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(71) Applicant(s)
Agenus Inc.;Ludwig Institute for Cancer Research Ltd;Memorial Sloan Kettering Cancer Center

(72) Inventor(s)
Van Dijk, Marc;Mundt, Cornelia Anne;Ritter, Gerd;Schaer, David;Wolchok, Jedd David;Merghoub, Taha;Wilson, Nicholas Stuart;Savitsky, David Adam;Findeis, Mark Arthur;Zappasodi, Roberta;Holmgaard, Rikke Bæk;Cuillerot, Jean-Marie;Proscurshim, Igor;Shebanova, Olga

(74) Agent / Attorney
AJ PARK, PO Box 949, Wellington, 6140, NZ

(56) Related Art
JEDD D. WOLCHOK ET AL: "Nivolumab plus Ipilimumab in Advanced Melanoma", NEW ENGLAND JOURNAL OF MEDICINE, vol. 369, no. 2, 11 July 2013 (2013-07-11), pages 122 - 133, XP055182024, ISSN: 0028-4793, DOI: 10.1056/NEJMoa1302369
MARK J. SELBY ET AL: "Preclinical Development of Ipilimumab and Nivolumab Combination Immunotherapy: Mouse Tumor Models, In Vitro Functional Studies, and Cynomolgus Macaque Toxicology", PLOS ONE, vol. 11, no. 9, 9 September 2016

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(71) Applicants: **AGENUS INC.** [US/US]; 3 Forbes Road, Lexington, MA 02421 (US). **LUDWIG INSTITUTE FOR CANCER RESEARCH LTD** [CH/CH]; Stadelhoferstrasse 22, 8001 Zurich (CH). **MEMORIAL SLOAN KETTERING CANCER CENTER** [US/US]; 1275 York Avenue, New York, NY 10065 (US).

(72) Inventors: **VAN DIJK, Marc**; Tolhuislaan 8A, 3735KG Bosch en Duin (NL). **MUNDT, Cornelia Anne**; Hangstrasse 34, 79539 Lörrach (DE). **RITTER, Gerd**; c/o Ludwig Institute for Cancer Research, 666 Third Avenue, New York, New York 10017 (US). **SCHAER, David**; 715 Shore Acres Drive, Mamaroneck, NY 10543 (US). **WOLCHOK, Jedd David**; 333 E. 30th St., Apt. 17C, New York, New York 10016 (US). **MERGHOUB, Taha**; 10 Huron Ave., Apt. 14K, Jersey City, NJ 07306 (US). **WILSON, Nicholas Stuart**; 292 Grove Street, Medford, Massachusetts 02155 (US). **SAVITSKY, David Adam**; 28 Sunrise Road, Boxford, MA 01921 (US). **FINDEIS, Mark Arthur**; 431 School Street, Belmont, Massachusetts 02478 (US). **ZAPPASODI, Roberta**; 475 Main Street, Apt. 2U, New York, NY 10044 (US). **HOLMGAARD, Rikke Bæk**; 200 W. 60th St., Apt. 14F, New York, New York 10023 (US). **CUILLEROT, Jean-Marie**; 5 Tower Court Apt. #4, Somerville, Massachusetts 02143 (US). **PROSCURSHIM, Igor**; 1193 Curve St., Carlisle, Massachusetts 01741 (US). **SHEBANOVA, Olga**; 13 Malvern Ave. #1, Somerville, Massachusetts 02144 (US).

(74) Agent: **WILKINS, Andrew T.** et al.; Lathrop & Gage LLP, 28 State Street, Suite 700, Boston, Massachusetts 02109 (US).

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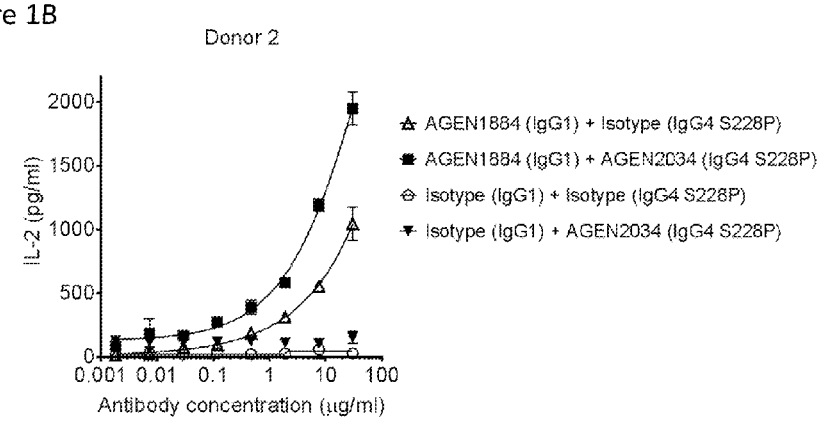
(54) Title: ANTIBODIES AND METHODS OF USE THEREOF

Figure 1B



(57) Abstract: Provided are antibodies that specifically bind to CTLA-4 and/or PD-1 and antagonize CTLA-4 and/or PD-1 function. Also provided are pharmaceutical compositions and kits comprising these antibodies, nucleic acids encoding these antibodies, expression vectors and host cells for making these antibodies, and methods of treating a subject using these antibodies either alone or in combination.

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ANTIBODIES AND METHODS OF USE THEREOF

1. RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos: 62/431,279, filed December 7, 2016; 62/570,451, filed October 10, 2017; 62/582,814, filed November 7, 2017; and 62/586,605, filed November 15, 2017, each of which is incorporated by reference herein in its entirety.

2. FIELD

[0002] The instant disclosure relates to antibodies that specifically bind to CTLA-4 (*e.g.*, human CTLA-4) and/or PD-1 (*e.g.*, human PD-1), and methods of using these antibodies.

3. BACKGROUND

[0003] CTLA-4 is an inhibitory receptor upregulated on T-cells (Alegre et al., 2001, Nat Rev Immunol 1:220-8). CTLA-4 inhibits the immune response in several ways: it competes with the T cell co-stimulatory receptor CD28 for its ligands, CD80 and CD86, and thus blocks co-stimulation; it negatively signals to inhibit T-cell activation; and it can also capture CD80 and CD86 from opposing cells by trans-endocytosis, resulting in impaired T cell costimulation via CD28 (Krummel and Allison, 1995, J Exp Med 182:459-465; Walunas et al., 1994, Immunity 1:405-413; Qureshi et al., 2011, Science 332:600-603).

[0004] PD-1 is another inhibitory receptor that is expressed on activated B cells, T cells, and myeloid cells (Agata et al. (1996) Int Immunol 8:765-72; Okazaki et al. (2002) Curr. Opin. Immunol. 14: 391779-82; Bennett et al. (2003) J Immunol 170:711-8). Two ligands for PD-1 have been identified, PD-L1 and PD-L2, that have been shown to downregulate T cell activation upon binding to PD-1 (Freeman et al. (2000) J Exp Med 192:1027-34; Latchman et al. (2001) Nat Immunol 2:261-8; Carter et al. (2002) Eur J Immunol 32:634-43). The interaction between PD-1 and PD-L1 results in a decrease in tumor infiltrating lymphocytes, a decrease in T cell receptor mediated proliferation, and immune evasion by the cancerous cells (Dong et al. (2003) J. Mol. Med. 81:281-7; Blank et al. (2005) Cancer Immunol. Immunother. 54:307-314; Konishi et al. (2004) Clin. Cancer Res. 10:5094-100). This immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1 (Iwai et al. (2002) Proc. Nat'l. Acad. Sci. USA 99:12293-7; Brown et al. (2003) J. Immunol. 170:1257-66).

[0005] Given the important role of CTLA-4 and PD-1 in modulating immune responses, therapies designed to antagonize both CTLA-4 and PD-1 signaling hold great promise for the treatment of diseases that involve CTLA-4- and/or PD-1-mediated immune suppression. It is

an object of the present invention to go some way towards meeting this promise and/or to at least provide the public with a usedful choice.

4. SUMMARY

[0005a] In a first aspect the present invention provides a pharmaceutical composition comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005b] In a second aspect the present invention provides a multispecific antibody comprising a first antigen-binding region that specifically binds to human CTLA-4 and a second antigen-binding region that specifically binds to human PD-1, wherein:

(a) the first antigen-binding region comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second antigen-binding region comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005c] In a third aspect the present invention provides a kit comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the

complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005d] In a fourth aspect the present invention provides a method of enhancing T cell activation and/or proliferation in a subject, the method comprising administering to the subject an effective amount of a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005e] In a fifth aspect the present invention provides a method of treating a cancer in a subject, the method comprising administering to the subject an effective amount of a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH

amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005f] In a sixth aspect the present invention provides a method of treating an infectious disease in a subject, the method comprising administering to the subject an effective amount of a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005g] In a seventh aspect the present invention provides a use of a first isolated antibody that specifically binds to human CTLA-4 in combination with a second isolated antibody that specifically binds to human PD-1 in a method of enhancing T cell activation and/or proliferation in a subject, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005h] In an eighth aspect the present invention provides a use of a first isolated antibody that specifically binds to human CTLA-4 in combination with a second isolated antibody that specifically binds to human PD-1 in a method of treating an infectious disease in

a subject, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005i] In a ninth aspect the present invention provides a use of a first isolated antibody that specifically binds to human CTLA-4 in combination with a second isolated antibody that specifically binds to human PD-1 in a method of treating a cancr in a subject, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005j] In a tenth aspect the present invention provides a use of a first isolated antibody that specifically binds to human CTLA-4 in combination with a second isolated antibody that specifically binds to human PD-1 in the manufacture of a medicament for treating a cancer in a subject, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the

complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

[0005k] In an eleventh aspect the present invention provides a method of enhancing T cell activation and/or proliferation in a subject, the method comprising administering to the subject an effective amount of the composition of the first aspect, or the multispecific antibody of the second aspect.

[0005l] In a twelfth aspect the present invention provides a method of treating an infectious disease in a subject, the method comprising administering to the subject an effective amount of the composition of the first aspect, or the multispecific antibody of the second aspect.

[0005m] In a thirteenth aspect the present invention provides a method of treating a cancer in a subject, the method comprising administering to the subject an effective amount of the composition of the first aspect, or the multispecific antibody of the second aspect.

[0005n] In a fourteenth aspect the present invention provides a use of the composition of the first aspect, or the multispecific antibody of the second aspect, or the kit of the third aspect, for enhancing T cell activation and/or proliferation, for treating an infectious disease, or for treating a cancer in subject.

[0005o] In a fifteenth aspect the present invention provides a use of the composition of the first aspect, or the multispecific antibody of the second aspect, or the kit of the third aspect, in the manufacture of a medicament for treating a cancer in a subject.

[0005p] In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

[0005q] In the description in this specification reference may be made to subject matter that is not within the scope of the claims of the current application. That subject matter should be readily identifiable by a person skilled in the art and may assist in putting into practice the invention as defined in the claims of this application.

4a. BRIEF DESCRIPTION

[0006] The instant disclosure provides antibodies that specifically bind to CTLA-4 (*e.g.*, human CTLA-4) and/or PD-1 (*e.g.*, human PD-1) and antagonize CTLA-4 and/or PD-1 function, *e.g.*, immune suppression mediated by CTLA-4 and/or PD-1. Also provided are pharmaceutical compositions and kits comprising these antibodies, nucleic acids encoding these antibodies, expression vectors and host cells for making these antibodies, and methods of treating a subject using these antibodies. The antibodies described herein are particularly useful for increasing T cell activation in response to an antigen (*e.g.*, a tumor antigen or an infectious disease antigen), and hence for treating cancer in a subject or treating or preventing an infectious disease in a subject.

[0007] Accordingly, in one aspect, the instant disclosure provides a method of enhancing or inducing an immune response in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein
X_1 is S or A; and
X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein:
X_1 is S or G;
X_2 is R, S, or T; and
X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein:
X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F,

and wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(g) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(h) CDRH2 comprises the amino acid sequence of $VIWX_1DGSNX_2YYADSVX_3G$ (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(i) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(j) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(k) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(l) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0008] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein

X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO:

22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of RASQSVX_1X_2YLX_3 (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3$RAT (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of QQYGX_1SPX_2T (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F,

and wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(g) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(h) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(i) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(j) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(k) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(l) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0009] In another aspect, the instant disclosure provides a method of treating an infectious

disease in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein

X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F,

and wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(g) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(h) CDRH2 comprises the amino acid sequence of $VIWX_1DGSNX_2YYADSVX_3G$ (SEQ

ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(i) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(j) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(k) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(l) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0010] In another aspect, the instant disclosure provides a method of enhancing or inducing an immune response in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein

X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F.

[0011] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein

X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F.

[0012] In another aspect, the instant disclosure provides a method of treating an infectious

disease in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein

X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F.

[0013] In another aspect, the instant disclosure provides a method of enhancing or inducing an immune response in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and

CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(b) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0014] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(b) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0015] In another aspect, the instant disclosure provides a method of treating an infectious disease in a subject, the method comprising administering to the subject an effective amount

of a therapeutic combination comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(b) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0016] In another aspect, the instant disclosure provides a method of enhancing or inducing an immune response in a subject, the method comprising administering to the subject an effective amount of a first isolated antibody that specifically binds to human CTLA-4, optionally as a monotherapy, wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein

X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of RASQSVX_1X_2YLX_3 (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F.

[0017] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a first isolated antibody that specifically binds to human CTLA-4, optionally as a monotherapy, wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein

X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F.

[0018] In another aspect, the instant disclosure provides a method of treating an infectious disease in a subject, the method comprising administering to the subject an effective amount of a first isolated antibody that specifically binds to human CTLA-4, optionally as a monotherapy, wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein

X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F.

[0019] In another aspect, the instant disclosure provides a method of enhancing or inducing an immune response in a subject, the method comprising administering to the subject an effective amount of a second isolated antibody that specifically binds to human PD-1, optionally as a monotherapy, wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(b) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0020] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a second isolated antibody that specifically binds to human PD-1, optionally as a monotherapy, wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(b) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0021] In another aspect, the instant disclosure provides a method of treating an infectious disease in a subject, the method comprising administering to the subject an effective amount of a second isolated antibody that specifically binds to human PD-1, optionally as a monotherapy, wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(b) CDRH2 comprises the amino acid sequence of $VIWX_1DGSNX_2YYADSVX_3G$ (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0022] In certain embodiments, CDRH1 of the first isolated antibody comprises the amino acid sequence of SEQ ID NO: 20 or 21. In certain embodiments, CDRH3 of the first isolated antibody comprises the amino acid sequence of SEQ ID NO: 24 or 26. In certain embodiments, CDRL1 of the first isolated antibody comprises the amino acid sequence of SEQ ID NO: 27, 28, or 29. In certain embodiments, CDRL2 of the first isolated antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30-35. In certain embodiments, CDRL3 of the first isolated antibody comprises the amino acid sequence of SEQ ID NO: 36, 37, or 38. In certain embodiments, CDRH1, CDRH2, and CDRH3 of the first isolated antibody comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 20, 22, and 24; 21, 22, and 24; or 21, 22, and 26, respectively. In certain embodiments, CDRL1, CDRL2, and CDRL3 of the first isolated antibody comprise the

CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 27, 30, and 36; 28, 31, and 36; 29, 32, and 37; 29, 33, and 38; 29, 34, and 36; or 29, 35, and 38, respectively.

[0023] In certain embodiments, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 20, 22, 24, 27, 30, and 36; 20, 22, 24, 29, 32, and 37; 20, 22, 24, 29, 33, and 38; 21, 22, 24, 27, 30, and 36; 21, 22, 24, 29, 33, and 38; 20, 22, 24, 28, 31, and 36; 20, 22, 24, 29, 34, and 36; 20, 22, 24, 29, 35, and 38; 21, 22, 26, 27, 30, and 36; 21, 22, 26, 29, 32, and 37; 21, 22, 26, 29, 33, and 38; or 21, 22, 26, 29, 35, and 38, respectively. In certain embodiments, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 20, 22, 24, 27, 30, and 36, respectively.

[0024] In certain embodiments, the first isolated antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 116. In certain embodiments, the first isolated antibody comprises a heavy chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 9-13. In certain embodiments, the heavy chain variable region of the first isolated antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 9-13.

[0025] In certain embodiments, the first isolated antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 47. In certain embodiments, the first isolated antibody comprises a light chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 14-19. In certain embodiments, the light chain variable region of the first isolated antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 14-19.

[0026] In certain embodiments, the heavy chain variable region and the light chain variable region of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and 15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively. In certain embodiments, the heavy chain variable region and the light chain variable region of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively.

[0027] In certain embodiments, the first isolated antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-21 germline sequence. In certain embodiments, the first isolated antibody comprises a light chain variable region

having an amino acid sequence derived from a human IGKV3-20 or IGKV3-11 germline sequence.

[0028] In certain embodiments, the first isolated antibody comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 51-54 and 117, and a light chain comprising the amino acid sequence of SEQ ID NO: 59. In certain embodiments, the first isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NOs: 51, and a light chain comprising the amino acid sequence of SEQ ID NO: 59. In certain embodiments, the first isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NOs: 117, and a light chain comprising the amino acid sequence of SEQ ID NO: 59.

[0029] In certain embodiments, the first isolated antibody comprises a heavy chain constant region selected from the group consisting of human IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, IgA_2. In certain embodiments, the first isolated antibody comprises an IgG_1 heavy chain constant region. In certain embodiments, the first isolated antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 60. In certain embodiments, the amino acid sequence of the IgG_1 heavy chain constant region comprises S239D/I332E mutations, numbered according to the EU numbering system. In certain embodiments, the first isolated antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 61. In certain embodiments, the amino acid sequence of the IgG_1 heavy chain constant region comprises S239D/A330L/I332E mutations, numbered according to the EU numbering system. In certain embodiments, the first isolated antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 62. In certain embodiments, the amino acid sequence of the IgG_1 heavy chain constant region comprises L235V/F243L/R292P/Y300L/P396L mutations, numbered according to the EU numbering system. In certain embodiments, the first isolated antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 63. In certain embodiments, the IgG_1 heavy chain constant region is non-fucosylated IgG_1. In certain embodiments, the first isolated antibody comprises an IgG_2 heavy chain constant region. In certain embodiments, the first isolated antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 118.

