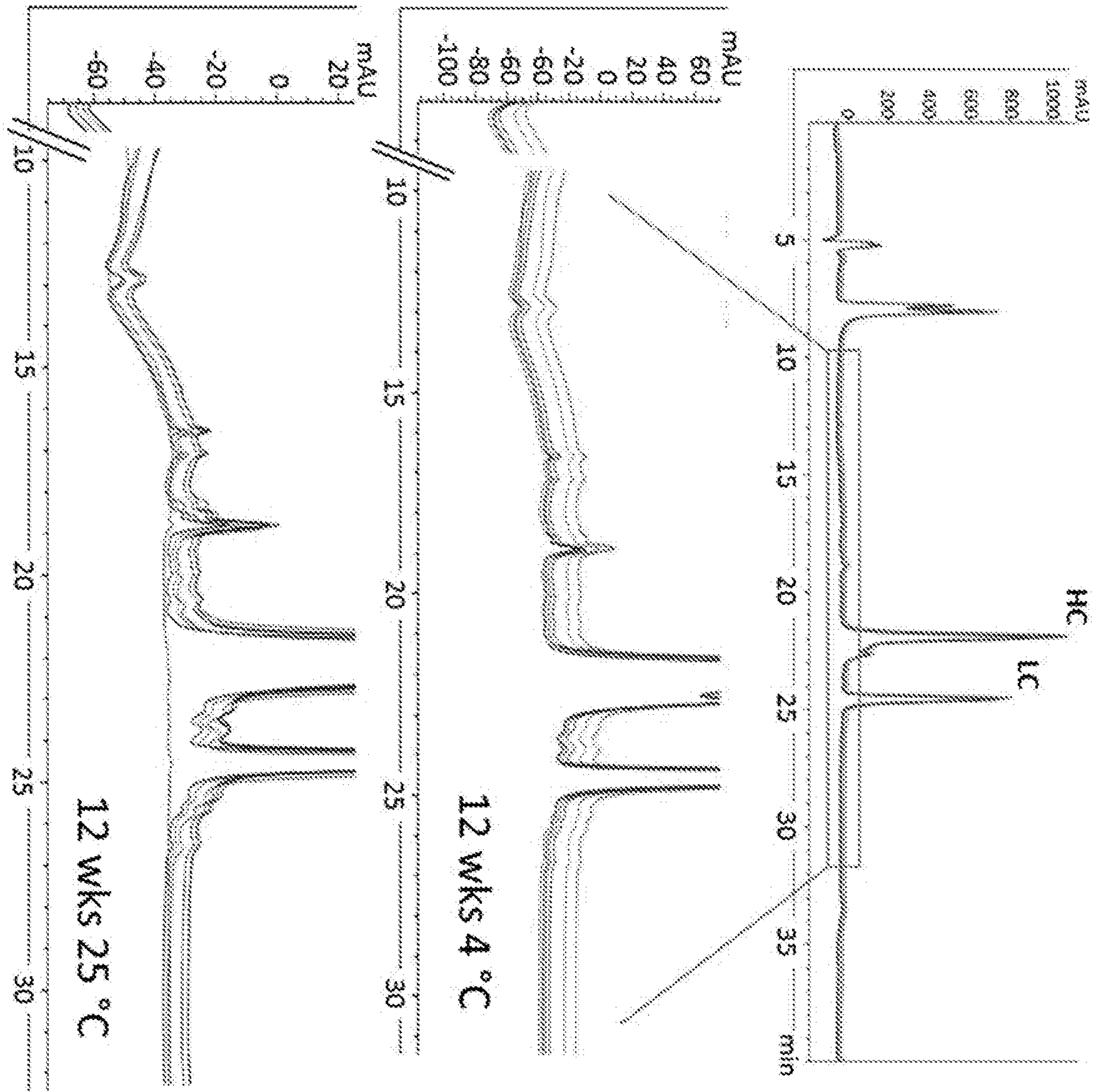


FIG. 32