[0030] In certain embodiments, the first isolated antibody comprises a light chain constant region selected from the group consisting of human Igκ and Igλ. In certain embodiments, the first isolated antibody comprises an Igκ light chain constant region. In certain embodiments, the first isolated antibody comprises a light chain constant region comprising the amino acid

sequence of SEQ ID NO: 64.

[0031] In certain embodiments, the first isolated antibody binds to the same epitope of human CTLA-4 as an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14. In certain embodiments, the first isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 97-102.

[0032] In certain embodiments, the first isolated antibody is antagonistic to human CTLA-4.

[0033] In certain embodiments, CDRH2 of the second isolated antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 76-79. In certain embodiments, CDRH3 of the second isolated antibody comprises the amino acid sequence of SEQ ID NO: 80, 81, or 82. In certain embodiments, CDRH1, CDRH2, and CDRH3 of the second isolated antibody comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 75, 76, and 80; 75, 76, and 81; 75, 76, and 82; 75, 77, and 81; 75, 78, and 81; or 75, 79, and 81, respectively.

[0034] In certain embodiments, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 75, 76, 80, 83, 84, and 85; 75, 76, 81, 83, 84, and 85; 75, 76, 82, 83, 84, and 85; 75, 77, 81, 83, 84, and 85; 75, 78, 81, 83, 84, and 85; or 75, 79, 81, 83, 84, and 85, respectively. In certain embodiments, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 75, 76, 81, 83, 84, and 85, respectively.

[0035] In certain embodiments, the second isolated antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 88. In certain embodiments, the second isolated antibody comprises a heavy chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-73. In certain embodiments, the heavy chain variable region of the second isolated antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-73. In certain embodiments, the second isolated antibody comprises a light chain variable region comprising an amino acid sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to the amino acid sequence of SEQ ID NO: 74. In certain embodiments, the light chain variable region of the second isolated antibody comprises the amino acid sequence of

SEQ ID NO: 74.

[0036] In certain embodiments, the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67 and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively. In certain embodiments, the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively.

[0037] In certain embodiments, the second isolated antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-33 germline sequence. In certain embodiments, the second isolated antibody comprises a light chain variable region having an amino acid sequence derived from a human IGKV3-15 germline sequence.

[0038] In certain embodiments, the second isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 93. In certain embodiments, the second isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 92 and a light chain comprising the amino acid sequence of SEQ ID NO: 93. In certain embodiments, the second isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 120 and a light chain comprising the amino acid sequence of SEQ ID NO: 93.

[0039] In certain embodiments, the second isolated antibody comprises a heavy chain constant region selected from the group consisting of human IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2. In certain embodiments, the second isolated antibody comprises an IgG_1 heavy chain constant region. In certain embodiments, the amino acid sequence of the IgG_1 heavy chain constant region comprises an N297A mutation, numbered according to the EU numbering system. In certain embodiments, the second isolated antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 94. In certain embodiments, the second isolated antibody comprises an IgG_4 heavy chain constant region. In certain embodiments, the amino acid sequence of the IgG_4 heavy chain constant region comprises an S228P mutation, numbered according to the EU numbering system. In certain embodiments, the second isolated antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 95.

[0040] In certain embodiments, the second isolated antibody comprises a light chain constant region selected from the group consisting of human Igκ and Igλ. In certain embodiments, the second isolated antibody comprises an Igκ light chain constant region. In

certain embodiments, the second isolated antibody comprises a light chain constant region comprising the amino acid sequence of SEQ ID NO: 64.

[0041] In certain embodiments, the second isolated antibody binds to the same epitope of human PD-1 as an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 74. In certain embodiments, the second isolated antibody binds to an epitope located within a region of human PD-1 consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 103-107.

[0042] In certain embodiments, the second isolated antibody is antagonistic to human PD-1.

[0043] In certain embodiments, the second isolated antibody is selected from the group consisting of pembrolizumab, nivolumab, and pidilizumab. In certain embodiments, the second isolated antibody is pembrolizumab.

[0044] In certain embodiments, the first isolated antibody is selected from the group consisting of ipilimumab and tremelimumab. In certain embodiments, the first isolated antibody is ipilimumab.

[0045] In certain embodiments, the first isolated antibody is administered at 0.3 mg/kg or 1 mg/kg. In certain embodiments, the second isolated antibody is administered at 1 mg/kg, 3 mg/kg, or 6 mg/kg. In certain embodiments, the second isolated antibody is administered at the dose of 200 mg, optionally wherein the second isolated antibody is pembrolizumab. In certain embodiments, the first isolated antibody is administered at 0.3 mg/kg or 1 mg/kg, and the second isolated antibody is administered at 1 mg/kg, 3 mg/kg, or 6 mg/kg. In certain embodiments, the first isolated antibody is administered at 0.3 mg/kg, and the second isolated antibody is administered at 1 mg/kg. In certain embodiments, the first isolated antibody is administered at 1 mg/kg, and the second isolated antibody is administered at 1 mg/kg. In certain embodiments, the first isolated antibody is administered at 1 mg/kg, and the second isolated antibody is administered at 3 mg/kg. In certain embodiments, the first isolated antibody is administered at 1 mg/kg, and the second isolated antibody is administered at 6 mg/kg. In certain embodiments, the first isolated antibody is administered at about 0.3 mg/kg or 1 mg/kg, and the second isolated antibody is administered at about 1 mg/kg or 3 mg/kg. In certain embodiments, the first isolated antibody is administered at about 0.3 mg/kg, and the second isolated antibody is administered at about 1 mg/kg. In certain embodiments, the first isolated antibody is administered at about 1 mg/kg, and the second isolated antibody is administered at about 1 mg/kg. In certain embodiments, the first isolated antibody is

administered at about 1 mg/kg, and the second isolated antibody is administered at about 3 mg/kg. In certain embodiments, the first isolated antibody is administered at about 1 mg/kg, and the second isolated antibody is administered at about 6 mg/kg. In certain embodiments, the first isolated antibody is administered every six weeks. In certain embodiments, the second isolated antibody is administered every two weeks or every three weeks. In certain embodiments, the first isolated antibody is administered every six weeks, and the second isolated antibody is administered every two weeks or every three weeks. In certain embodiments, the first isolated antibody is administered about every six weeks, and the second isolated antibody is administered about every two weeks or about every three weeks. In certain embodiments, the first isolated antibody is administered at 0.3 mg/kg every six weeks, and the second isolated antibody is administered at 1 mg/kg every two weeks. In certain embodiments, the first isolated antibody is administered at 1 mg/kg every six weeks, and the second isolated antibody is administered at 1 mg/kg every two weeks. In certain embodiments, the first isolated antibody is administered at 1 mg/kg every six weeks, and the second isolated antibody is administered at 3 mg/kg every two weeks. In certain embodiments, the first isolated antibody is administered at 1 mg/kg every six weeks, and the second isolated antibody is administered at 6 mg/kg every three weeks. In certain embodiments, the first isolated antibody is administered at about 0.3 mg/kg about every six weeks, and the second isolated antibody is administered at about 1 mg/kg about every two weeks. In certain embodiments, the first isolated antibody is administered at about 1 mg/kg about every six weeks, and the second isolated antibody is administered at about 1 mg/kg about every two weeks. In certain embodiments, the first isolated antibody is administered at about 1 mg/kg about every six weeks, and the second isolated antibody is administered at about 3 mg/kg about every two weeks. In certain embodiments, the first isolated antibody is administered at about 1 mg/kg about every six weeks, and the second isolated antibody is administered at about 6 mg/kg about every three weeks. In certain embodiments, the first isolated antibody is administered intravenously. In certain embodiments, the second isolated antibody is administered intravenously. In certain embodiments, the first isolated antibody and the second isolated antibody are both administered intravenously.

[0046] In certain embodiments, the subject has cancer. In certain embodiments, the subject has a metastatic or locally advanced solid tumor.

[0047] In certain embodiments, the cancer is a cervical cancer. In certain embodiments, the cancer is a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix. In certain embodiments, the

metastatic or locally advanced solid tumor is a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix. In certain embodiments, no standard therapy is available for the cancer (e.g., cervical cancer) or metastatic or locally advanced solid tumor. In certain embodiments, the cancer (e.g., cervical cancer) or metastatic or locally advanced solid tumor is refractory to a standard therapy. In certain embodiments, the cancer (e.g., cervical cancer) or metastatic or locally advanced solid tumor has relapsed after a standard therapy. In certain embodiments, the standard therapy comprises a platinum-containing chemotherapy. In certain embodiments, the standard therapy is a platinum-containing doublet. In certain embodiments, the cancer (e.g., cervical cancer) is a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix that has relapsed after a platinum-containing doublet administered for treatment of advanced (recurrent, unresectable, or metastatic) disease. In certain embodiments, the cancer (e.g., cervical cancer) or metastatic or locally advanced solid tumor is HPV positive. In certain embodiments, the cancer or metastatic or locally advanced solid tumor is head and neck cancer, melanoma, renal cell carcinoma, urothelial carcinoma, or endometrial carcinoma. In certain embodiments, the cancer (e.g., cervical cancer) or metastatic or locally advanced solid tumor is associated with microsatellite instability.

[0048] In certain embodiments, the subject has cervical cancer (e.g., a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix), and the method comprises administering to the subject an effective amount of an anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody as a first cancer therapy after diagnosis of the cervical cancer (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis), optionally wherein the anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P) or pharmaceutical composition comprising such anti-PD-1 antibody is administered at the dosage and at the frequency shown in a single row of Table 13 herein. In certain embodiments, the subject has cervical cancer (e.g., a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix), and the method comprises administering to the subject an effective amount of a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) an anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody as a first

cancer therapy after diagnosis of the cervical cancer (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis), optionally wherein the anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody, and the anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody, are administered at the dosage and at the frequency shown in a single row of Table 13 herein. In certain embodiments, the subject has cervical cancer (e.g., a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix), and the method comprises administering to the subject an effective amount of a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody and (b) pembrolizumab or pharmaceutical composition comprising pembrolizumab as a first cancer therapy after diagnosis of the cervical cancer (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis), optionally wherein the anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody is administered at the dosage and at the frequency shown in a single row of Table 13 herein, and pembrolizumab or composition comprising pembrolizumab is administered at 200 mg every three weeks.

[0049] In certain embodiments, the cancer expresses PD-L1. In certain embodiments, the percentage of tumor cells in a sample of the cancer that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%). In certain embodiments, the percentage of tumor cells in a sample of the cancer that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1%. In certain embodiments, the percentage of tumor cells in a sample of the cancer that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 5%. In certain embodiments, the percentage of tumor cells in a sample of the cancer that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 25%. In certain embodiments, the percentage of tumor cells in a sample of the cancer that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 50%. Membrane expression of PD-L1 may be detected by any method known in the art, e.g., immunohistochemistry. Exemplary immunohistochemistry assays for detecting PD-L1 membrane expression in tumor cells are provided in Hirsch et al. (2017, J. Thoracic Oncol. 12(2): 208-222), Rimm et al. (2017, JAMA

Oncol. 3(8): 1051-1058), and Diggs and Hsueh (2017, Biomarker Res. 5:12), which are incorporated by reference herein in their entirety.

[0050] In certain embodiments, the metastatic or locally advanced tumor expresses PD-L1. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced tumor that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%). In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced tumor that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1%. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced tumor that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 5%. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced tumor that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 25%. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced tumor that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 50%. Membrane expression of PD-L1 may be detected by any method known in the art, e.g., immunohistochemistry. Exemplary immunohistochemistry assays for detecting PD-L1 membrane expression in tumor cells are provided in Hirsch et al. (2017, J. Thoracic Oncol. 12(2): 208-222), Rimm et al. (2017, JAMA Oncol. 3(8): 1051-1058), and Diggs and Hsueh (2017, Biomarker Res. 5:12), which are incorporated by reference herein in their entirety.

[0051] In certain embodiments, the cancer is a non-small cell lung cancer (NSCLC). In certain embodiments, the NSCLC is a Stage IV NSCLC. In certain embodiments, the NSCLC is diagnosed histologically or cytologically according to the eighth edition of the American Joint Committee on Cancer staging manual. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%). In certain embodiments, the percentage of tumor cells in a sample of the NSCLC that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1%. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 5%. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC

that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 25%. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 50%. In certain embodiments, the NSCLC has no EGFR or ALK genomic tumor aberrations. In certain embodiments, the NSCLC has no EGFR sensitizing mutation (e.g., mutation that is amenable to treatment with a tyrosine kinase inhibitor including erlotinib, gefitinib, or afatanib) or ALK translocation. In certain embodiments, the subject has received no prior systemic chemotherapy treatment for NSCLC.

[0052] In certain embodiments, the metastatic or locally advanced solid tumor is a metastatic or locally advanced NSCLC. In certain embodiments, the metastatic or locally advanced solid tumor is a metastatic NSCLC. In certain embodiments, the metastatic or locally advanced solid tumor is a Stage IV, metastatic, or locally advanced NSCLC. In certain embodiments, the metastatic or locally advanced solid tumor is a Stage IV NSCLC. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced NSCLC that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%). In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced NSCLC that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1%. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced NSCLC that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 5%. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced NSCLC that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 25%. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced NSCLC that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 50%. In certain embodiments, the metastatic or locally advanced NSCLC has no EGFR or ALK genomic tumor aberrations. In certain embodiments, the metastatic or locally advanced NSCLC has no EGFR sensitizing mutation (e.g., mutation that is amenable to treatment with a tyrosine kinase inhibitor including erlotinib, gefitinib, or afatanib) or ALK translocation. In certain embodiments, the subject has received no prior systemic chemotherapy treatment for metastatic or locally advanced NSCLC.

[0053] In certain embodiments, the subject has NSCLC (e.g., Stage IV, metastatic, or locally advanced NSCLC), optionally wherein the percentage of tumor cells in a sample of the

NSCLC that exhibit detectable expression (e.g., membrane expression, partial or complete membrane expression) of PD-L1 is at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%, and the method comprises administering to the subject an effective amount of an anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody as a first cancer therapy after diagnosis of the cervical cancer (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis), optionally wherein the anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody is administered at the dosage and at the frequency shown in a single row of Table 13 herein. In certain embodiments, the subject has NSCLC (e.g., Stage IV, metastatic, or locally advanced NSCLC), optionally wherein the percentage of tumor cells in a sample of the NSCLC that exhibit detectable expression (e.g., membrane expression, partial or complete membrane expression) of PD-L1 is at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%, and the method comprises administering to the subject an effective amount of a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) an anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody as a first cancer therapy after diagnosis of the cervical cancer (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis), optionally wherein the anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody, and the anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody, are administered at the dosage and at the frequency shown in a single row of Table 13 herein. In certain embodiments, the subject has NSCLC (e.g., Stage IV, metastatic, or locally advanced NSCLC), optionally wherein the percentage of tumor cells in a sample of the NSCLC that exhibit detectable expression (e.g., membrane expression, partial or complete membrane expression) of PD-L1 is at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%, and the method comprises administering to the subject a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody, and (b) pembrolizumab or pharmaceutical composition comprising pembrolizumab as a first cancer therapy after diagnosis of the cervical cancer (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks;

or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis), optionally wherein the anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody is administered at the dosage and at the frequency shown in a single row of Table 13 herein, and pembrolizumab or pharmaceutical composition comprising pembrolizumab is administered at 200 mg every three weeks.

[0054] In certain embodiments, the cancer is a cutaneous squamous-cell carcinoma (cSCC) (e.g., a Stage IV cSCC). In certain embodiments, the metastatic or locally advanced solid tumor is a Stage IV cSCC. In certain embodiments, the cSCC is diagnosed histologically or cytologically according to the eighth edition of the American Joint Committee on Cancer staging manual. In certain embodiments, the cSCC is not curable with radiation therapy. In certain embodiments, the subject has cSCC (e.g., Stage IV cSCC), and the method comprises administering to the subject an effective amount of an anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody as a first cancer therapy after diagnosis of the cSCC (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis), optionally wherein the anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody is administered at the dosage and at the frequency shown in a single row of Table 13 herein. In certain embodiments, the subject has cSCC (e.g., Stage IV cSCC), and the method comprises administering to the subject an effective amount of a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) an anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody as a first cancer therapy after diagnosis of the cSCC (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis), optionally wherein the anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody and the anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody are administered at the dosage and at the frequency shown in a single row of Table 13 herein. In certain embodiments, the subject has cSCC (e.g., Stage IV cSCC), and the method comprises administering to the subject an effective amount of a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) pembrolizumab or pharmaceutical composition comprising pembrolizumab as a first cancer therapy after

diagnosis of the cSCC (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis), optionally wherein the anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody is administered at the dosage and at the frequency shown in a single row of Table 13 herein, and pembrolizumab or pharmaceutical composition comprising pembrolizumab is administered at 200 mg every three weeks.

[0055] In certain embodiments, any of the antibodies and therapeutic combinations described herein (e.g., the first and/or second isolated antibodies, or a combination of the first antibody and pembrolizumab) can be administered as a first cancer therapy after diagnosis of the metastatic or locally advanced solid tumor (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis). In certain embodiments, any of the antibodies and therapeutic combinations described herein (e.g., the first and/or second isolated antibodies, or a combination of the first antibody and pembrolizumab) can be administered as the first cancer therapy after diagnosis of tumor progression (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of tumor progression) that has occurred despite previous treatment of the tumor with a different cancer therapy, optionally wherein the isolated antibody or therapeutic combination is the second cancer therapy administered. In certain embodiments, any of the antibodies and therapeutic combinations described herein (e.g., the first and/or second isolated antibodies, or a combination of the first antibody and pembrolizumab) can be administered as the first cancer therapy after diagnosis of toxicity of a different cancer therapy (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of toxicity of the different cancer therapy), optionally wherein the isolated antibody or therapeutic combination is the second cancer therapy administered. In certain embodiments, the first and second isolated antibodies are administered as the first cancer therapy about 1, 2, 3, 4, 5, or 6 days after diagnosis of the metastatic or locally advanced solid tumor. In certain embodiments, the first and second isolated antibodies are administered as the first cancer therapy about 1 or 2 weeks after diagnosis of the metastatic or locally advanced solid tumor.

[0056] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first isolated antibody binds to the same epitope of human CTLA-4 as an antibody comprising a heavy chain variable region comprising the amino acid sequence

of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14.

[0057] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the second isolated antibody binds to the same epitope of human PD-1 as an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 74.

[0058] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first isolated antibody binds to the same epitope of human CTLA-4 as an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14, and wherein the second isolated antibody binds to the same epitope of human PD-1 as an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 74.

[0059] In certain embodiments, the second isolated antibody is antagonistic to human PD-1.

[0060] In another aspect, the instant disclosure provides a method of enhancing or inducing an immune response in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

a) the first isolated antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-21 germline sequence, and optionally a light chain variable region having an amino acid sequence derived from a human IGKV3-20 or IGKV3-11 germline sequence; and/or

b) the second isolated antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-33 germline sequence, and optionally a light chain

variable region having an amino acid sequence derived from a human IGKV3-15 germline sequence.

[0061] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

a) the first isolated antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-21 germline sequence, and optionally a light chain variable region having an amino acid sequence derived from a human IGKV3-20 or IGKV3-11 germline sequence; and/or

b) the second isolated antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-33 germline sequence, and optionally a light chain variable region having an amino acid sequence derived from a human IGKV3-15 germline sequence.

[0062] In another aspect, the instant disclosure provides a method of treating infectious disease in a subject, the method comprising administering to the subject an effective amount of a therapeutic combination comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

a) the first isolated antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-21 germline sequence, and optionally a light chain variable region having an amino acid sequence derived from a human IGKV3-20 or IGKV3-11 germline sequence; and/or

b) the second isolated antibody comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-33 germline sequence, and optionally a light chain variable region having an amino acid sequence derived from a human IGKV3-15 germline sequence.

[0063] In another aspect, the instant disclosure provides a pharmaceutical composition comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of RASQSVX_1X_2YLX_3 (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3$RAT (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of QQYGX_1SPX_2T (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F,

and wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(g) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(h) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(i) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(j) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(k) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(l) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0064] In certain embodiments of the pharmaceutical composition, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 20, 22, 24, 27, 30, and 36; 20, 22, 24, 29, 32, and 37; 20, 22, 24, 29, 33, and 38; 21, 22, 24, 27, 30, and 36; 21, 22, 24, 29, 33, and 38; 20, 22, 24, 28, 31, and 36; 20, 22, 24, 29, 34, and 36; 20, 22, 24, 29, 35, and 38; 21, 22, 26, 27, 30, and 36; 21, 22, 26, 29, 32, and 37; 21, 22, 26, 29, 33, and 38; or 21, 22, 26, 29, 35, and 38, respectively, and wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 75, 76, 80, 83, 84, and 85; 75, 76, 81, 83, 84, and 85; 75, 76, 82, 83, 84, and 85; 75, 77, 81, 83, 84, and 85; 75, 78, 81, 83, 84, and 85; or 75, 79, 81, 83, 84, and 85, respectively.

[0065] In certain embodiments of the pharmaceutical composition, the heavy chain variable region and the light chain variable region of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and 15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively, and wherein the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67 and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively.

[0066] In another aspect, the instant disclosure provides a kit comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein
X_1 is S or A; and
X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein:

X_1 is S or G;

X_2 is R, S, or T; and

X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein:

X_1 is G or A;

X_2 is A or T; and

X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein:

X_1 is S or T; and

X_2 is W or F,

and wherein the second isolated antibody comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(g) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(h) CDRH2 comprises the amino acid sequence of $VIWX_1DGSNX_2YYADSVX_3G$ (SEQ ID NO: 86), wherein

X_1 is Y or F;

X_2 is K or E; and

X_3 is K or M;

(i) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein

X_1 is G or V; and

X_2 is H or Y;

(j) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(k) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(l) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0067] In certain embodiments of the kit, the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 20, 22, 24, 27, 30, and 36; 20, 22, 24, 29, 32, and 37; 20, 22, 24, 29, 33, and 38; 21, 22, 24, 27, 30, and 36; 21, 22, 24, 29, 33, and 38; 20, 22, 24, 28, 31, and 36; 20, 22, 24, 29, 34, and 36; 20, 22, 24, 29, 35, and 38; 21, 22, 26, 27, 30, and 36; 21, 22, 26, 29, 32, and 37; 21, 22, 26, 29, 33, and 38; or 21, 22, 26, 29, 35, and 38, respectively, and wherein CDRH1,

CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 75, 76, 80, 83, 84, and 85; 75, 76, 81, 83, 84, and 85; 75, 76, 82, 83, 84, and 85; 75, 77, 81, 83, 84, and 85; 75, 78, 81, 83, 84, and 85; or 75, 79, 81, 83, 84, and 85, respectively.

[0068] In certain embodiments of the kit, the heavy chain variable region and the light chain variable region of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and 15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively, and wherein the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67 and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively.

[0069] In another aspect, the instant disclosure provides a kit comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain variable region and the light chain variable region of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively, and wherein the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively.

[0070] In another aspect, the instant disclosure provides a kit comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain variable region and the light chain variable region of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively, and wherein the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 67 and 74, respectively.

[0071] In another aspect, the instant disclosure provides a kit comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain and the light chain of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 51 and 59; or 117 and 59, respectively, and wherein the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 91 and 93; 92 and 93; or 120 and 93, respectively.

[0072] In another aspect, the instant disclosure provides a kit comprising a first isolated

antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain and the light chain of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 51 and 59, respectively, and wherein the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 91 and 93, respectively.

[0073] In another aspect, the instant disclosure provides a kit comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain and the light chain of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 51 and 59, respectively, and wherein the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 92 and 93, respectively.

In another aspect, the instant disclosure provides a kit comprising a first isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain and the light chain of the first isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 51 and 59, respectively, and wherein the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 120 and 93, respectively.

[0074] In another aspect, the instant disclosure provides a multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first antigen-binding region comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2, and CDRL3, wherein:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein X_1 is S or A; and

X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of RASQSVX$_1$X$_2$YLX$_3$ (SEQ ID NO: 43), wherein:

X$_1$ is S or G;

X$_2$ is R, S, or T; and

X$_3$ is G or A;

(e) CDRL2 comprises the amino acid sequence of X$_1$X$_2$SX$_3$RAT (SEQ ID NO: 44), wherein:

X$_1$ is G or A;

X$_2$ is A or T; and

X$_3$ is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of QQYGX$_1$SPX$_2$T (SEQ ID NO: 45), wherein:

X$_1$ is S or T; and

X$_2$ is W or F,

and wherein the second antigen-binding region comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3 and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein:

(g) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(h) CDRH2 comprises the amino acid sequence of VIWX$_1$DGSNX$_2$YYADSVX$_3$G (SEQ ID NO: 86), wherein

X$_1$ is Y or F;

X$_2$ is K or E; and

X$_3$ is K or M;

(i) CDRH3 comprises the amino acid sequence of NX$_1$DX$_2$ (SEQ ID NO: 87), wherein

X$_1$ is G or V; and

X$_2$ is H or Y;

(j) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(k) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(l) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[0075] In certain embodiments of the multispecific antibody, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding region comprise the amino acid sequences set forth in SEQ ID NOs: 20, 22, 24, 27, 30, and 36; 20, 22, 24, 29, 32, and 37; 20, 22, 24, 29, 33, and 38; 21, 22, 24, 27, 30, and 36; 21, 22, 24, 29, 33, and 38; 20, 22, 24, 28, 31,

and 36; 20, 22, 24, 29, 34, and 36; 20, 22, 24, 29, 35, and 38; 21, 22, 26, 27, 30, and 36; 21, 22, 26, 29, 32, and 37; 21, 22, 26, 29, 33, and 38; or 21, 22, 26, 29, 35, and 38, respectively, and wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding region comprise the amino acid sequences set forth in SEQ ID NOs: 75, 76, 80, 83, 84, and 85; 75, 76, 81, 83, 84, and 85; 75, 76, 82, 83, 84, and 85; 75, 77, 81, 83, 84, and 85; 75, 78, 81, 83, 84, and 85; or 75, 79, 81, 83, 84, and 85, respectively.

[0076] In certain embodiments of the multispecific antibody, the heavy chain variable region and the light chain variable region of the first antigen-binding region comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and 15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively, and wherein the heavy chain variable region and the light chain variable region of the second antigen-binding region comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67 and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively.

In another aspect, the instant disclosure provides a multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first antigen-binding region comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively, and wherein the second antigen-binding region comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively.

[0077] In another aspect, the instant disclosure provides a multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first antigen-binding region comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively, and wherein the second antigen-binding region comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 67 and 74, respectively.

[0078] In another aspect, the instant disclosure provides a multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first antigen-binding region comprises a heavy chain and a light chain

comprising the amino acid sequences set forth in SEQ ID NOs: 51 and 59; or 117 and 59, respectively, and wherein the second antigen-binding region comprises a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 91 and 93; 92 and 93; or 120 and 93, respectively.

[0079] In another aspect, the instant disclosure provides a multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first antigen-binding region comprises a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 51 and 59, respectively, and wherein the second antigen-binding region comprises a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 91 and 93, respectively.

[0080] In another aspect, the instant disclosure provides a multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first antigen-binding region comprises a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 51 and 59, respectively, and wherein the second antigen-binding region comprises a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 92 and 93, respectively.

[0081] In another aspect, the instant disclosure provides a multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the first antigen-binding region comprises a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 51 and 59, respectively, and wherein the second antigen-binding region comprises a heavy chain and a light chain comprising the amino acid sequences set forth in SEQ ID NOs: 120 and 93, respectively.

[0082] A multispecific antibody comprising a first antigen-binding region that specifically binds to human CTLA-4 and a second antigen-binding region that specifically binds to human PD-1, wherein:

a) the first antigen-binding region comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-21 germline sequence, and optionally a light chain variable region having an amino acid sequence derived from a human IGKV3-20 or IGKV3-11 germline sequence; and/or

b) the second antigen-binding region comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-33 germline sequence, and optionally a light

chain variable region having an amino acid sequence derived from a human IGKV3-15 germline sequence.

[0083] In another aspect, the instant disclosure provides a method of enhancing or inducing an immune response in a subject, the method comprising administering to the subject a multispecific antibody described herein.

[0084] In another aspect, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject a multispecific antibody described herein.

[0085] In another aspect, the instant disclosure provides a method of treating infectious disease in a subject, the method comprising administering to the subject a multispecific antibody described herein.

[0086] In another aspect, the instant disclosure provides a therapeutic combination, a multispecific antibody, a kit, and/or a pharmaceutical composition described herein for use in treating cancer, treating infectious disease, or enhancing or inducing an immune response in a subject.

[0087] In another aspect, the instant disclosure provides a therapeutic combination, a multispecific antibody, a kit, and/or a pharmaceutical composition described herein for use in the preparation of a medicament for treating cancer, treating infectious disease, or enhancing or inducing an immune response in a subject.

[0088] In another aspect, the instant disclosure provides the use of a therapeutic combination, a multispecific antibody, a kit, and/or a pharmaceutical composition described herein in the preparation of a medicament for treating cancer, treating infectious disease, or enhancing or inducing an immune response in a subject. The instant disclosure also provides the use of the therapeutic combination or multispecific antibody for preparing a kit, and/or a pharmaceutical composition for treating cancer, treating infectious disease, or enhancing or inducing an immune response in a subject.

[0089] In certain embodiments of any one of the methods, pharmaceutical compositions, therapeutic combinations, or kits described herein, the N-terminal amino acid residue of the heavy chain variable region and/or the light chain variable region of the first antibody has been converted to pyroglutamate. In certain embodiments of any one of the methods, pharmaceutical compositions, therapeutic combinations, or kits described herein, the N-terminal amino acid residue of the heavy chain variable region and/or the light chain variable region of the second antibody has been converted to pyroglutamate. In certain embodiments of any one of the methods, pharmaceutical compositions, therapeutic combinations, or kits

described herein, the N-terminal amino acid residue of the heavy chain variable region and/or the light chain variable region of the first antibody has been converted to pyroglutamate, and the N-terminal amino acid residue of the heavy chain variable region and/or the light chain variable region of the second antibody has been converted to pyroglutamate.

[0090] In certain embodiments of any one of the multispecific antibodies described herein, the N-terminal amino acid residue of the heavy chain variable region and/or the light chain variable region of the first antigen-binding region has been converted to pyroglutamate. In certain embodiments of any one of the multispecific antibodies described herein, the N-terminal amino acid residue of the heavy chain variable region and/or the light chain variable region of the second antigen-binding region has been converted to pyroglutamate. In certain embodiments of any one of the multispecific antibodies described herein, the N-terminal amino acid residue of the heavy chain variable region and/or the light chain variable region of the first antigen-binding region has been converted to pyroglutamate, and the N-terminal amino acid residue of the heavy chain variable region and/or the light chain variable region of the second antigen-binding region has been converted to pyroglutamate.

5. BRIEF DESCRIPTION OF THE DRAWINGS

[0091] **Figures 1A and 1B** are graphs showing IL-2 production of primary human PBMCs following incubation with the Staphylococcal Enterotoxin A (SEA) superantigen in the presence of a dose titration of an anti-CTLA-4 antibody AGEN1884 (IgG_1) or an isotype control antibody (IgG_1) in combination with 10 μg/ml of an anti-PD-1 antibody AGEN2034 (IgG_4 S228P) or an isotype control antibody (IgG_4 S228P). Shown in Figures 1A and 1B are data generated using PBMCs from two different donors.

[0092] **Figures 2A and 2B** are graphs showing IL-2 production by primary human PBMCs following incubation with SEA superantigen in the presence of a dose titration of anti-CTLA-4 antibody AGEN1884 (IgG_1) in combination with 20 μg/ml of anti-PD-1 antibody AGEN2034 (IgG_4 S228P) or an isotype control antibody (IgG_4 S228P). Shown in Figures 2A and 2B are data generated using PBMCs from two different donors.

[0093] **Figure 3** is a series of graphs showing IL-2 production by primary human PBMCs following incubation with SEA superantigen in the presence of 10 μg/ml of an anti-CTLA-4 antibody AGEN1884 (IgG_1) or an isotype control antibody (IgG_1) in combination with 10 μg/ml of an anti-PD-1 antibody AGEN2034 (IgG_4 S228P) or an isotype control antibody (IgG_4 S228P). Each graph in Figure 3 shows data generated using PBMCs from a different donor,

as indicated. Calculated p-values are shown as: ns = not significant, * = $p<0.05$, ** = $p<0.005$.

[0094] **Figure 4** is a series of graphs showing IL-2 production by primary human PBMCs following incubation with SEA superantigen in the presence of 10 μg/ml of an anti-CTLA-4 antibody AGEN1884 (IgG_1) or an isotype control antibody (IgG_1) in combination with 10 μg/ml of an anti-PD-1 antibody AGEN2034 (IgG_4 S228P) or an isotype control antibody (IgG_4 S228P). Each graph in Figure 4 shows data generated using PBMCs from a different donor, as indicated. Calculated p-values are shown as ns = not significant, * = $p<0.05$, ** = $p<0.005$.

[0095] **Figures 5A-5C** are a series of graphs showing the effect of the combination of anti-CTLA-4 antibody AGEN1884 (IgG_1) and anti-PD-1 antibody AGEN2034 (IgG_4 S228P) on central memory T cell activation and proliferation in a non-human primate. Figure 5A shows a gating strategy and representative flow cytometry plots for T cell populations from primary PBMCs isolated from a cynomolgus monkey. In this gating strategy, lymphocytes were gated based on side scatter (SSC-A) vs. forward scatter (FSC-A), followed by singlets (FSC-A vs FSC-H). Live cells were selected (SSC-A vs. amine dye NearIR) and then CD20+ B cells and CD3+ T cells were selected. T cell populations were then defined as follows: CD4 naïve T cells (CD3+, CD4+, CD28+, CD95-), CD8 naïve T cells (CD3+, CD8+, CD28+, CD95-), CD4 central memory T cells (CD3+, CD4+, CD28+, CD95+), CD8 central memory T cells (CD3+, CD8+, CD28+, CD95+), CD4 effector memory T cells (CD3+, CD4+, CD28-, CD95+), and CD8 effector memory T cells (CD3+, CD8+, CD28-, CD95+). Figures 5B and 5C show representative flow cytometry plots for the frequencies of Ki67+ (proliferating) or ICOS+ (activated) CD4+ central memory T cells, or Ki67+ (proliferating) or ICOS+ (activated) CD8+ central memory T cells, respectively.

[0096] **Figures 6A-6D** are a series of graphs showing elevated central memory T cell activation and proliferation in cynomolgus monkey PBMCs three days after treatment with AGEN1884 (IgG_1) and AGEN2034 (IgG_4 S228P), relative to pre-dose levels (n=4 animals, including the animal for which flow cytometry plots are shown in Figure 5). The frequency of each of the following T cell populations was determined by flow cytometry: $CD4^+$ $ICOS^+$ central memory T cells (Figure 6A); $CD4^+$ $Ki67^+$ central memory T cells (Figure 6B); $CD8^+$ $ICOS^+$ central memory T cells (Figure 6C); and $CD8^+$ $Ki67^+$ central memory T cells (Figure 6D).