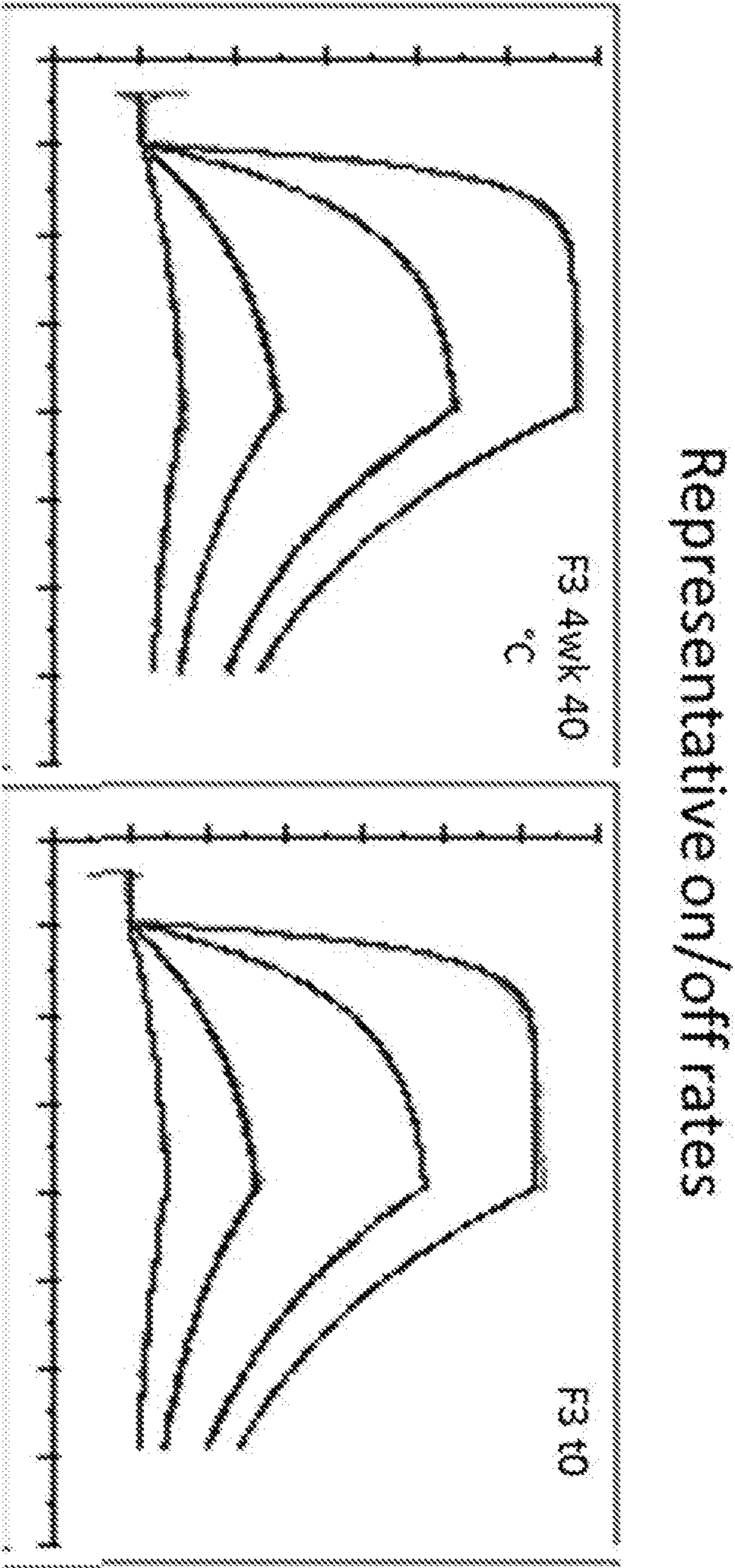
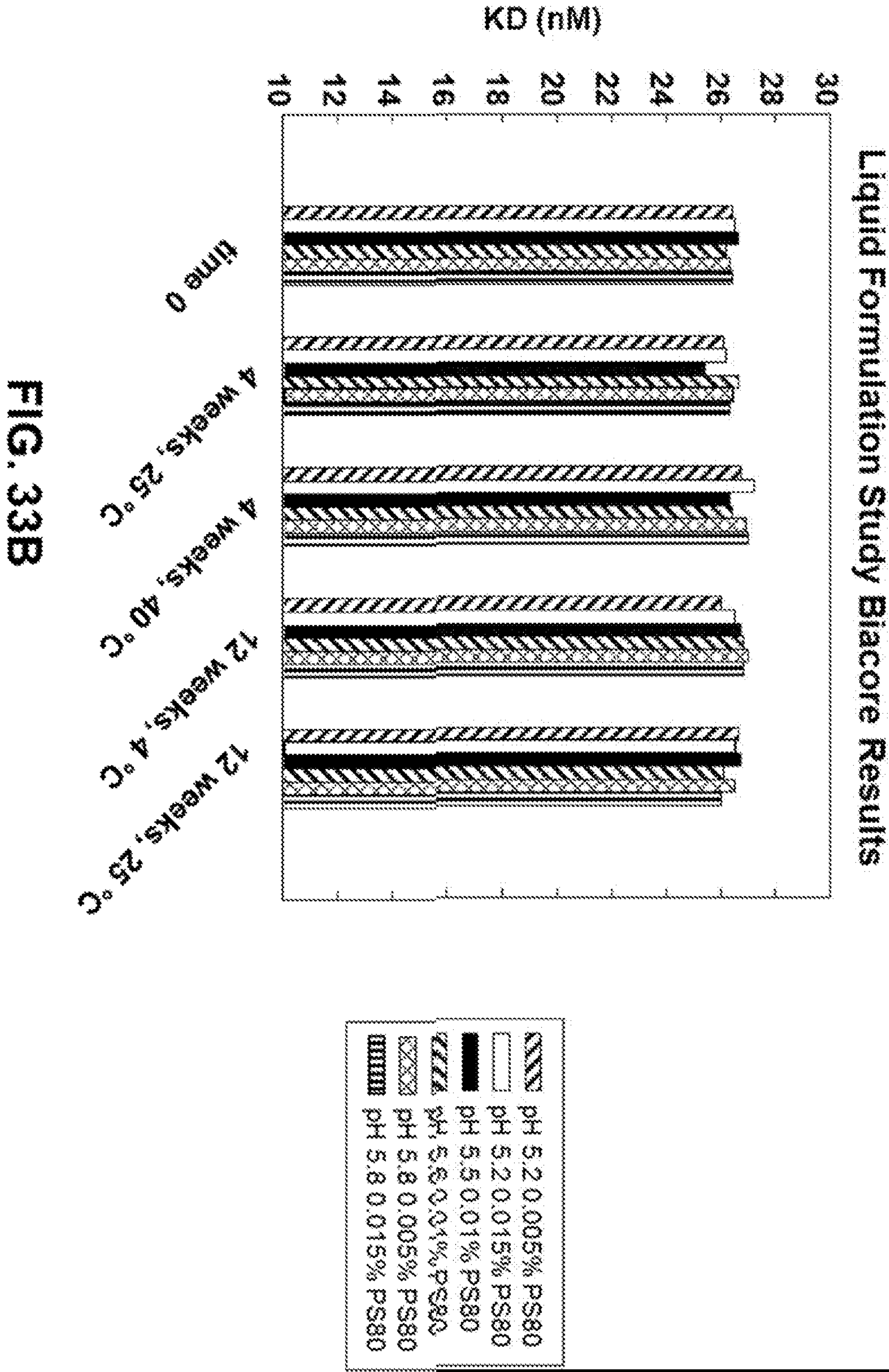


FIG. 33A



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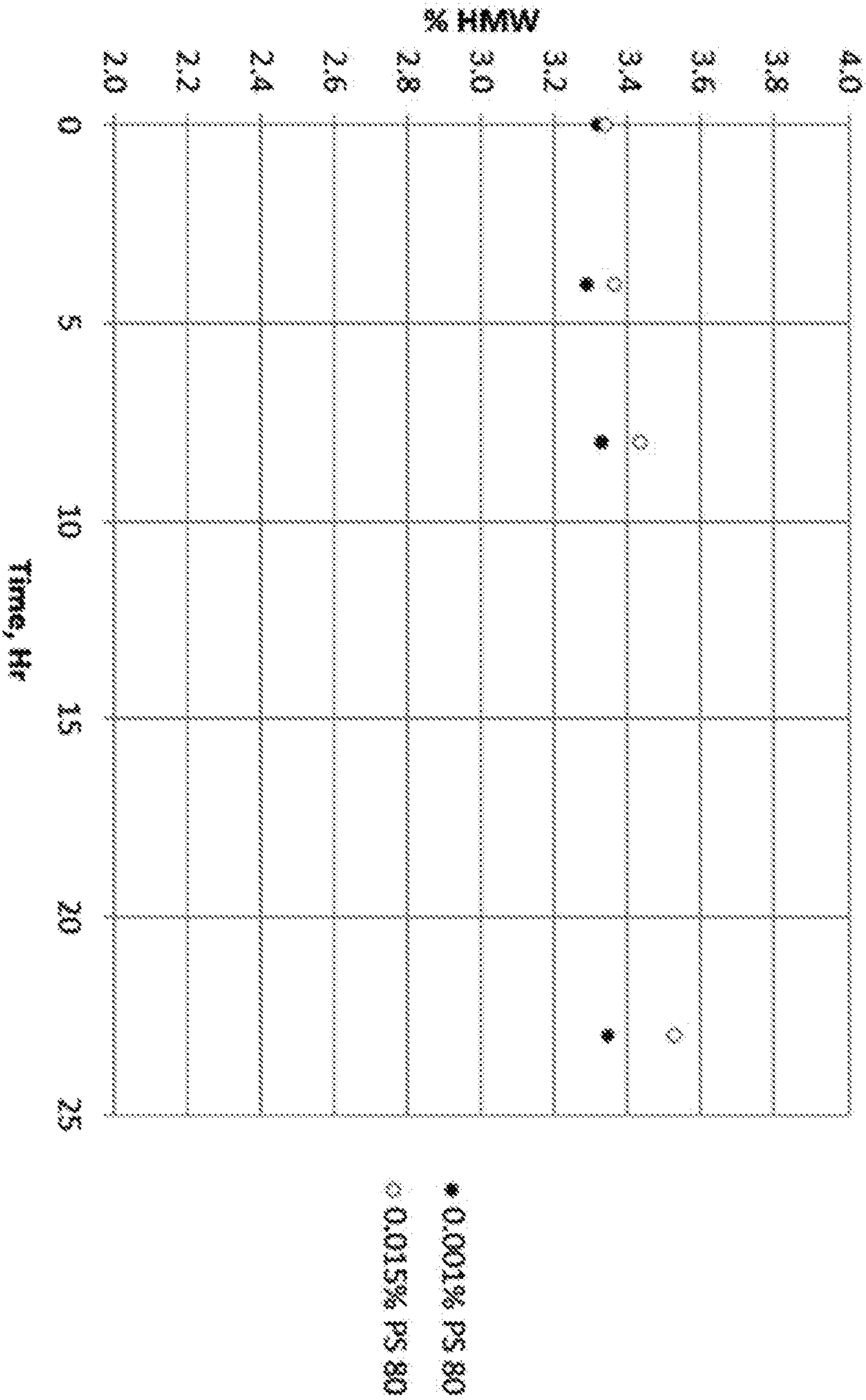