[0097] **Figures 7A, 7B, and 7C** are a series of sequence alignments. Figure 7A is a sequence alignment for human CTLA-4 (SEQ ID NO: 65), cynomolgus monkey CTLA-4 (SEQ ID NO: 108), mouse CTLA-4 (SEQ ID NO: 109), and rat CTLA-4 (SEQ ID NO: 110). Dots represent residues identical to corresponding human residues. An "*" (asterisk) indicates

positions which have a single, fully conserved residue. A ":" (colon) indicates conservation between groups of strongly similar properties. A "." (period) indicates conservation between groups of weakly similar properties. Figures 7B and 7C are sequence alignments for human CTLA-4 (residues 1-144 and 145-223 of SEQ ID NO: 65, respectively), cynomolgus monkey CTLA-4 (residues 1-144 and 145-223 of SEQ ID NO: 108, respectively), human CD28 (residues 1-127 and 128-220 of SEQ ID NO: 111, respectively), human ICOS (residues 1-124 and 125-199 of SEQ ID NO: 112, respectively), human BTLA (residues 1-125 and 126-289 of SEQ ID NO: 113, respectively), and human PD-1 (residues 1-143 and 144-288 of SEQ ID NO: 96, respectively). The two regions showing strong decrease in deuterium uptake when human CTLA-4 was bound to AGEN1884-Fab are underlined in Figures 7A-C: residues 80-82 (QVT, SEQ ID NO: 102) and residues 135-149 (YPPPYYLGIGNGTQI, SEQ ID NO: 100), numbered according to SEQ ID NO: 65.

6. DETAILED DESCRIPTION

[0098] The instant disclosure provides antibodies that specifically bind to CTLA-4 (*e.g.*, human CTLA-4) and/or PD-1 (*e.g.*, human PD-1) and antagonize CTLA-4 and/or PD-1 function, *e.g.*, immune suppression mediated by CTLA-4 and/or PD-1. Also provided are pharmaceutical compositions and kits comprising these antibodies, nucleic acids encoding these antibodies, expression vectors and host cells for making these antibodies, and methods of treating a subject using these antibodies. The antibodies described herein are particularly useful for increasing T cell activation in response to an antigen (*e.g.*, a tumor antigen or an infectious disease antigen), and hence for treating cancer in a subject or treating or preventing an infectious disease in a subject.

[0099] The skilled worker will appreciate that a glutamate (E) or glutamine (Q) amino acid residue at the N-terminus of a heavy chain variable region and/or a light chain variable region of any one of the antibodies described herein (e.g., an anti-PD-1 antibody, an anti-CTLA4 antibody, or an anti-CTLA-4/PD-1 antibody) can, under certain conditions, spontaneously convert to pyroglutamate by post-translational cyclization of the free amino group to form a lactam. Accordingly, in certain embodiments of each and every one of the methods, uses, pharmaceutical compositions, multispecific antibodies, or kits described herein, the N-terminal amino acid residue of one or more heavy chain variable regions and/or light chain variable regions of an anti-PD-1 antibody, an anti-CTLA4 antibody, and/or an anti-CTLA-4/PD-1 antibody has been converted to pyroglutamate (e.g., as a result of post-translational cyclization of the free amino group of the N-terminal E or Q residue).

6.1 Definitions

[00100] As used herein, the terms "about" and "approximately," when used to modify a numeric value or numeric range, indicate that deviations of 5% to 10% above and 5% to 10% below the value or range remain within the intended meaning of the recited value or range.

[00101] As used herein, the term "CTLA-4" refers to cytotoxic T-lymphocyte-associated protein 4. As used herein, the term "human CTLA-4" refers to a human CTLA-4 protein encoded by a wild type human CTLA-4 gene, *e.g.*, GenBank™ accession number NM_005214.4 or NM_001037631.2. An exemplary immature amino acid sequence of human CTLA-4 is provided as SEQ ID NO: 65.

[00102] As used herein, the term "PD-1" refers to programmed cell death protein 1. As used herein, the term "human PD-1" refers to a human PD-1 protein encoded by a wild type human PD-1 gene, *e.g.*, GenBank™ accession number NM_005018.2, XM_006712573.2 or XM_017004293.1. An exemplary immature amino acid sequence of human PD-1 is provided as SEQ ID NO: 96.

[00103] As used herein, the terms "antibody" and "antibodies" include full length antibodies, antigen-binding fragments of full length antibodies, and molecules comprising antibody CDRs, VH regions or VL regions. Examples of antibodies include monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain- antibody heavy chain pair, intrabodies, heteroconjugate antibodies, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affybodies, Fab fragments, $F(ab')_2$ fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-anti-Id antibodies), and antigen-binding fragments of any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations. Antibodies can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA or IgY), any class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 or IgA_2), or any subclass (*e.g.*, IgG_{2a} or IgG_{2b}) of immunoglobulin molecule. In certain embodiments, antibodies described herein are IgG antibodies, or a class (*e.g.*, human IgG_1 or IgG_4) or subclass thereof. In a specific embodiment, the antibody is a humanized monoclonal antibody. In another specific

embodiment, the antibody is a human monoclonal antibody.

[00104] "Multispecific" antibodies are antibodies with at least two different antigen-binding sites. Multispecific antibodies include bispecific antibodies that contain two different antigen-binding sites (exclusive of the Fc region). Examples of multispecific antibodies include recombinantly produced antibodies, human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain- antibody heavy chain pair, intrabodies, heteroconjugate antibodies, antibody-drug conjugates, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affybodies, Fab fragments, F(ab')2 fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-anti-Id antibodies), and antigen-binding fragments of any of the above. Multispecific antibodies can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA or IgY), any class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2), or any subclass (*e.g.*, IgG2a or IgG2b) of immunoglobulin molecule. In certain embodiments, multispecific antibodies described herein are IgG antibodies, or a class (*e.g.*, human IgG1 or IgG4) or subclass thereof.

[00105] As used herein, the term "anti-CTLA-4/PD-1" antibody refers to a multispecific antibody (*e.g.*, a bispecific antibody) that contains an antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and an antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1).

[00106] As used herein, the term "CDR" or "complementarity determining region" means the noncontiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. These particular regions have been described by Kabat *et al.*, J. Biol. Chem. 252, 6609-6616 (1977) and Kabat *et al.*, Sequences of protein of immunological interest. (1991), by Chothia *et al.*, J. Mol. Biol. 196:901-917 (1987), and by MacCallum *et al.*, J. Mol. Biol. 262:732-745 (1996), all of which are incorporated by reference in their entireties, where the definitions include overlapping or subsets of amino acid residues when compared against each other. CDRH1, CDRH2 and CDRH3 denote the heavy chain CDRs, and CDRL1, CDRL2 and CDRL3 denote the light chain CDRs.

[00107] As used herein, the term "framework (FR) amino acid residues" refers to those amino acids in the framework region of an immunoglobulin chain. The term "framework region" or "FR region" as used herein, includes the amino acid residues that are part of the variable region, but are not part of the CDRs (*e.g.*, using the Kabat or MacCallum definition of

CDRs).

[00108] As used herein, the terms "variable region" and "variable domain" are used interchangeably and are common in the art. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids or 110 to 125 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable region are called framework regions (FR). Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

[00109] The terms "VL" and "VL domain" are used interchangeably to refer to the light chain variable region of an antibody.

[00110] The terms "VH" and "VH domain" are used interchangeably to refer to the heavy chain variable region of an antibody.

[00111] As used herein, the terms "constant region" and "constant domain" are interchangeable and are common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable region.

[00112] As used herein, the term "heavy chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ε), gamma (γ), and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG_1, IgG_2, IgG_3, and IgG_4.

[00113] As used herein, the term "light chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, 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. In specific embodiments, the light chain is a human light chain.

[00114] The term "Kabat numbering" and like terms are recognized in the art and refer to a system of numbering amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen-binding portion thereof. In certain aspects, the CDRs of an antibody can be determined according to the Kabat numbering system (see, *e.g.*, Kabat EA & Wu TT (1971) Ann NY Acad Sci 190: 382-391 and Kabat EA et al., (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, each of which is herein incorporated by reference in its entirety). Using the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35A and 35B) (CDR1), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDR1), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Kabat numbering scheme.

[00115] As used herein, the terms "constant region" and "constant domain" are interchangeable and have its meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable region.

[00116] As used herein, the term "heavy chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ε), gamma (γ), and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG1, IgG2, IgG3, and IgG4.

[00117] As used herein, the term "light chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, 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. In specific embodiments, the light chain is a human light chain.

[00118] As used herein, the term "EU numbering system" refers to the EU numbering convention for the constant regions of an antibody, as described in Edelman, G.M. et al., Proc. Natl. Acad. USA, 63, 78-85 (1969) and Kabat et al, Sequences of Proteins of Immunological Interest, U.S. Dept. Health and Human Services, 5th edition, 1991.

[00119] "Binding affinity" generally refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, 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 molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured and/or expressed in a number of ways known in the art, including, but not limited to, equilibrium dissociation constant (K_D), and equilibrium association constant (K_A). The K_D is calculated from the quotient of k_{off}/k_{on}, whereas K_A is calculated from the quotient of k_{on}/k_{off}. k_{on} refers to the association rate constant of, *e.g.*, an antibody to an antigen, and k_{off} refers to the dissociation of, *e.g.*, an antibody to an antigen. The k_{on} and k_{off} can be determined by techniques known to one of ordinary skill in the art, such as BIAcore® or KinExA.

[00120] As used herein, the terms "specifically binds," "specifically recognizes," "immunospecifically binds," and "immunospecifically recognizes" are analogous terms in the context of antibodies and refer to molecules that bind to an antigen (*e.g.*, epitope or immune complex) as such binding is understood by one skilled in the art. For example, a molecule that specifically binds to an antigen can bind to other peptides or polypeptides, generally with lower affinity as determined by, *e.g.*, immunoassays, BIAcore®, KinExA 3000 instrument (Sapidyne Instruments, Boise, ID), or other assays known in the art. In a specific embodiment, molecules that specifically bind to an antigen bind to the antigen with a K_A that is at least 2 logs, 2.5 logs, 3 logs, 4 logs or greater than the K_A when the molecules bind non-specifically to another antigen.

[00121] In another embodiment, molecules that specifically bind to an antigen do not cross react with other proteins under similar binding conditions. In one specific embodiment, an anti-CTLA-4 antibody, an anti-PD-1 antibody, and an anti-CTLA-4/anti-PD-1 antibody do not cross react with other non-CTLA-4 proteins, non PD-1-proteins, and non-CTLA-4 and non PD-1-proteins, respectively. In a specific embodiment, provided herein is an antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and/or PD-1 (*e.g.*, human PD-1) with higher affinity than to another unrelated antigen. In certain embodiments, provided herein is an antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and/or PD-1 (*e.g.*, human

PD-1) with a 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or higher affinity than to another, unrelated antigen as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay. In a specific embodiment, the extent of binding of an anti-CTLA-4 antibody described herein to an unrelated, non-CTLA-4 protein is less than 10%, 15%, or 20% of the binding of the antibody to CTLA-4 protein as measured by, *e.g.*, a radioimmunoassay. In another specific embodiment, the extent of binding of an anti-PD-1 antibody described herein to an unrelated, non-PD-1 protein is less than 10%, 15%, or 20% of the binding of the antibody to PD-1 protein as measured by, *e.g.*, a radioimmunoassay. In another specific embodiment, the extent of binding of an anti-CTLA-4/PD-1 antibody described herein to an unrelated, non-CTLA-4 and non-PD-1 protein is less than 10%, 15%, or 20% of the binding of the antibody to CTLA-4 and/or PD-1 protein as measured by, *e.g.*, a radioimmunoassay.

[00122] As used herein, the term "afucosylation" or "afucosylated" in the context of an Fc refers to a substantial lack of a fucose covalently attached, directly or indirectly, to residue 297 of the human IgG_1 Fc region, numbered according to the EU index (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)), or the corresponding residue in non-IgG_1 or non-human IgG_1 immunoglobulins. Thus, in a composition comprising a plurality of afucosylated antibodies, at least 70% of the antibodies will not be fucosylated, directly or indirectly (*e.g.*, via intervening sugars) at residue 297 of the Fc region of the antibodies, and in some embodiments at least 80%, 85%, 90%, 95%, or 99% will not be fucosylated, directly or indirectly, at residue 297 of the Fc region.

[00123] As used herein, an "epitope" is a term in the art and refers to a localized region of an antigen to which an antibody can specifically bind. An epitope can be, for example, contiguous amino acids of a polypeptide (linear or contiguous epitope) or an epitope can, for example, come together from two or more non-contiguous regions of a polypeptide or polypeptides (conformational, non-linear, discontinuous, or non-contiguous epitope). In certain embodiments, the epitope to which an antibody binds can be determined by, *e.g.*, NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (*e.g.*, liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization may be accomplished using any of the known methods in the art (*e.g.*, Giegé R *et al.*, (1994) Acta Crystallogr D Biol Crystallogr 50(Pt 4): 339-350; McPherson A (1990) Eur J Biochem 189: 1-

23; Chayen NE (1997) Structure 5: 1269-1274; McPherson A (1976) J Biol Chem 251: 6300-6303). Antibody:antigen crystals may be studied using well known X-ray diffraction techniques and may be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; see *e.g.* Meth Enzymol (1985) volumes 114 & 115, eds Wyckoff HW *et al.*,; U.S. 2004/0014194), and BUSTER (Bricogne G (1993) Acta Crystallogr D Biol Crystallogr 49(Pt 1): 37-60; Bricogne G (1997) Meth Enzymol 276A: 361-423, ed Carter CW; Roversi P *et al.,* (2000) Acta Crystallogr D Biol Crystallogr 56(Pt 10): 1316-1323). Mutagenesis mapping studies may be accomplished using any method known to one of skill in the art. *See, e.g.*, Champe M *et al.,* (1995) J Biol Chem 270: 1388-1394 and Cunningham BC & Wells JA (1989) Science 244: 1081-1085 for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques. In a specific embodiment, the epitope of an antibody is determined using alanine scanning mutagenesis studies.

[00124] As used herein, the term "treat," "treating," and "treatment" refer to therapeutic or preventative measures described herein. The methods of "treatment" employ administration of an antibody to a subject having a disease or disorder, or predisposed to having such a disease or disorder, in order to prevent, cure, delay, reduce the severity of, or ameliorate one or more symptoms of the disease or disorder or recurring disease or disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

[00125] As used herein, the term “therapeutic combination” refers to the combination of a first therapy and the second therapy administered to a subject. The first therapy and the second therapy can be administered simultaneously (in the same pharmaceutical composition or in separate pharmaceutical compositions) or sequentially in any order.

[00126] As used herein, the term “effective amount” in the context of the administration of a therapy to a subject refers to the amount of a therapy that achieves a desired prophylactic or therapeutic effect. The effective amount of a therapeutic combination of a first therapy and a second therapy includes a first amount of the first therapy and a second amount of the second therapy, wherein the administration of the therapeutic combination achieves a desired prophylactic or therapeutic effect.

[00127] As used herein with respect to the response of a cancer to a therapy, the terms “refractory” and “resistant” have their art-recognized meaning and are used interchangeably.

[00128] As used herein, the term "subject" includes any human or non-human animal.

[00129] As used herein, the term “host cell” can be any type of cell, *e.g.*, a primary cell, a cell in culture, or a cell from a cell line. In specific embodiments, the term “host cell” refers to a cell transfected with a nucleic acid molecule and the progeny or potential progeny of such

a cell. Progeny of such a cell are not necessarily identical to the parent cell transfected with the nucleic acid molecule, *e.g.*, due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[00130] The determination of "percent identity" between two sequences (*e.g.,* amino acid sequences or nucleic acid sequences) can also be accomplished using a mathematical algorithm. A specific, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin S & Altschul SF (1990) PNAS 87: 2264-2268, modified as in Karlin S & Altschul SF (1993) PNAS 90: 5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul SF *et al.*, (1990) J Mol Biol 215: 403. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, *e.g.,* for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules described herein. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.,* to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul SF *et al.*, (1997) Nuc Acids Res 25: 3389 3402. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (*e.g.,* of XBLAST and NBLAST) can be used (*see*, *e.g.,* National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov). Another specific, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11 17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

[00131] As used herein, the term "internalization" or "internalized" refers to the uptake of an antibody into an intracellular compartment of a cell upon binding of the antibody to an antigen expressed at the surface of the cell.

[00131a] The term "comprising" as used in this specification and claims means "consisting at least in part of". When interpreting statements in this specification, and claims which include the term "comprising", it is to be understood that other features that are

additional to the features prefaced by this term in each statement or claim may also be present. Related terms such as "comprise" and "comprised" are to be interpreted in similar manner.

6.2 Antibodies

6.2.1 Anti-CTLA-4 antibodies

[00132] In one aspect, the instant disclosure provides antibodies that specifically bind to CTLA-4 (*e.g.*, human CTLA-4) and antagonize CTLA-4 function. Also provided herein are multispecific antibodies that comprise a first antigen-binding region that specifically binds to human CTLA-4 (*e.g.*, human CTLA-4) and, optionally, a second antigen-binding region that does not specifically bind to CTLA-4 (*e.g.*, human CTLA-4). The amino acid sequences of exemplary antibodies are set forth in Tables 1-5, herein.