FIG. 34A

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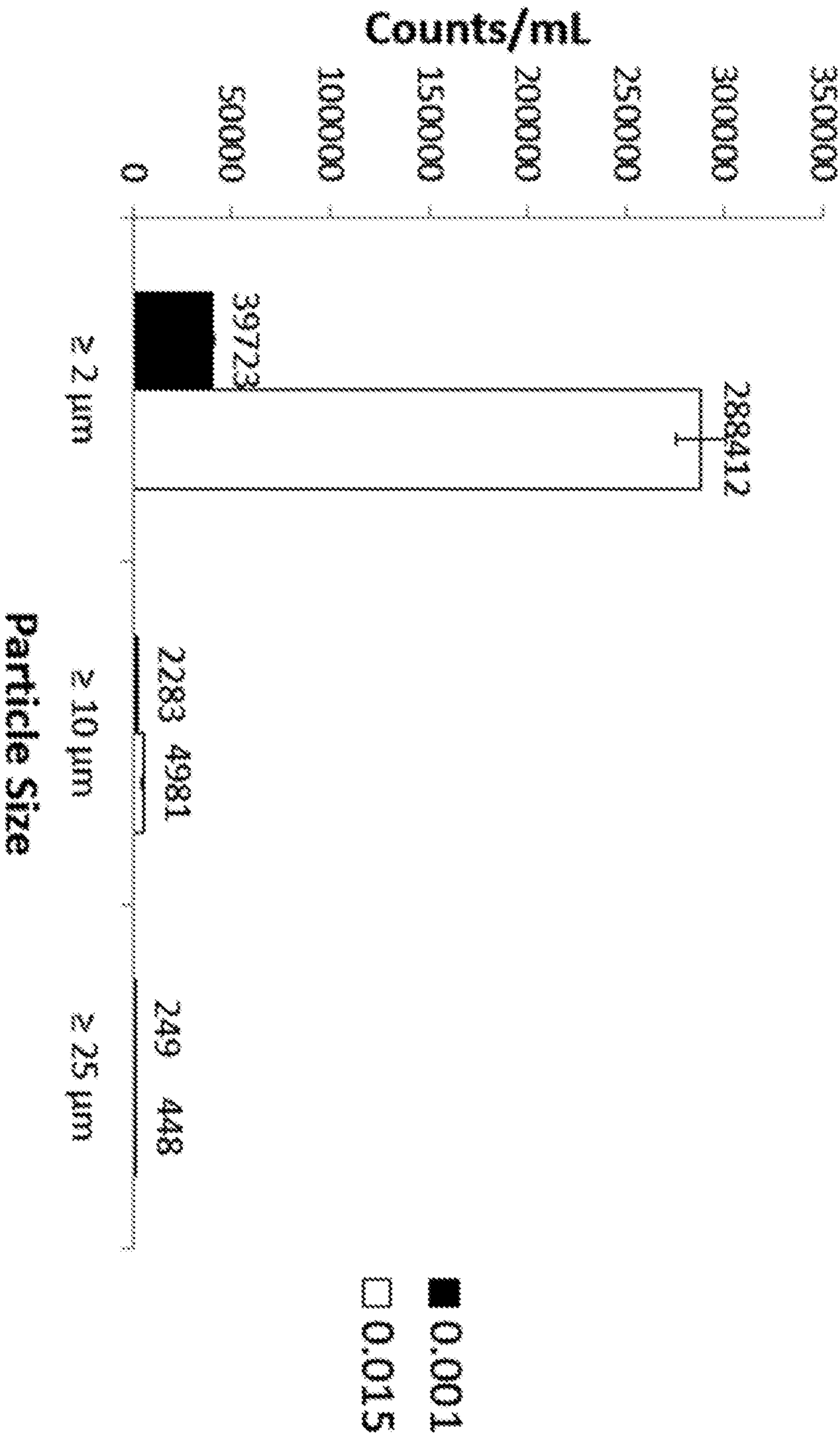