Table 1. Amino acid sequences of exemplary anti-CTLA-4 antibodies.*

SEQ ID NO:	Description	Amino acid sequence
1	AGEN1884 VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSS
9	BADD412-2356 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLVWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSS
10	BADD412-2357 VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNTLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSS
11	BADD412-2358 VH	EVQLLESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSS
12	BADD412-2359 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLVWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFNIWGQGTMVTVSS
13	BADD412-2360 VH	EVQLVESGGGLVQPGGSLTLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSS
14	AGEN1884 VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSRYLGWYQQKPG QAPRLLIYGASTRATGIPDRFSGSGSGTDFTLTITRLEPED FAVYYCQQYGSSPWTFGQGTKVEIK
15	BADD412-2367 VL	EIVLTQSPATLSLSPGERATLSCRASQSVGTYLAWYQHKVG QAPRLLIYGASRRATGIPDRFSGSGSGTDFTLTISRLEPED FAVYYCQQYGSSPWTFGQGTKVEIK
16	BADD412-2382 VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPSLLIYATSSRATGIPDRFSGSVSGTDFTLTISRLEPED FAVYYCQQYGTSPWTFGQGTKVEIK

SEQ ID NO:	Description	Amino acid sequence
17	BADD412-2384 VL	EIVLTQSPATLSFSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYGASSRATGIPDRFSGSGSGTDFTFTISRLEPED FAVYYCQQYGSSPFTFGPGTKVDIK
18	BADD412-2390 VL	EIVLTQSPATLSVSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYAASTRATGIPDRFSGSASGTDFTLTISRLEPED FAVYYCQQYGSSPWTFGQGTKVEIK
19	BADD412-2393 VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYGASNRATGIPARFSGSGSGTDFTLTISSLEPED FAVYYCQQYGSSPFTFGPGTKVDIK
20	CDRH1	SYSMN
21	CDRH1	SYAMS
22	CDRH2	SISSSSSYIYYADSVKG
24	CDRH3	VGLMGPFDI
26	CDRH3	VGLMGPFNI
27	CDRL1	RASQSVSRYLG
28	CDRL1	RASQSVGTYLA
29	CDRL1	RASQSVSSYLA
30	CDRL2	GASTRAT
31	CDRL2	GASRRAT
32	CDRL2	ATSSRAT
33	CDRL2	GASSRAT
34	CDRL2	AASTRAT
35	CDRL2	GASNRAT
36	CDRL3	QQYGSSPWT
37	CDRL3	QQYGTSPWT
38	CDRL3	QQYGSSPFT
39	CDRH1 consensus sequence	SYX_1MX_2, wherein X_1 is S or A; and X_2 is N or S
115	CDRH3 consensus sequence 1	VGLMGPFXI, wherein X is D or N
43	CDRL1 consensus sequence	$RASQSVX_1X_2YLX_3$, wherein X_1 is S or G; X_2 is R, S, or T; and X_3 is G or A
44	CDRL2 consensus sequence	$X_1X_2SX_3RAT$, wherein X_1 is G or A; X_2 is A or T; and X_3 is T, S, R, or N
45	CDRL3 consensus sequence	$QQYGX_1SPX_2T$, wherein X_1 is S or T; and X_2 is W or F

SEQ ID NO:	Description	Amino acid sequence
116	VH consensus sequence	EVQLX$_1$ESGGGLVX$_2$PGGSLX$_3$LSCAASGFTFSSYX$_4$MX$_5$WVR QAPGKGLX$_6$WVSSISSSSSYIYYADSVKGRFTISRDNAKNX$_7$ LYLQMNSLRAEDTAVYYCARVGLMGPFX$_8$IWGQGTMVTVSS , wherein X$_1$ is V or L; X$_2$ is K or Q; X$_3$ is R or T; X$_4$ is S or A; X$_5$ is N or S; X$_6$ is E or V; X$_7$ is S or T; and X$_8$ is D or N
47	VL consensus sequence	EIVLTQSPX$_1$TLSX$_2$SPGERATLSCRASQSVX$_3$X$_4$YLX$_5$WYQX $_6$KX$_7$GQAPX$_8$LLIYX$_9$X$_{10}$SX$_{11}$RATGIPX$_{12}$RFSGSX$_{13}$SGTDF TX$_{14}$TIX$_{15}$X$_{16}$LEPEDFAVYYCQQYGX$_{17}$SPX$_{18}$TFGX$_{19}$GTKV X$_{20}$IK, wherein X$_1$ is G or A; X$_2$ is L, V, or F; X$_3$ is S or G; X$_4$ is R, T, or S; X$_5$ is G or A; X$_6$ is Q or H; X$_7$ is P or V; X$_8$ is R or S; X$_9$ is G or A; X$_{10}$ is A or T; X$_{11}$ is T, R, S, or N; X$_{12}$ is D or A; X$_{13}$ is G, V, or A; X$_{14}$ is L or F; X$_{15}$ is T or S; X$_{16}$ is R or S; X$_{17}$ is S or T; X$_{18}$ is W or F; X$_{19}$ is Q or P; and X$_{20}$ is E or D
48	Germline sequence: IGHV3-21*01	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCAR
49	Germline sequence: IGKV3-20*01	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKP GQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPE DFAVYYCQQYGSSP
50	Germline sequence: IGKV3-11*01	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPED FAVYYCQQRSNWPP

SEQ ID NO:	Description	Amino acid sequence
51	AGEN1884 (IgG1) heavy chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
52	AGEN1884 (IgG1 S239D/I332E) heavy chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPDVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPEEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
53	AGEN1884 (IgG1 S239D/A330L/I332E) heavy chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPDVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPLPEEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
54	AGEN1884 (IgG1 L235V/F243L/R292P/Y300L/P396L) heavy chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRVEPKSCDKTHTCPPCPAPELVGGPSVFLLPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPPEEQYNSTLRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPLVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO:	Description	Amino acid sequence
117	AGEN2041 (IgG2) heavy chain	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTAVYYCARVGLMGPFDIWGQGTMVTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDH KPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAP IEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
59	AGEN1884 light chain	EIVLTQSPGTLSLSPGERATLSCRASQSVSRYLGWYQQKPG QAPRLLIYGASTRATGIPDRFSGSGSGTDFTLTITRLEPED FAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
60	IgG1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G
61	IgG1 S239D/I332E	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPDV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPEEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G
62	IgG1 S239D/A330L/I332E	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPDV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPLPEEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G

SEQ ID NO:	Description	Amino acid sequence
63	IgG1 L235V/F243L/R292P/Y300L/P396L	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELVGGPSV FLLPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPPEEQYNSTLRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPLVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G
118	IgG2	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYT CNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNK GLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
64	Light chain constant region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC

* CDRs are defined according to the Kabat numbering system.

Table 2. Heavy chain CDR amino acid sequences of exemplary anti-CTLA-4 antibodies.*

VH (SEQ ID NO:)	CDRH1 (SEQ ID NO:)	CDRH2 (SEQ ID NO:)	CDRH3 (SEQ ID NO:)
AGEN1884 VH (1)	SYSMN (20)	SISSSSSYIYYADSVKG (22)	VGLMGPFDI (24)
BADD412-2356 VH (9)	SYAMS (21)	SISSSSSYIYYADSVKG (22)	VGLMGPFDI (24)
BADD412-2357 VH (10)	SYSMN (20)	SISSSSSYIYYADSVKG (22)	VGLMGPFDI (24)
BADD412-2358 VH (11)	SYSMN (20)	SISSSSSYIYYADSVKG (22)	VGLMGPFDI (24)
BADD412-2359 VH (12)	SYAMS (21)	SISSSSSYIYYADSVKG (22)	VGLMGPFNI (26)
BADD412-2360 VH (13)	SYSMN (20)	SISSSSSYIYYADSVKG (22)	VGLMGPFDI (24)

*Defined according to the Kabat numbering system.

Table 3. Light chain CDR amino acid sequences of exemplary anti-CTLA-4 antibodies.*

VL (SEQ ID NO:)	CDRL1 (SEQ ID NO:)	CDRL2 (SEQ ID NO:)	CDRL3 (SEQ ID NO:)
AGEN1884 VL (14)	RASQSVSRYLG (27)	GASTRAT (30)	QQYGSSPWT (36)
BADD412-2367 VL (15)	RASQSVGTYLA (28)	GASRRAT (31)	QQYGSSPWT (36)
BADD412-2382 VL (16)	RASQSVSSYLA (29)	ATSSRAT (32)	QQYGTSPWT (37)

VL (SEQ ID NO:)	CDRL1 (SEQ ID NO:)	CDRL2 (SEQ ID NO:)	CDRL3 (SEQ ID NO:)
BADD412-2384 VL (17)	RASQSVSSYLA (29)	GASSRAT (33)	QQYGSSPFT (38)
BADD412-2390 VL (18)	RASQSVSSYLA (29)	AASTRAT (34)	QQYGSSPWT (36)
BADD412-2393 VL (19)	RASQSVSSYLA (29)	GASNRAT (35)	QQYGSSPFT (38)

*Defined according to the Kabat numbering system.

Table 4. Exemplary anti-CTLA-4 antibodies.

Antibody	Heavy chain variable region	SEQ ID NO:	Light chain variable region	SEQ ID NO:
AGEN1884	AGEN1884 VH	1	AGEN1884 VL	14
AGEN1885	AGEN1884 VH	1	BADD412-2382 VL	16
AGEN1886	AGEN1884 VH	1	BADD412-2384 VL	17
AGEN1887	BADD412-2356 VH	9	AGEN1884 VL	14
AGEN1888	BADD412-2356 VH	9	BADD412-2384 VL	17
AGEN1889	BADD412-2357 VH	10	BADD412-2367 VL	15
AGEN1890	BADD412-2357 VH	10	BADD412-2384 VL	17
AGEN1891	BADD412-2357 VH	10	BADD412-2390 VL	18
AGEN1892	BADD412-2357 VH	10	BADD412-2393 VL	19
AGEN1893	BADD412-2358 VH	11	BADD412-2367 VL	15
AGEN1894	BADD412-2358 VH	11	AGEN1884 VL	14
AGEN1895	BADD412-2358 VH	11	BADD412-2382 VL	16
AGEN1896	BADD412-2358 VH	11	BADD412-2384 VL	17
AGEN1897	BADD412-2359 VH	12	AGEN1884 VL	14
AGEN1898	BADD412-2359 VH	12	BADD412-2382 VL	16
AGEN1899	BADD412-2359 VH	12	BADD412-2384 VL	17
AGEN1900	BADD412-2359 VH	12	BADD412-2393 VL	19
AGEN1901	BADD412-2360 VH	13	BADD412-2367 VL	15
AGEN1902	BADD412-2360 VH	13	BADD412-2384 VL	17

Table 5. Exemplary sequences of CTLA-4.

SEQ ID NO:	Description*	Amino acid Sequence
65	Human CTLA-4 immature protein (P16410)	MACLGFQRHKAQLNLATRTWPCTLLFFLLFIPVFCKA MHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVL RQADSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQ VNLTIQGLRAMDTGLYICKVELMYPPPYYLGIGNGTQ IYVIDPEPCPDSDFLLWILAAVSSGLFFYSFLLTAVS LSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPI N
97	CTLA-4 epitope	YLGI
98	CTLA-4 epitope	YPPPYYLGI
99	CTLA-4 epitope	YLGIGNGTQI
100	CTLA-4 epitope	YPPPYYLGIGNGTQI

SEQ ID NO:	Description*	Amino acid Sequence
101	CTLA-4 epitope	MYPPPYY
102	CTLA-4 epitope	QVT
108	MACFA CTLA-4 (G7PL88)	MACLGFQRHKARLNLATRTRPYTLLFSLLFIPVFSKA MHVAQPAVVLANSRGIASFVCEYASPGKATEVRVTVL RQADSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQ VNLTIQGLRAMDTGLYICKVELMYPPPYYMGIGNGTQ IYVIDPEPCPDSDFLLWILAAVSSGLFFYSFLLTAVS LSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPI N
109	Mouse CTLA-4 (P09793)	MACLGLRRYKAQLQLPSRTWPFVALLTLLFIPVFSEA IQVTQPSVVLASSHGVASFPCEYSPSHNTDEVRVTVL RQTNDQMTEVCATTFTEKNTVGFLDYPFCSGTFNESR VNLTIQGLRAVDTGLYLCKVELMYPPPYFVGMGNGTQ IYVIDPEPCPDSDFLLWILVAVSLGLFFYSFLVSAVS LSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPI N
110	Rat CTLA-4 (Q62859)	MACLGLQRYKTHLQLPSRTWPFGVLLSLLFIPIFSEA IQVTQPSVVLASSHGVASFPCEYASSHNTDEVRVTVL RQTNDQVTEVCATTFTVKNTLGFLDDPFCSGTFNESR VNLTIQGLRAADTGLYFCKVELMYPPPYFVGMGNGTQ IYVIDPEPCPDSDFLLWILAAVSSGLFFYSFLVTAVS LNRTLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPI N
111	Human CD28 (P10747)	MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVN LSCKYSYNLFSREFRASLHKGLDSAVEVCVVYGNYSQ QLQVYSKTGFNCDGKLGNESVTFYLQNLYVNQTDIYF CKIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPG PSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS
112	Human ICOS (Q9Y6W8)	MKSGLWYFFLFCLRIKVLTGEINGSANYEMFIFHNGG VQILCKYPDIVQQFKMQLLKGGQILCDLTKTKGSGNT VSIKSLKFCHSQLSNNSVSFFLYNLDHSHANYYFCNL SIFDPPPFKVTLTGGYLHIYESQLCCQLKFWLPIGCA AFVVVCILGCILICWLTKKKYSSSVHDPNGEYMFMRA VNTAKKSRLTDVTL
113	Human BTLA (Q7Z6A9)	MKTLPAMLGTGKLFWVFFLIPYLDIWNIHGKESCDVQ LYIKRQSEHSILAGDPFELECPVKYCANRPHVTWCKL NGTTCVKLEDRQTSWKEEKNISFFILHFEPVLPNDNG SYRCSANFQSNLIESHSTTLYVTDVKSASERPSKDEM ASRPWLLYRLLPLGGLPLLITTCFCLFCCLRRHQGKQ NELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSE TGIYDNDPDLCFRMQEGSEVYSNPCLEENKPGIVYAS LNHSVIGPNSRLARNVKEAPTEYASICVRS

[00133] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the antibody comprising a VH domain comprising one, two, or all three of the CDRs of a VH domain set forth in in Table 1 herein.

In certain embodiments, the antibody comprises the CDRH1 of one of the VH domains set forth in in Table 1 herein. In certain embodiments, the antibody comprises the CDRH2 of one of the VH domains set forth in in Table 1 herein. In certain embodiments, the antibody comprises the CDRH3 of one of the VH domains set forth in in Table 1 herein.

[00134] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the antibody comprising a VL domain comprising one, two, or all three of the CDRs of a VL domain set forth in in Table 1 herein. In certain embodiments, the antibody comprises the CDRL1 of a VL domain set forth in in Table 1 herein. In certain embodiments, the antibody comprises the CDRL2 of a VL domain set forth in in Table 1 herein. In certain embodiments, the antibody comprises the CDRL3 of a VL domain set forth in in Table 1 herein.

[00135] In certain embodiments, the CDRs of an antibody can be determined according to Kabat et al., J. Biol. Chem. 252, 6609-6616 (1977) and Kabat et al., Sequences of protein of immunological interest (1991), each of which is herein incorporated by reference in its entirety.

[00136] In certain embodiments, the CDRs of an antibody can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (see, *e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B et al., (1997) J Mol Biol 273: 927-948; Chothia C et al., (1992) J Mol Biol 227: 799-817; Tramontano A et al., (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226, all of which are herein incorporated by reference in their entireties). Typically, when using the Kabat numbering convention, the Chothia CDRH1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDRH2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDRH3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDRL1 loop is present at light chain amino acids 24 to 34, the Chothia CDRL2 loop is present at light chain amino acids 50 to 56, and the Chothia CDRL3 loop is present at light chain amino acids 89 to 97. The end of the Chothia CDRH1 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).

[00137] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the antibody comprising the Chothia VH CDRs of a VH disclosed in Table 1 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the

antibody comprising the Chothia VL CDRs of a VL disclosed in Table 1 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the antibody comprising the Chothia VH CDRs and Chothia VL CDRs of an antibody disclosed in Table 1 herein. In certain embodiments, antibodies that specifically bind to CTLA-4 (*e.g.*, human CTLA-4) comprise one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and comprises a combination of Kabat CDRs and Chothia CDRs.

[00138] In certain embodiments, the CDRs of an antibody can be determined according to the IMGT numbering system as described in Lefranc M-P, (1999) The Immunologist 7: 132-136 and Lefranc M-P et al., (1999) Nucleic Acids Res 27: 209-212, each of which is herein incorporated by reference in its entirety. In certain embodiments, the instant disclosure provides antibodies that specifically bind to CTLA-4 (*e.g.*, human CTLA-4) and comprise CDRs of an antibody disclosed in Table 1 herein, as determined by the IMGT numbering system, for example, as described in Lefranc M-P (1999) supra and Lefranc M-P et al., (1999) supra.

[00139] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the antibody comprising the IMGT VH CDRs of a VH disclosed in Table 1 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the antibody comprising the IMGT VL CDRs of a VL disclosed in Table 1 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the antibody comprising the IMGT VH CDRs and IMGT VL CDRs of an antibody disclosed in Table 1 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and comprises a combination of Kabat CDRs and IMGT CDRs.

[00140] In certain embodiments, the CDRs of an antibody can be determined according to the AbM numbering scheme, which refers to AbM hypervariable regions, which represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (Oxford Molecular Group, Inc.), herein incorporated by reference in its entirety. In a particular embodiment, the instant disclosure provides antibodies that specifically bind to CTLA-4 (*e.g.*, human CTLA-4) and comprise CDRs of an antibody disclosed in Table 1 herein as determined by the AbM numbering scheme.

[00141] In certain embodiments, the CDRs of an antibody can be determined according to

MacCallum RM et al., (1996) J Mol Biol 262: 732-745, herein incorporated by reference in its entirety. See also, *e.g.*, Martin A. "Protein Sequence and Structure Analysis of Antibody Variable Domains," in Antibody Engineering, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001), herein incorporated by reference in its entirety. In a particular embodiment, the instant disclosure provides antibodies that specifically bind to CTLA-4 (*e.g.*, human CTLA-4) and comprise CDRs of an antibody disclosed in Table 1 herein as determined by the MacCallum numbering scheme.

[00142] Accordingly, in certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), wherein the antibody comprises a heavy chain variable region comprising the CDRH1, CDRH2, and CDRH3 region amino acid sequences of a heavy chain variable region set forth in SEQ ID NO: 1, 9, 10, 11, 12, or 13, and a light chain variable region comprising the CDRL1, CDRL2, and CDRL3 region amino acid sequences of a light chain variable region set forth in SEQ ID NO: 14, 15, 16, 17, 18, or 19, wherein each CDR is defined in accordance with the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the IMGT numbering system, the AbM definition, or the contact definition of CDR.