FIG. 34B

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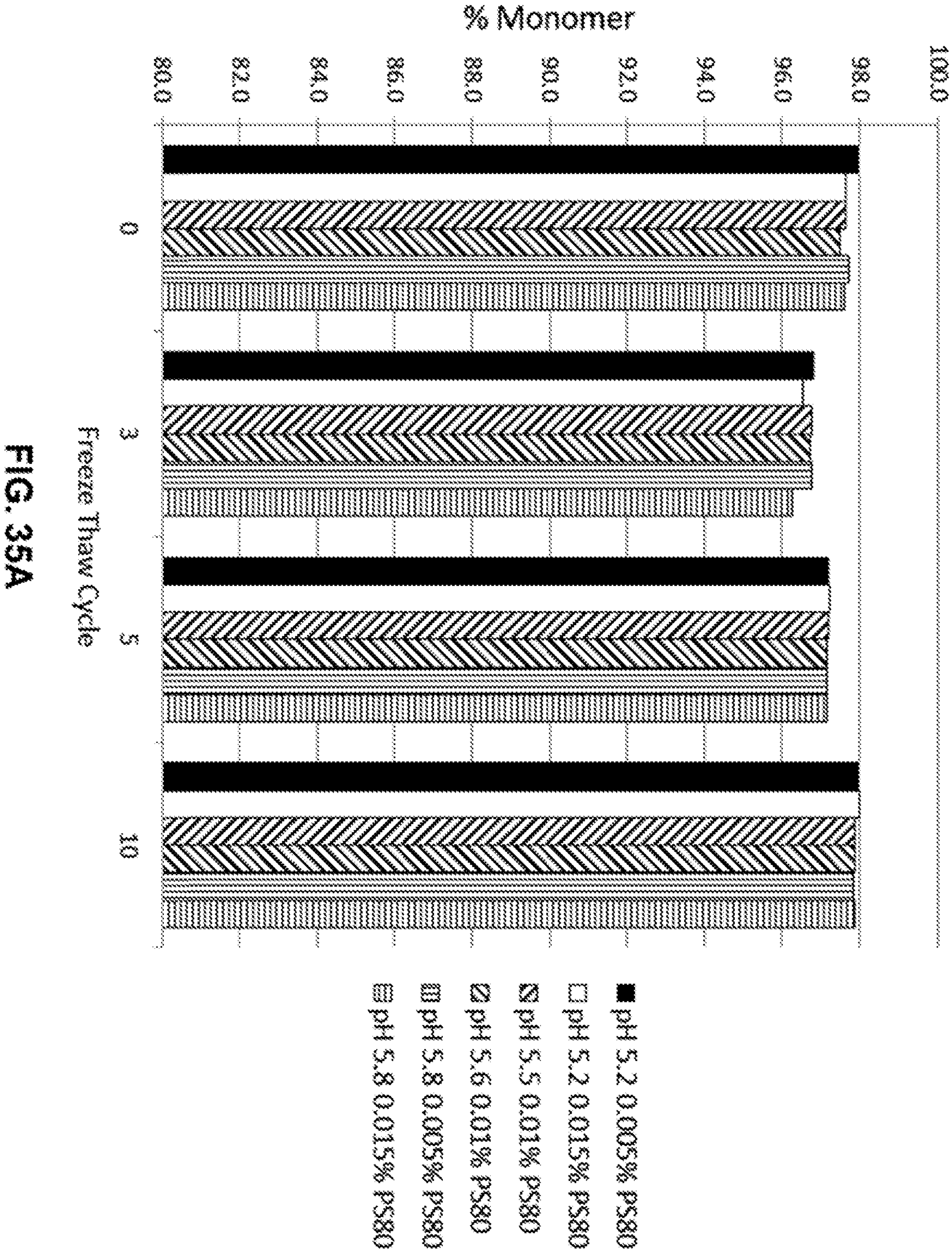


FIG. 35A

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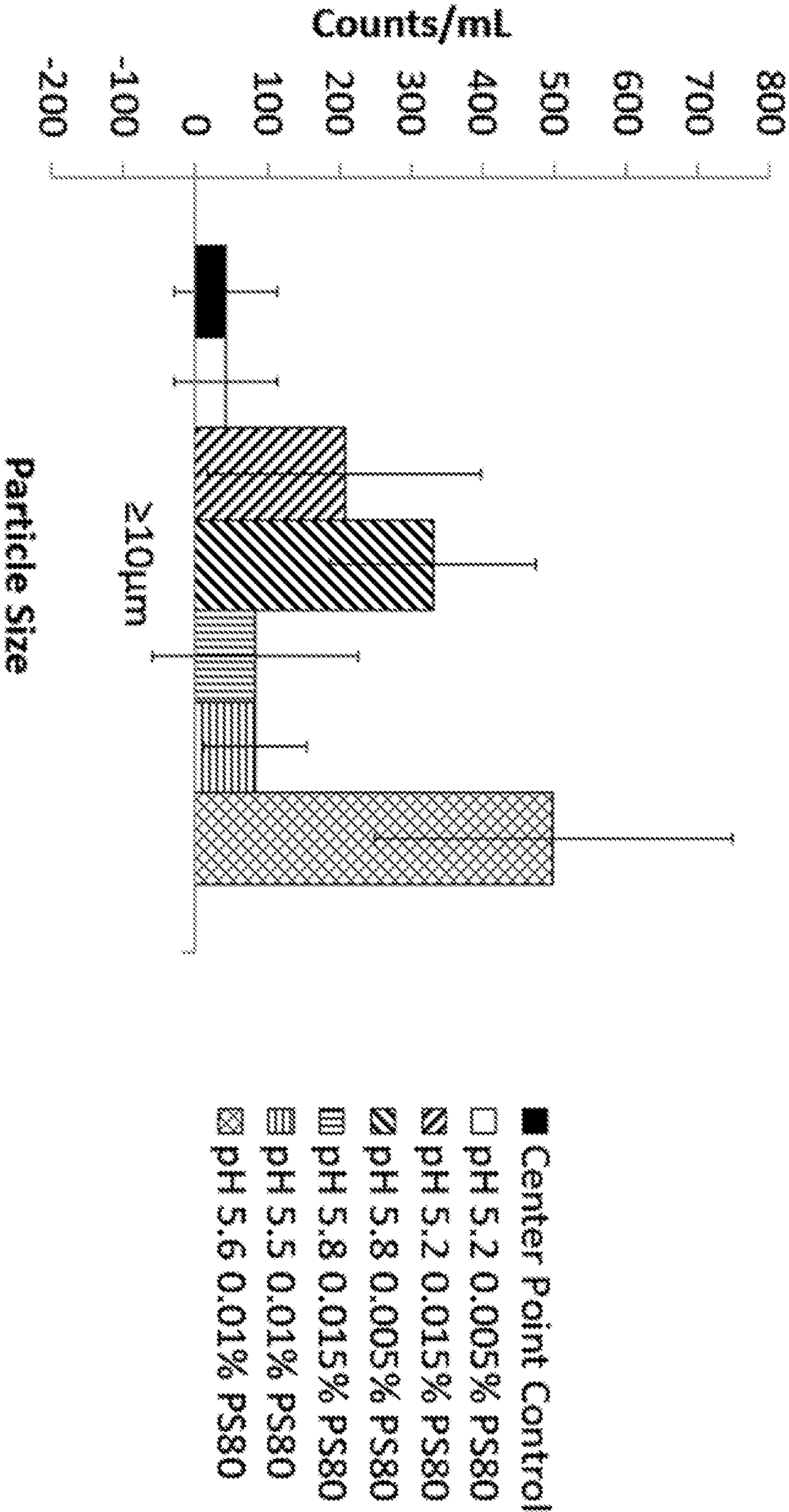