[00143] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the antibody comprising:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein X_1 is S or A; and X_2 is N or S; and/or

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22); wherein X is D or E; and/or

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N; and/or

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein X_1 is S or G; X_2 is R, S, or T; and X_3 is G or A; and/or

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein X_1 is G or A; X_2 is A or T; and X_3 is T, S, R, or N; and/or

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein X_1 is S or T; and X_2 is W or F.

[00144] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), the antibody comprising:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein X_1 is S or A; and X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of $RASQSVX_1X_2YLX_3$ (SEQ ID NO: 43), wherein X_1 is S or G; X_2 is R, S, or T; and X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3RAT$ (SEQ ID NO: 44), wherein X_1 is G or A; X_2 is A or T; and X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of $QQYGX_1SPX_2T$ (SEQ ID NO: 45), wherein X_1 is S or T; and X_2 is W or F.

[00145] In certain embodiments, the CDRH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 20 and 21. In certain embodiments, the CDRH3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24 and 26. In certain embodiments, CDRL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 28, and 29. In certain embodiments, CDRL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30-35. In certain embodiments, CDRL3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 36, 37, and 38. In certain embodiments, CDRH1, CDRH2, and CDRH3 comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences, respectively, of an antibody in Table 2. In certain embodiments, CDRL1, CDRL2, and CDRL3 comprise the CDRL1, CDRL2, and CDRL3 amino acid sequences, respectively, of an antibody in Table 3.

[00146] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3, wherein the CDRH1, CDRH2 and CDRH3 comprise the CDRH1, CDRH2 and CDRH3 amino acid sequences, respectively, set forth in SEQ ID NOs: 20, 22, and 24; 20, 22, and ; 21, 22, and 24; or 21, 22, and 26.

[00147] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein the CDRL1, CDRL2 and CDRL3 comprise the CDRL1, CDRL2 and CDRL3 amino acid sequences, respectively, set forth in SEQ ID NOs: 27, 30, and 36; 28, 31, and 36; 29, 32, and 37; 29, 33, and 38; 29, 34, and 36; or 29, 35, and 38.

[00148] In certain embodiments, the instant disclosure provides an isolated antibody that

specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3, and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 comprise the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 amino acid sequences, respectively, set forth in SEQ ID NOs: 20, 22, 24, 27, 30, and 36; 20, 22, 24, 29, 32, and 37; 20, 22, 24, 29, 33, and 38; 21, 22, 24, 27, 30, and 36; 21, 22, 24, 29, 33, and 38; 20, 22, 24, 28, 31, and 36; 20, 22, 24, 29, 34, and 36; 20, 22, 24, 29, 35, and 38; 21, 22, 26, 27, 30, and 36; 21, 22, 26, 29, 32, and 37; 21, 22, 26, 29, 33, and 38; or 21, 22, 26, 29, 35, and 38, respectively.

[00149] In certain embodiments, the antibody comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 regions, and a light chain variable region comprising CDRL1, CDRL2, and CDRL3 regions, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences, respectively, set forth in SEQ ID NOs: 20, 22, 24, 27, 30, and 36.

[00150] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 116.

[00151] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 9, 10, 11, 12, or 13. In certain embodiments, the antibody comprises a heavy chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 9, 10, 11, 12, or 13. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 9. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 10. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 11. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 12. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 13.

[00152] In certain embodiments, the instant disclosure provides an isolated antibody that

specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a light chain variable region comprising the amino acid sequence of SEQ ID NO: 47.

[00153] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 14-19. In certain embodiments, the antibody comprises a light chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14-19. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 14. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 15. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 16. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 17. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 18. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 19.

[00154] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 9, 10, 11, 12, or 13, and a light chain variable region that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 14, 15, 16, 17, 18, or 19. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 1, 9, 10, 11, 12, or 13, and a light chain variable region set forth in SEQ ID NO: 14, 15, 16, 17, 18, or 19. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and 15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively. In certain embodiments, the antibody comprises a heavy chain variable region

and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 1 and 16, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 1 and 17, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 9 and 14, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 9 and 17, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 10 and 15, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 10 and 17, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 10 and 18, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 10 and 19, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 11 and 15, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 11 and 14, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 11 and 16, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 11 and 17, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 12 and 14, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 12 and 16, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 12 and 17, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable

region having the amino acid sequences set forth in SEQ ID NOs: 12 and 19, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 13 and 15, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 13 and 17, respectively.

[00155] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-21 germline sequence (*e.g.*, IGHV3-21*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 48). One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 (*e.g.*, two, three, four or five of these regions) can be derived from a human IGHV3-21 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 are all derived from a human IGHV3-21 germline sequence.

[00156] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a light chain variable region having an amino acid sequence derived from a human IGKV3-20 germline sequence (*e.g.*, IGKV3-20*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 49) or a human IGKV3-11 germline sequence (*e.g.*, IGKV3-11*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 50). One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 (*e.g.*, two, three, four or five of these regions) can be derived from a human IGKV3-20 or IGKV3-11 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 are all derived from a human IGKV3-20 or IGKV3-11 germline sequence.

[00157] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-21 germline sequence (*e.g.*, IGHV3-21*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 48), and a light chain variable region having an amino acid sequence derived from a human IGKV3-20 germline sequence (*e.g.*, IGKV3-20*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 49) or a human IGKV3-11 germline sequence (*e.g.*, IGKV3-11*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 50). One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 of the heavy chain variable region (*e.g.*, two, three, four or five of these regions) can be derived from a human IGHV3-21 germline sequence. In one

embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 are all derived from a human IGHV3-21 germline sequence. One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 of the light chain variable region (*e.g.*, two, three, four or five of these regions) can be derived from a human IGKV3-20 or IGKV3-11 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 are all derived from a human IGKV3-20 or IGKV3-11 germline sequence.

[00158] In certain embodiments, the antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 51-54, and 117. In certain embodiments, the antibody comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 51. In certain embodiments, the antibody comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 52. In certain embodiments, the antibody comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 53. In certain embodiments, the antibody comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 54. In certain embodiments, the antibody comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 117.

[00159] In certain embodiments, the antibody comprises a light chain having the amino acid sequence of SEQ ID NO: 59.

[00160] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), comprising a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 51-54, and 117, and a light chain comprising the amino acid sequence of SEQ ID NO: 59. In certain embodiments, the antibody comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 51 and 59, respectively. In certain embodiments, the antibody comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 52 and 59, respectively. In certain embodiments, the antibody comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 53 and 59, respectively. In certain embodiments, the antibody comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 54 and 59, respectively. In certain embodiments, the antibody comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 117 and 59, respectively.

[00161] In certain embodiments, the instant disclosure provides an isolated antibody that cross-competes for binding to CTLA-4 (*e.g.*, human CTLA-4) with an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and

15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that cross-competes for binding to CTLA-4 (*e.g.*, human CTLA-4) with an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively.

[00162] In certain embodiments, the instant disclosure provides an isolated antibody that binds to the same epitope on CTLA-4 (*e.g.*, human CTLA-4) as an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and 15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that binds to the same epitope on CTLA-4 (*e.g.*, human CTLA-4) as an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 100. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 99. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 98. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 97. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 101. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 102.

[00163] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and functions as an antagonist.

[00164] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and decreases CTLA-4 activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to CTLA-4 activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4). In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and

decreases CTLA-4 activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to CTLA-4 activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4). Non-limiting examples of CTLA-4 activity can include CTLA-4 signaling, CTLA-4 binding to CTLA-4 ligand (*e.g.*, CD80 or CD86), inhibition of cytokine production (*e.g.*, IL-2 or IFNγ), and inhibition of T cell proliferation. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and deactivates, reduces, or inhibits a CTLA-4 activity. In specific embodiments, a decrease in a CTLA-4 activity is assessed as described in the Examples, *infra*.

[00165] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and decreases CTLA-4 binding to its ligand (*e.g.*, CD80 or CD86) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to CTLA-4 binding to its ligand (*e.g.*, CD80 or CD86) without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4). In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and decreases CTLA-4 binding to its ligand (*e.g.*, CD80 or CD86) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to CTLA-4 binding to its ligand (*e.g.*, CD80 or CD86) without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4).

[00166] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and increases cytokine production (*e.g.*, IL-2 or IFNγ) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to cytokine production without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4). In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and increases cytokine production (*e.g.*, IL-2 or IFNγ) by

at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to cytokine production without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4).

[00167] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and either alone or in combination with an anti-CTLA-4 antibody (*e.g.*, ipilimumab or tremelimumab), an anti-TIGIT antibody, an anti-CD137 antibody (*e.g.*, urelumab or utomilumab), or an anti-OX40 antibody (*e.g.*, pogalizumab or tavolixizumab) increases IL-2 production in human peripheral blood mononuclear cells (PBMCs) in response to Staphylococcus Enterotoxin A (SEA) stimulation by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to IL-2 production without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4).

[00168] In certain embodiments, human peripheral blood mononuclear cells (PBMCs) stimulated with Staphylococcus Enterotoxin A (SEA) in the presence of an antibody described herein, which specifically binds to human CTLA-4, either alone or in combination with an anti-PD-1 antibody (*e.g.*, nivolumab or pembrolizumab), an anti-TIGIT antibody, an anti-CD137 antibody (*e.g.*, urelumab or utomilumab), or an anti-OX40 antibody (*e.g.*, pogalizumab or tavolixizumab), have increased IL-2 production by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold relative to PBMCs only stimulated with SEA without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4), as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art.

[00169] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and increases IFNγ production of a co-culture of human T cells and allogenic dendritic cells by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative

to IFNγ production of a co-culture of human T cells and allogenic dendritic cells without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4).

[00170] In certain embodiments, a co-culture of human T cells and allogenic dendritic cells in the presence of an antibody described herein, which specifically binds to human CTLA-4, has increased IFNγ production by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold relative to a co-culture of human T cells and allogenic dendritic cells without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4), as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art.

[00171] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and increases T cell proliferation by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to T cell proliferation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4). In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and increases T cell proliferation by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to T cell proliferation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4).

In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human CTLA-4 and increases proliferation of anti-CD3-antibody-stimulated CD4+ or CD8+ T cells co-cultured with ovarian cancer ascites fluid by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to proliferation of anti-CD3-antibody-stimulated CD4+ or CD8+ T cells co-cultured with ovarian cancer ascites fluid without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4).

[00172] In certain embodiments, an antibody described herein is an activatable antibody that

in an activated state binds human CTLA-4 protein. In certain embodiments, the activatable antibody comprises a masking moiety that inhibits the binding of the antibody in an uncleaved state to human CTLA-4 protein, and at least one cleavable moiety coupled to the antibody, *e.g.*, wherein the cleavable moiety is a polypeptide that functions as a substrate for a protease that is enriched in the tumor microenvironment. Exemplary activatable antibodies are described, *e.g.*, in U.S. Patent Nos. 8,513,390 and 8,518,404, and U.S. Patent Application Publication Nos. US 2014/0255313, US 2014/0010810, US 2014/0023664, which are incorporated herein by reference. In certain embodiments, the activatable antibody comprises a human IgG heavy chain constant region that is a variant of a wild type human IgG heavy chain constant region, wherein the variant human IgG heavy chain constant region binds to human FcγRIIIA with higher affinity than the wild type human IgG heavy chain constant region binds to human FcγRIIIA.

6.2.2 Anti-PD-1 antibodies

[00173] In one aspect, the instant disclosure provides antibodies that specifically bind to PD-1 (*e.g.*, human PD-1) and antagonize PD-1 function. Also provided herein are multispecific antibodies that comprise a first antigen-binding region that specifically binds to human PD-1 (*e.g.*, human PD-1) and, optionally, a second antigen-binding region that does not specifically bind to PD-1 (*e.g.*, human PD-1). The amino acid sequences of exemplary antibodies are set forth in Tables 6-10, herein.

Table 6. Amino acid sequences of exemplary anti-PD-1 antibodies.*

SEQ ID NO:	Description	Amino acid sequence
66	AGEN2034 VH (BADD438-2744)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNGDHWGQGTLVTVSS
67	BADD438-2742 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNVDYWGQGTLVTVSS
68	BADD426-2614 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCATNGDYWGQGTLVTVSS
69	BADD426-2615 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNGDYWGQGTLVTVSS
70	BADD438-2743 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNEYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNGDHWGQGTLVTVSS
71	BADD438-2745 VH	QVQLVESGGGMVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWFDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNGDHWGQGTLVTVSS

SEQ ID NO:	Description	Amino acid sequence
72	BADD438-2746 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNGDHWGHGTLVTVSS
73	BADD438-2747 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVMGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNGDHWGQGTLVTVSS
74	AGEN2034 VL/3738 VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSED FAVYYCQQYNNWPRTFGQGTKVEIK
75	CDRH1	SYGMH
76	CDRH2	VIWYDGSNKYYADSVKG
77	CDRH2	VIWYDGSNEYYADSVKG
78	CDRH2	VIWFDGSNKYYADSVKG
79	CDRH2	VIWYDGSNKYYADSVMG
80	CDRH3	NVDY
81	CDRH3	NGDH
82	CDRH3	NGDY
83	CDRL1	RASQSVSSNLA
84	CDRL2	GASTRAT
85	CDRL3	QQYNNWPRT
86	CDRH2 consensus	VIWX_1DGSNX_2YYADSVX_3G, wherein X_1 is Y or F; X_2 is K or E; and X_3 is K or M
87	CDRH3 consensus	NX_1DX_2, wherein X_1 is G or V; and X_2 is H or Y
88	VH consensus sequence	QVQLVESGGGX_1VQPGRSLRLSCAASGFTFSSYGMHWVRQA PGKGLEWVAVIWX_2DGSNX_3YYADSVX_4GRFTISRDNSKNTL YLQMNSLRAEDTAVYYCAX_5NX_6DX_7WGX_8GTLVTVSS, wherein X_1 is V or M; X_2 is Y or F; X_3 is K or E; X_4 is K or M; X_5 is S or T; X_6 is G or V; X_7 is H or Y; and X_8 is Q or H
89	Germline sequence: IGHV3-33*01	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAR
90	Germline sequence: IGKV3-15*01	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSED FAVYYCQQYNNWP

SEQ ID NO:	Description	Amino acid sequence
91	AGEN2034 (IgG4 S228P) heavy chain	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNGDHWGQGTLVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKT ISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLG
92	AGEN2034 (IgG1 N297A) heavy chain	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNGDHWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
120	AGEN2033 (IgG4 S228P) heavy chain	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCASNVDYWGQGTLVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKT ISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLG
93	AGEN2034 light chain	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSED FAVYYCQQYNNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
60	IgG1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G

SEQ ID NO:	Description	Amino acid sequence
94	IgG1 N297A	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP G
95	IgG4 S228P	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYT CNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
64	Light chain constant region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC

* CDRs are defined according to the Kabat numbering system.

Table 7. Heavy chain CDR amino acid sequences of exemplary anti-PD-1 antibodies.*

VH (SEQ ID NO:)	CDRH1 (SEQ ID NO:)	CDRH2 (SEQ ID NO:)	CDRH3 (SEQ ID NO:)
BADD438-2742 VH (67)	SYGMH (75)	VIWYDGSNKYYADSVKG (76)	NVDY (80)
AGEN2034 VH (66)	SYGMH (75)	VIWYDGSNKYYADSVKG (76)	NGDH (81)
BADD426-2614 VH (68)	SYGMH (75)	VIWYDGSNKYYADSVKG (76)	NGDY (82)
BADD426-2615 VH (69)	SYGMH (75)	VIWYDGSNKYYADSVKG (76)	NGDY (82)
BADD438-2743 VH (70)	SYGMH (75)	VIWYDGSNEYYADSVKG (77)	NGDH (81)
BADD438-2745 VH (71)	SYGMH (75)	VIWFDGSNKYYADSVKG (78)	NGDH (81)
BADD438-2746 VH (72)	SYGMH (75)	VIWYDGSNKYYADSVKG (76)	NGDH (81)
BADD438-2747 VH (73)	SYGMH (75)	VIWYDGSNKYYADSVMG (79)	NGDH (81)

*Defined according to the Kabat numbering system.

Table 8. Light chain CDR amino acid sequences of exemplary anti-PD-1 antibodies.

VL (SEQ ID NO:)	CDRL1 (SEQ ID NO:)	CDRL2 (SEQ ID NO:)	CDRL3 (SEQ ID NO:)
AGEN2034 VL/3738 VL (74)	RASQSVSSNLA (83)	GASTRAT (84)	QQYNNWPRT (85)

*Defined according to the Kabat numbering system.

Table 9. Exemplary anti-PD-1 antibodies.

Antibody	Heavy chain variable region	SEQ ID NO:	Light chain variable region	SEQ ID NO:
AGEN2033	BADD438-2742 VH	67	3738 VL	74
AGEN2034	AGEN2034 VH	66	3738 VL	74
AGEN2001	BADD426-2614 VH	68	3738 VL	74
AGEN2002	BADD426-2615 VH	69	3738 VL	74
EP11_pl1_B03	BADD438-2743 VH	70	3738 VL	74
EP11_pl1_B05	BADD438-2745 VH	71	3738 VL	74
EP11_pl1_C02	BADD438-2746 VH	72	3738 VL	74
EP11_pl1_C03	BADD438-2747 VH	73	3738 VL	74

Table 10. Exemplary sequences of PD-1.

SEQ ID NO:	Description*	Amino acid Sequence
96	Human PD-1 immature protein (Q15116)	MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPAL LVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAF PEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLC GAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAG QFQTLVVGVVGGLLGSLVLLVWVLAVICSRAARGTIGARRT GQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQT EYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWP L
103	PD-1 epitope	SLAPKAQIKESLRAEL
104	PD-1 epitope	LDSPDRPWNPPTFSPALL
105	PD-1 epitope	DSPDRPWNPP
106	PD-1 epitope	EVPTAHPSP
107	PD-1 epitope	ISLAPKAQ

[00174] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising a heavy chain variable region comprising one, two, or all three of the CDRs of a heavy chain variable region set forth in Table 6 herein. In certain embodiments, the antibody comprises the CDRH1 of one of heavy chain variable regions set forth in Table 6. In certain embodiments, the antibody comprises the CDRH2 of one of the heavy chain variable regions set forth in Table 6. In certain embodiments, the antibody comprises the CDRH3 of one of the heavy chain variable regions set forth in Table 6.