FIG. 35B

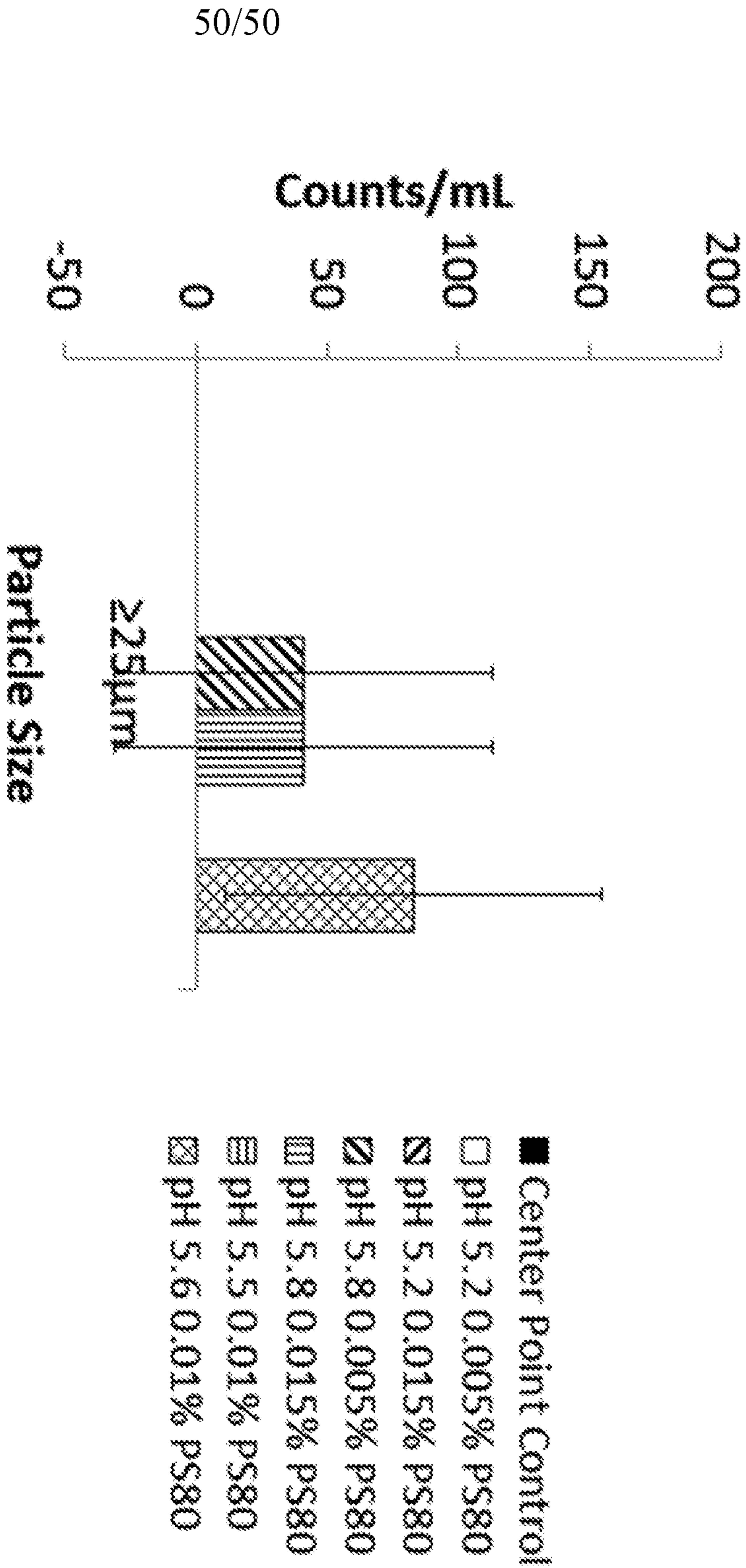


FIG. 35C

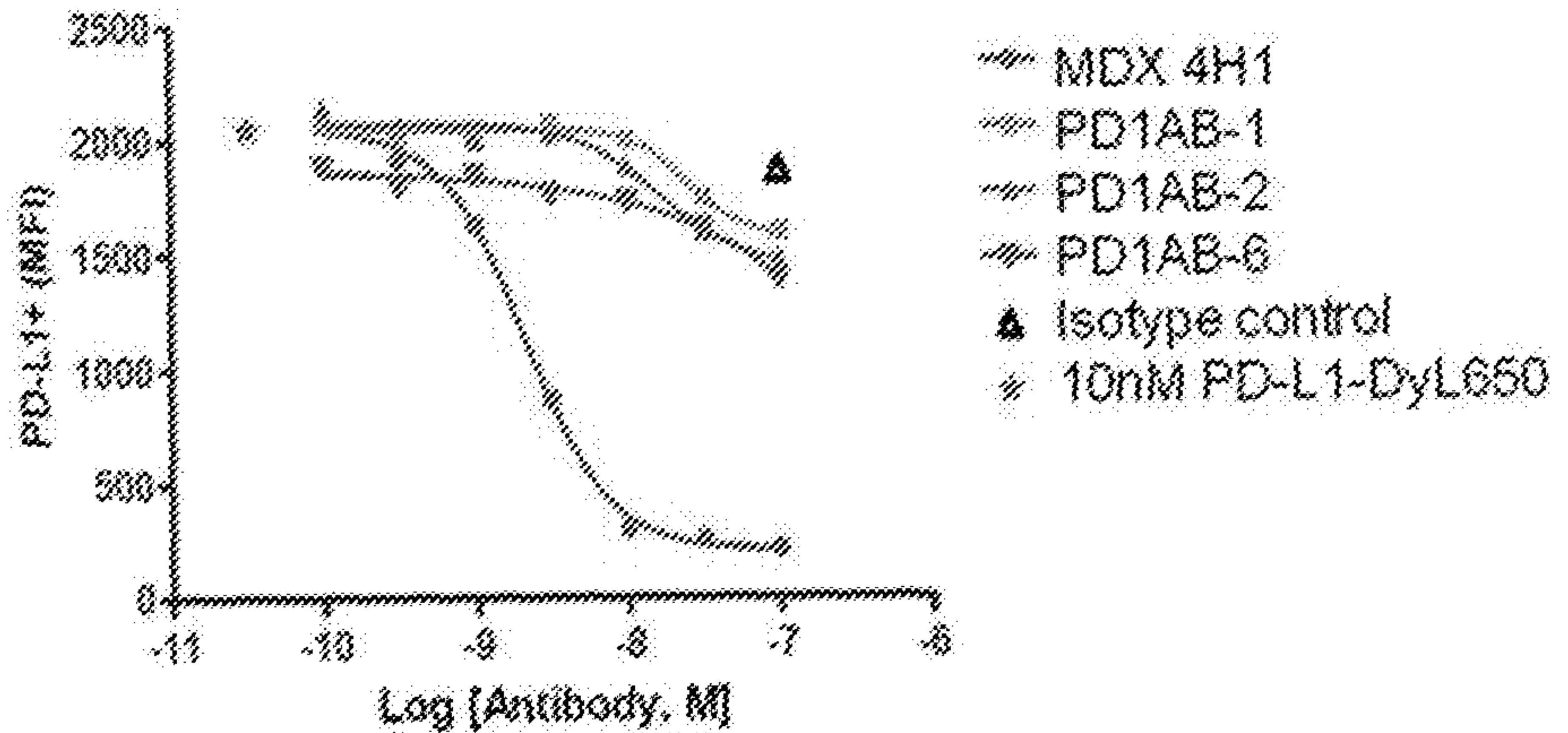


FIG. 1A