[00175] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising a light chain variable

region comprising one, two, or all three of the CDRs of a light chain variable region disclosed in Table 6 herein. In certain embodiments, the antibody comprises the CDRL1 of one of light chain variable regions set forth in Table 6. In certain embodiments, the antibody comprises the CDRL2 of one of the light chain variable regions set forth in Table 6. In certain embodiments, the antibody comprises the CDRL3 of one of the light chain variable regions set forth in Table 6.

[00176] In certain embodiments, the CDRs of an antibody can be determined according to Kabat et al., J. Biol. Chem. 252, 6609-6616 (1977) and Kabat et al., Sequences of protein of immunological interest (1991), each of which is herein incorporated by reference in its entirety.

[00177] In certain embodiments, the CDRs of an antibody can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (see, *e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B et al., (1997) J Mol Biol 273: 927-948; Chothia C et al., (1992) J Mol Biol 227: 799-817; Tramontano A et al., (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226, all of which are herein incorporated by reference in their entireties). Typically, when using the Kabat numbering convention, the Chothia CDRH1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDRH2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDRH3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDRL1 loop is present at light chain amino acids 24 to 34, the Chothia CDRL2 loop is present at light chain amino acids 50 to 56, and the Chothia CDRL3 loop is present at light chain amino acids 89 to 97. The end of the Chothia CDRH1 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).

[00178] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising the Chothia VH CDRs of a VH disclosed in Table 6 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising the Chothia VL CDRs of a VL disclosed in Table 6 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising the Chothia VH CDRs and Chothia VL CDRs of an antibody disclosed in Table 6 herein. In certain embodiments, antibodies that specifically bind to PD-1 (*e.g.*, human PD-1) comprise one or more CDRs, in which the Chothia and Kabat CDRs have

the same amino acid sequence. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1) and comprises a combination of Kabat CDRs and Chothia CDRs.

[00179] In certain embodiments, the CDRs of an antibody can be determined according to the IMGT numbering system as described in Lefranc M-P, (1999) supra and Lefranc M-P et al., (1999) supra, each of which is herein incorporated by reference in its entirety. In certain embodiments, the instant disclosure provides antibodies that specifically bind to PD-1 (*e.g.*, human PD-1) and comprise CDRs of an antibody disclosed in Table 6 herein, as determined by the IMGT numbering system, for example, as described in Lefranc M-P (1999) supra and Lefranc M-P et al., (1999) supra.

[00180] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising the IMGT VH CDRs of a VH disclosed in Table 6 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising the IMGT VL CDRs of a VL disclosed in Table 6 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising the IMGT VH CDRs and IMGT VL CDRs of an antibody disclosed in Table 6 herein. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1) and comprises a combination of Kabat CDRs and IMGT CDRs.

[00181] In certain embodiments, the CDRs of an antibody can be determined according to the AbM numbering scheme, which refers to AbM hypervariable regions, which represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (Oxford Molecular Group, Inc.), herein incorporated by reference in its entirety. In a particular embodiment, the instant disclosure provides antibodies that specifically bind to PD-1 (*e.g.*, human PD-1) and comprise CDRs of an antibody disclosed in Table 6 herein as determined by the AbM numbering scheme.

[00182] In certain embodiments, the CDRs of an antibody can be determined according to MacCallum RM et al., (1996) J Mol Biol 262: 732-745, herein incorporated by reference in its entirety. See also, *e.g.*, Martin A. "Protein Sequence and Structure Analysis of Antibody Variable Domains," in Antibody Engineering, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001), herein incorporated by reference in its entirety. In a particular embodiment, the instant disclosure provides antibodies that specifically bind to PD-1 (*e.g.*, human PD-1) and comprise CDRs of an antibody disclosed in Table 6 herein as

determined by the MacCallum numbering scheme.

[00183] Accordingly, in certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the antibody comprises a heavy chain variable region comprising the CDRH1, CDRH2, and CDRH3 region amino acid sequences of a heavy chain variable region set forth in SEQ ID NO: 66, 67, 68, 69, 70, 71, 72, or 73, and a light chain variable region comprising the CDRL1, CDRL2, and CDRL3 region amino acid sequences of a light chain variable region set forth in SEQ ID NO: 74, wherein each CDR is defined in accordance with the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the IMGT numbering system, the AbM definition, or the contact definition of CDR.

[00184] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising:

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75); and/or

(b) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein X_1 is Y or F; X_2 is K or E; and X_3 is K or M; and/or

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein X_1 is G or V; and X_2 is H or Y; and/or

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83); and/or

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and/or

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[00185] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), the antibody comprising:

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(b) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein X_1 is Y or F; X_2 is K or E; and X_3 is K or M;

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein X_1 is G or V; and X_2 is H or Y;

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[00186] In certain embodiments, the CDRH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 76-79. In certain embodiments, the CDRH3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 80-82.

In certain embodiments, CDRH1, CDRH2, and CDRH3 comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences, respectively, of an antibody in Table 7. In certain embodiments, CDRL1, CDRL2, and CDRL3 comprise the CDRL1, CDRL2, and CDRL3 amino acid sequences, respectively, of an antibody in Table 8.

[00187] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3, wherein the CDRH1, CDRH2 and CDRH3 comprise the CDRH1, CDRH2 and CDRH3 amino acid sequences, respectively, set forth in SEQ ID NOs: 75, 76, and 80; 75, 76, and 81; 75, 76, and 82; 75, 77, and 81; 75, 78, and 81; or 75, 79, and 81.

[00188] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein the CDRL1, CDRL2 and CDRL3 comprise the CDRL1, CDRL2 and CDRL3 amino acid sequences, respectively, set forth in SEQ ID NOs: 83, 84, and 85.

[00189] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3, and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 comprise the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 amino acid sequences, respectively, set forth in SEQ ID NOs: 75, 76, 80, 83, 84, and 85; 75, 76, 81, 83, 84, and 85; 75, 76, 82, 83, 84, and 85; 75, 77, 81, 83, 84, and 85; 75, 78, 81, 83, 84, and 85; or 75, 79, 81, 83, 84, and 85, respectively.

[00190] In certain embodiments, the antibody comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 regions, and a light chain variable region comprising CDRL1, CDRL2, and CDRL3 regions, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences set forth in SEQ ID NOs: 75, 76, 81, 83, 84, and 85, respectively.

[00191] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 88.

[00192] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a heavy chain variable region

comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-73. In certain embodiments, the antibody comprises a heavy chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-73. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 66. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 67. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 68. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 69. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 70. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 71. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 72. In certain embodiments, the antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 73.

[00193] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence of SEQ ID NO: 74. In certain embodiments, the antibody comprises a light chain variable region having the amino acid sequence of SEQ ID NO: 74.

[00194] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 66, 67, 68, 69, 70, 71, 72, or 73, and a light chain variable region that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 74. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 66, 67, 68, 69, 70, 71, 72, or 73, and a light chain variable region set forth in SEQ ID NO: 74. In certain embodiments, the

antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67 and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 67 and 74, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 68 and 74, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 69 and 74, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 70 and 74, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 71 and 74, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 72 and 74, respectively. In certain embodiments, the antibody comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 73 and 74, respectively.

[00195] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-33 germline sequence (*e.g.*, IGHV3-33*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 89). One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 (*e.g.*, two, three, four or five of these regions) can be derived from a human IGHV3-33 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 are all derived from a human IGHV3-33 germline sequence.

[00196] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a light chain variable region having an amino acid sequence derived from a human IGKV3-15 germline sequence (*e.g.*, IGKV3-15*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 90). One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 (*e.g.*, two, three, four or five of these regions) can be derived from a human IGKV3-15 germline sequence. In one

embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 are all derived from a human IGKV3-15 germline sequence.

[00197] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a heavy chain variable region having an amino acid sequence derived from a human IGHV3-33 germline sequence (*e.g.*, IGHV3-33*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 89), and a light chain variable region having an amino acid sequence derived from a human IGKV3-15 germline sequence (*e.g.*, IGKV3-15*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 90). One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 of the heavy chain variable region (*e.g.*, two, three, four or five of these regions) can be derived from a human IGHV3-33 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 are all derived from a human IGHV3-33 germline sequence. One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 of the light chain variable region (*e.g.*, two, three, four or five of these regions) can be derived from a human IGKV3-15 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 are all derived from a human IGKV3-15 germline sequence.

[00198] In certain embodiments, the antibody comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 91 and 92. In certain embodiments, the antibody comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 91. In certain embodiments, the antibody comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 92.

[00199] In certain embodiments, the antibody comprises a light chain having the amino acid sequence of SEQ ID NO: 93.

[00200] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1), comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 or 92, and a light chain comprising the amino acid sequence of SEQ ID NO: 93. In certain embodiments, the antibody comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 91 and 93, respectively. In certain embodiments, the antibody comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 92 and 93, respectively.

[00201] In certain embodiments, the instant disclosure provides an isolated antibody that cross-competes for binding to PD-1 (*e.g.*, human PD-1), with an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67

and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that cross-competes for binding to PD-1 (*e.g.*, human PD-1), with an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively.

[00202] In certain embodiments, the instant disclosure provides an isolated antibody that binds to the same epitope on CTLA-4 (*e.g.*, human CTLA-4) as an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67 and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively. In certain embodiments, the instant disclosure provides an isolated antibody that binds to the same epitope on CTLA-4 (*e.g.*, human CTLA-4) as an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 103. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 104. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 105. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 106. In certain embodiments, the isolated antibody binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 107.

[00203] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and functions as an antagonist.

[00204] In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and decreases PD-1 activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to PD-1 activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1). In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and decreases PD-1 activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to PD-1 activity without any antibody or with an unrelated

antibody (*e.g.*, an antibody that does not specifically bind to PD-1). Non-limiting examples of PD-1 activity can include PD-1 signaling, PD-1 binding to PD-1 ligand (*e.g.*, PD-L1 or PD-L2), inhibition of cytokine production (*e.g.*, IL-2 or IFNγ), and inhibition of T cell proliferation. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and deactivates, reduces, or inhibits a PD-1 activity. In specific embodiments, a decrease in a PD-1 activity is assessed as described in the Examples, *infra*.

[00205] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and decreases PD-1 binding to its ligand (*e.g.*, PD-L1 or PD-L2) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to PD-1 binding to its ligand (*e.g.*, PD-L1 or PD-L2) without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1). In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and decreases PD-1 binding to its ligand (*e.g.*, PD-L1 or PD-L2) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to PD-1 binding to its ligand (*e.g.*, PD-L1 or PD-L2) without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[00206] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and increases cytokine production (*e.g.*, IL-2 or IFNγ) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to cytokine production without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1). In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and increases cytokine production (*e.g.*, IL-2 or IFNγ) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to cytokine production without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[00207] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to PD-1 (*e.g.*, human PD-1) and either alone or in combination with an anti-CTLA-4 antibody (*e.g.*, ipilimumab or tremelimumab), an anti-TIGIT antibody, an anti-CD137 antibody (*e.g.*, urelumab or utomilumab), or an anti-OX40 antibody (*e.g.*, pogalizumab or tavolixizumab) increases IL-2 production in human peripheral blood mononuclear cells (PBMCs) in response to Staphylococcus Enterotoxin A (SEA) stimulation by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to IL-2 production without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[00208] In certain embodiments, human peripheral blood mononuclear cells (PBMCs) stimulated with Staphylococcus Enterotoxin A (SEA) in the presence of an antibody described herein, which specifically binds to human PD-1, either alone or in combination with an anti-CTLA-4 antibody (*e.g.*, ipilimumab or tremelimumab), an anti-TIGIT antibody, an anti-CD137 antibody (*e.g.*, urelumab or utomilumab), or an anti-OX40 antibody (*e.g.*, pogalizumab or tavolixizumab), have increased IL-2 production by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold relative to PBMCs only stimulated with SEA without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1), as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art.

[00209] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and increases IFNγ production of a co-culture of human T cells and allogenic dendritic cells by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to IFNγ production of a co-culture of human T cells and allogenic dendritic cells without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[00210] In certain embodiments, a co-culture of human T cells and allogenic dendritic cells in the presence of an antibody described herein, which specifically binds to human PD-1, has increased IFNγ production by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5

fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold relative to a co-culture of human T cells and allogenic dendritic cells without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1), as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art.

[00211] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and increases T cell proliferation by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to T cell proliferation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1). In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and increases T cell proliferation by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to T cell proliferation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[00212] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and increases proliferation of anti-CD3-antibody-stimulated CD4+ or CD8+ T cells co-cultured with ovarian cancer ascites fluid by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to proliferation of anti-CD3-antibody-stimulated CD4+ or CD8+ T cells co-cultured with ovarian cancer ascites fluid without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[00213] In specific embodiments, the instant disclosure provides an isolated antibody that specifically binds to human PD-1 and increases NFAT signaling in PD-1-expressing NFAT-luciferase reporter cells co-cultured with PD-L1-expressing target cells by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to NFAT signaling in PD-1-expressing NFAT-

luciferase reporter cells co-cultured with PD-L1-expressing target cells without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

6.2.3 Multispecific Antibodies that Specifically Bind to CTLA-4 and/or PD-1

[00214] In one aspect, provided herein are multispecific antibodies (*e.g.*, bispecific antibodies) that specifically bind to CTLA-4 and PD-1 (*e.g.*, human CTLA-4 and human PD-1). For instance, a multispecific (*e.g.*, bispecific) antibody provided herein can comprise a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1). Such multispecific antibodies advantageously show greater specificity for certain subsets of immune cells containing the combination of target proteins than monospecific bivalent antibodies that only bind to CTLA-4 or PD-1.

[00215] In one embodiment, an antibody provided herein that specifically binds to CTLA-4 and PD-1 contains a combination of CDRs shown in a single row of Table 11 below.

Table 11. CDR sequences of exemplary anti-CTLA-4/PD-1 antibodies.*

SEQ ID NOs of CDRs of the first antigen-binding domain that specifically binds to human CTLA-4						SEQ ID NOs of CDRs of the second antigen-binding domain that specifically binds to human PD-1					
VH CDR 1	VH CDR 2	VH CDR 3	VL CDR 1	VL CDR 2	VL CDR 3	VH CDR 1	VH CDR 2	VH CDR 3	VL CDR 1	VL CDR 2	VL CDR 3
20	22	24	27	30	36	75	76	80	83	84	85
20	22	24	29	32	37	75	76	80	83	84	85
20	22	24	29	33	38	75	76	80	83	84	85
21	22	24	27	30	36	75	76	80	83	84	85
21	22	24	29	33	38	75	76	80	83	84	85
20	22	24	28	31	36	75	76	80	83	84	85
20	22	24	29	34	36	75	76	80	83	84	85
20	22	24	29	35	38	75	76	80	83	84	85
21	22	26	27	30	36	75	76	80	83	84	85
21	22	26	29	32	37	75	76	80	83	84	85
21	22	26	29	33	38	75	76	80	83	84	85
21	22	26	29	35	38	75	76	80	83	84	85
20	22	24	27	30	36	75	76	81	83	84	85
20	22	24	29	32	37	75	76	81	83	84	85
20	22	24	29	33	38	75	76	81	83	84	85
21	22	24	27	30	36	75	76	81	83	84	85
21	22	24	29	33	38	75	76	81	83	84	85
20	22	24	28	31	36	75	76	81	83	84	85
20	22	24	29	34	36	75	76	81	83	84	85
20	22	24	29	35	38	75	76	81	83	84	85

SEQ ID NOs of CDRs of the first antigen-binding domain that specifically binds to human CTLA-4						SEQ ID NOs of CDRs of the second antigen-binding domain that specifically binds to human PD-1					
VH CDR 1	VH CDR 2	VH CDR 3	VL CDR 1	VL CDR 2	VL CDR 3	VH CDR 1	VH CDR 2	VH CDR 3	VL CDR 1	VL CDR 2	VL CDR 3
21	22	26	27	30	36	75	76	81	83	84	85
21	22	26	29	32	37	75	76	81	83	84	85
21	22	26	29	33	38	75	76	81	83	84	85
21	22	26	29	35	38	75	76	81	83	84	85
20	22	24	27	30	36	75	76	82	83	84	85
20	22	24	29	32	37	75	76	82	83	84	85
20	22	24	29	33	38	75	76	82	83	84	85
21	22	24	27	30	36	75	76	82	83	84	85
21	22	24	29	33	38	75	76	82	83	84	85
20	22	24	28	31	36	75	76	82	83	84	85
20	22	24	29	34	36	75	76	82	83	84	85
20	22	24	29	35	38	75	76	82	83	84	85
21	22	26	27	30	36	75	76	82	83	84	85
21	22	26	29	32	37	75	76	82	83	84	85
21	22	26	29	33	38	75	76	82	83	84	85
21	22	26	29	35	38	75	76	82	83	84	85
20	22	24	27	30	36	75	77	81	83	84	85
20	22	24	29	32	37	75	77	81	83	84	85
20	22	24	29	33	38	75	77	81	83	84	85
21	22	24	27	30	36	75	77	81	83	84	85
21	22	24	29	33	38	75	77	81	83	84	85
20	22	24	28	31	36	75	77	81	83	84	85
20	22	24	29	34	36	75	77	81	83	84	85
20	22	24	29	35	38	75	77	81	83	84	85
21	22	26	27	30	36	75	77	81	83	84	85
21	22	26	29	32	37	75	77	81	83	84	85
21	22	26	29	33	38	75	77	81	83	84	85
21	22	26	29	35	38	75	77	81	83	84	85
20	22	24	27	30	36	75	78	81	83	84	85
20	22	24	29	32	37	75	78	81	83	84	85
20	22	24	29	33	38	75	78	81	83	84	85
21	22	24	27	30	36	75	78	81	83	84	85
21	22	24	29	33	38	75	78	81	83	84	85
20	22	24	28	31	36	75	78	81	83	84	85
20	22	24	29	34	36	75	78	81	83	84	85
20	22	24	29	35	38	75	78	81	83	84	85
21	22	26	27	30	36	75	78	81	83	84	85
21	22	26	29	32	37	75	78	81	83	84	85
21	22	26	29	33	38	75	78	81	83	84	85
21	22	26	29	35	38	75	78	81	83	84	85
20	22	24	27	30	36	75	79	81	83	84	85
20	22	24	29	32	37	75	79	81	83	84	85

SEQ ID NOs of CDRs of the first antigen-binding domain that specifically binds to human CTLA-4						SEQ ID NOs of CDRs of the second antigen-binding domain that specifically binds to human PD-1					
VH CDR 1	VH CDR 2	VH CDR 3	VL CDR 1	VL CDR 2	VL CDR 3	VH CDR 1	VH CDR 2	VH CDR 3	VL CDR 1	VL CDR 2	VL CDR 3
20	22	24	29	33	38	75	79	81	83	84	85
21	22	24	27	30	36	75	79	81	83	84	85
21	22	24	29	33	38	75	79	81	83	84	85
20	22	24	28	31	36	75	79	81	83	84	85
20	22	24	29	34	36	75	79	81	83	84	85
20	22	24	29	35	38	75	79	81	83	84	85
21	22	26	27	30	36	75	79	81	83	84	85
21	22	26	29	32	37	75	79	81	83	84	85
21	22	26	29	33	38	75	79	81	83	84	85
21	22	26	29	35	38	75	79	81	83	84	85

*Defined according to the Kabat numbering system.

[00216] In one embodiment, an antibody provided herein that specifically binds to CTLA-4 and PD-1 contains a combination of two heavy chain variable regions and two light chain variable regions shown in a single row of Table 12 below.

Table 12. Heavy chain variable region (VH) and light chain variable region (VL) sequences of exemplary anti-CTLA-4/PD-1 antibodies.

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human CTLA-4		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human PD-1	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
1	14	67	74
1	16	67	74
1	17	67	74
9	14	67	74
9	17	67	74
10	15	67	74
10	17	67	74
10	18	67	74
10	19	67	74
11	15	67	74
11	14	67	74
11	16	67	74
11	17	67	74
12	14	67	74
12	16	67	74
12	17	67	74

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human CTLA-4		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human PD-1	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
12	19	67	74
13	15	67	74
13	17	67	74
1	14	66	74
1	16	66	74
1	17	66	74
9	14	66	74
9	17	66	74
10	15	66	74
10	17	66	74
10	18	66	74
10	19	66	74
11	15	66	74
11	14	66	74
11	16	66	74
11	17	66	74
12	14	66	74
12	16	66	74
12	17	66	74
12	19	66	74
13	15	66	74
13	17	66	74
1	14	68	74
1	16	68	74
1	17	68	74
9	14	68	74
9	17	68	74
10	15	68	74
10	17	68	74
10	18	68	74
10	19	68	74
11	15	68	74
11	14	68	74
11	16	68	74
11	17	68	74
12	14	68	74
12	16	68	74
12	17	68	74
12	19	68	74
13	15	68	74
13	17	68	74
1	14	69	74
1	16	69	74
1	17	69	74

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human CTLA-4		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human PD-1	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
9	14	69	74
9	17	69	74
10	15	69	74
10	17	69	74
10	18	69	74
10	19	69	74
11	15	69	74
11	14	69	74
11	16	69	74
11	17	69	74
12	14	69	74
12	16	69	74
12	17	69	74
12	19	69	74
13	15	69	74
13	17	69	74
1	14	70	74
1	16	70	74
1	17	70	74
9	14	70	74
9	17	70	74
10	15	70	74
10	17	70	74
10	18	70	74
10	19	70	74
11	15	70	74
11	14	70	74
11	16	70	74
11	17	70	74
12	14	70	74
12	16	70	74
12	17	70	74
12	19	70	74
13	15	70	74
13	17	70	74
1	14	71	74
1	16	71	74
1	17	71	74
9	14	71	74
9	17	71	74
10	15	71	74
10	17	71	74
10	18	71	74
10	19	71	74

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human CTLA-4		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human PD-1	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
11	15	71	74
11	14	71	74
11	16	71	74
11	17	71	74
12	14	71	74
12	16	71	74
12	17	71	74
12	19	71	74
13	15	71	74
13	17	71	74
1	14	72	74
1	16	72	74
1	17	72	74
9	14	72	74
9	17	72	74
10	15	72	74
10	17	72	74
10	18	72	74
10	19	72	74
11	15	72	74
11	14	72	74
11	16	72	74
11	17	72	74
12	14	72	74
12	16	72	74
12	17	72	74
12	19	72	74
13	15	72	74
13	17	72	74
1	14	73	74
1	16	73	74
1	17	73	74
9	14	73	74
9	17	73	74
10	15	73	74
10	17	73	74
10	18	73	74
10	19	73	74
11	15	73	74
11	14	73	74
11	16	73	74
11	17	73	74
12	14	73	74
12	16	73	74

SEQ ID NOs of variable regions of the first antigen-binding domain that specifically binds to human CTLA-4		SEQ ID NOs of variable regions of the second antigen-binding domain that specifically binds to human PD-1	
VH SEQ ID NO:	VL SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
12	17	73	74
12	19	73	74
13	15	73	74
13	17	73	74

[00217] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region comprising one, two, or all three of the CDRs of a heavy chain variable region set forth in Table 1 herein. In certain embodiments, the first antigen-binding region comprises the CDRH1 of one of heavy chain variable regions set forth in Table 1. In certain embodiments, the first antigen-binding region comprises the CDRH2 of one of the heavy chain variable regions set forth in Table 1. In certain embodiments, the first antigen-binding region comprises the CDRH3 of one of the heavy chain variable regions set forth in Table 1.

[00218] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a light chain variable region comprising one, two, or all three of the CDRs of a light chain variable region disclosed in Table 1 herein. In certain embodiments, the first antigen-binding region comprises the CDRL1 of one of light chain variable regions set forth in Table 1. In certain embodiments, the first antigen-binding region comprises the CDRL2 of one of the light chain variable regions set forth in Table 1. In certain embodiments, the first antigen-binding region comprises the CDRL3 of one of the light chain variable regions set forth in Table 1.

[00219] In certain embodiments, the CDRs of the first antigen-binding region can be determined according to Kabat et al., J. Biol. Chem. 252, 6609-6616 (1977) and Kabat et al., Sequences of protein of immunological interest (1991), each of which is herein incorporated by reference in its entirety.

[00220] In certain embodiments, the CDRs of the first antigen-binding region can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (see, *e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B et al., (1997) J Mol Biol 273: 927-948; Chothia C et al., (1992) J Mol Biol 227: 799-817; Tramontano A et al., (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226, all of which are herein incorporated by reference in their entireties). In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human

CTLA-4) comprises the Chothia VH CDRs of a VH disclosed in Table 1 herein. In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises the Chothia VL CDRs of a VL disclosed in Table 1. In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises the Chothia VH CDRs and Chothia VL CDRs of an antibody disclosed in Table 1 herein. In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a combination of Kabat CDRs and Chothia CDRs.

[00221] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises CDRs of an antibody disclosed in Table 1 herein, as determined by the IMGT numbering system, for example, as described in Lefranc M-P (1999) *supra* and Lefranc M-P *et al.*, (1999) *supra*.

[00222] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises CDRs of an antibody disclosed in Table 1 herein as determined by the AbM numbering scheme.

[00223] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises CDRs of an antibody disclosed in Table 1 herein as determined by the MacCallum numbering scheme.

[00224] Accordingly, in certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region comprising the CDRH1, CDRH2, and CDRH3 region amino acid sequences of a heavy chain variable region set forth in SEQ ID NO: 1, 9, 10, 11, 12, or 13, and a light chain variable region comprising the CDRL1, CDRL2, and CDRL3 region amino acid sequences of a light chain variable region set forth in SEQ ID NO: 14, 15, 16, 17, 18, or 19, wherein each CDR is defined in accordance with the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the IMGT numbering system, the AbM definition, or the contact definition of CDR.

[00225] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein X_1 is S or A; and X_2 is N or S; and/or

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO:

22); and/or

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO:115), wherein X is D or N; and/or

(d) CDRL1 comprises the amino acid sequence of RASQSVX_1X_2YLX_3 (SEQ ID NO: 43), wherein X_1 is S or G; X_2 is R, S, or T; and X_3 is G or A; and/or

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3$RAT (SEQ ID NO: 44), wherein X_1 is G or A; X_2 is A or T; and X_3 is T, S, R, or N; and/or

(f) CDRL3 comprises the amino acid sequence of QQYGX_1SPX_2T (SEQ ID NO: 45), wherein X_1 is S or T; and X_2 is W or F.

[00226] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises:

(a) CDRH1 comprises the amino acid sequence of SYX_1MX_2 (SEQ ID NO: 39), wherein X_1 is S or A; and X_2 is N or S;

(b) CDRH2 comprises the amino acid sequence of SISSSSSYIYYADSVKG (SEQ ID NO: 22);

(c) CDRH3 comprises the amino acid sequence of VGLMGPFXI (SEQ ID NO: 115), wherein X is D or N;

(d) CDRL1 comprises the amino acid sequence of RASQSVX_1X_2YLX_3 (SEQ ID NO: 43), wherein X_1 is S or G; X_2 is R, S, or T; and X_3 is G or A;

(e) CDRL2 comprises the amino acid sequence of $X_1X_2SX_3$RAT (SEQ ID NO: 44), wherein X_1 is G or A; X_2 is A or T; and X_3 is T, S, R, or N; and

(f) CDRL3 comprises the amino acid sequence of QQYGX_1SPX_2T (SEQ ID NO: 45), wherein X_1 is S or T; and X_2 is W or F.

[00227] In certain embodiments, the CDRH1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 20 and 21. In certain embodiments, the CDRH3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24 and 26. In certain embodiments, CDRL1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 28, and 29. In certain embodiments, CDRL2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30-35. In certain embodiments, CDRL3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 36, 37, and 38. In certain embodiments, CDRH1, CDRH2, and CDRH3 comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences, respectively, of an antibody in Table 2. In certain embodiments, CDRL1, CDRL2, and CDRL3 comprise the CDRL1, CDRL2, and CDRL3 amino acid sequences, respectively, of an antibody in Table 3.

[00228] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3, wherein the CDRH1, CDRH2 and CDRH3 comprise the CDRH1, CDRH2 and CDRH3 amino acid sequences, respectively, set forth in SEQ ID NOs: 20, 22, and 24; 21, 22, and 24; or 21, 22, and 26.

[00229] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein the CDRL1, CDRL2 and CDRL3 comprise the CDRL1, CDRL2 and CDRL3 amino acid sequences, respectively, set forth in SEQ ID NOs: 27, 30, and 36; 28, 31, and 36; 29, 32, and 37; 29, 33, and 38; 29, 34, and 36; or 29, 35, and 38.

[00230] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3, and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 comprise the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 amino acid sequences, respectively, set forth in SEQ ID NOs: 20, 22, 24, 27, 30, and 36; 20, 22, 24, 29, 32, and 37; 20, 22, 24, 29, 33, and 38; 21, 22, 24, 27, 30, and 36; 21, 22, 24, 29, 33, and 38; 20, 22, 24, 28, 31, and 36; 20, 22, 24, 29, 34, and 36; 20, 22, 24, 29, 35, and 38; 21, 22, 26, 27, 30, and 36; 21, 22, 26, 29, 32, and 37; 21, 22, 26, 29, 33, and 38; or 21, 22, 26, 29, 35, and 38, respectively.

[00231] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 regions, and a light chain variable region comprising CDRL1, CDRL2, and CDRL3 regions, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences set forth in SEQ ID NOs: 20, 22, 24, 27, 30, and 36, respectively.

[00232] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 46.

[00233] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ

ID NO: 1, 9, 10, 11, 12, or 13. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1, 9, 10, 11, 12, or 13. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 1. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 9. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 10. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 11. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 12. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 13.

[00234] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 47.

[00235] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 14, 15, 16, 17, 18, or 19. In certain embodiments, the first antigen-binding region comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 14, 15, 16, 17, 18, or 19. In certain embodiments, the first antigen-binding region comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 14. In certain embodiments, the first antigen-binding region comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 15. In certain embodiments, the first antigen-binding region comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 16. In certain embodiments, the first antigen-binding region comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 17. In certain embodiments, the first antigen-binding region comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 18. In certain embodiments, the first antigen-binding region comprises a light chain variable region having the amino acid sequence set forth in SEQ ID NO: 19.

[00236] In certain embodiments, the first antigen-binding region that specifically binds to

CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 1, 9, 10, 11, 12, or 13, and a light chain variable region that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 14, 15, 16, 17, 18, or 19. In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 1, 9, 10, 11, 12, or 13, and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 14, 15, 16, 17, 18, or 19. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and 15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 1 and 16, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 1 and 17, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 9 and 14, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 9 and 17, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 10 and 15, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 10 and 17, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 10 and 18, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region

having the amino acid sequences set forth in SEQ ID NOs: 10 and 19, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 11 and 15, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 11 and 14, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 11 and 16, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 11 and 17, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 12 and 14, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 12 and 16, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 12 and 17, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 12 and 19, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 13 and 15, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 13 and 17, respectively.

[00237] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-21 germline sequence (*e.g.*, IGHV3-21*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 48). One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 (*e.g.*, two, three, four or five of these regions) can be derived from a human IGHV3-21 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 are all derived from a human IGHV3-21 germline sequence.

[00238] In certain embodiments, the first antigen-binding region that specifically binds to

CTLA-4 (*e.g.*, human CTLA-4) comprises a light chain variable region having an amino acid sequence derived from a human IGKV3-20 germline sequence (*e.g.*, IGKV3-20*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 49) or a human IGKV3-11 germline sequence (*e.g.*, IGKV3-11*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 50). One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 (*e.g.*, two, three, four or five of these regions) can be derived from a human IGKV3-20 or IGKV3-11 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 are all derived from a human IGKV3-20 or IGKV3-11 germline sequence.

[00239] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-21 germline sequence (*e.g.*, IGHV3-21*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 48), and a light chain variable region having an amino acid sequence derived from a human IGKV3-20 germline sequence (*e.g.*, IGKV3-20*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 49) or a human IGKV3-11 germline sequence (*e.g.*, IGKV3-11*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 50). One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 of the heavy chain variable region (*e.g.*, two, three, four or five of these regions) can be derived from a human IGHV3-21 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 are all derived from a human IGHV3-21 germline sequence. One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 of the light chain (*e.g.*, two, three, four or five of these regions) can be derived from a human IGKV3-20 or IGKV3-11 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 are all derived from a human IGKV3-20 or IGKV3-11 germline sequence.

[00240] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 51-54 and 117. In certain embodiments, the first antigen-binding region comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 51. In certain embodiments, the first antigen-binding region comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 52. In certain embodiments, the first antigen-binding region comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 53. In certain embodiments, the first antigen-binding region comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 54. In certain embodiments, the first antigen-binding region comprises a heavy chain having the amino acid

sequence set forth in SEQ ID NO: 117.

[00241] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a light chain having the amino acid sequence of SEQ ID NO: 59.

[00242] In certain embodiments, the first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) comprises a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 51-54 and 117, and a light chain comprising the amino acid sequence of SEQ ID NO: 59. In certain embodiments, the first antigen-binding region comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 51 and 59, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 52 and 59, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 53 and 59, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 54 and 59, respectively. In certain embodiments, the first antigen-binding region comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 117 and 59, respectively.

[00243] In certain embodiments, the first antigen-binding region cross-competes for binding to CTLA-4 (*e.g.*, human CTLA-4) with an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and 15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively. In certain embodiments, the first antigen-binding region cross-competes for binding to CTLA-4 (*e.g.*, human CTLA-4) with an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively.

[00244] In certain embodiments, the first antigen-binding region binds to the same epitope on CTLA-4 (*e.g.*, human CTLA-4) as an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 1 and 14; 1 and 16, 1 and 17; 9 and 14; 9 and 17; 10 and 15; 10 and 17; 10 and 18; 10 and 19; 11 and 15; 11 and 14; 11 and 16; 11 and 17; 12 and 14; 12 and 16; 12 and 17; 12 and 19; 13 and 15; or 13 and 17, respectively. In certain embodiments, the first antigen-binding region binds to the same epitope on CTLA-4 (*e.g.*, human CTLA-4) as an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively. In certain embodiments,

the first antigen-binding region binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 100. In certain embodiments, the first antigen-binding region binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 99. In certain embodiments, the first antigen-binding region binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 98. In certain embodiments, the first antigen-binding region binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 97. In certain embodiments, the first antigen-binding region binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 101. In certain embodiments, the first antigen-binding region binds to an epitope located within a region of human CTLA-4 consisting of the amino acid sequence of SEQ ID NO: 102.

[00245] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region comprising one, two, or all three of the CDRs of a heavy chain variable region set forth in Table 6 herein. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises the CDRH1 of one of heavy chain variable regions set forth in Table 6. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises the CDRH2 of one of the heavy chain variable regions set forth in Table 6. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises the CDRH3 of one of the heavy chain variable regions set forth in Table 6.

[00246] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a light chain variable region comprising one, two, or all three of the CDRs of a light chain variable region disclosed in Table 6 herein. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises the CDRL1 of one of light chain variable regions set forth in Table 6. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises the CDRL2 of one of the light chain variable regions set forth in Table 6. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises the CDRL3 of one of the light chain variable regions set forth in Table 6.

[00247] In certain embodiments, the CDRs of the second antigen-binding region can be determined according to Kabat et al., J. Biol. Chem. 252, 6609-6616 (1977) and Kabat et al.,

Sequences of protein of immunological interest (1991), each of which is herein incorporated by reference in its entirety.

[00248] In certain embodiments, the CDRs of the second antigen-binding region can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (see, *e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B et al., (1997) J Mol Biol 273: 927-948; Chothia C et al., (1992) J Mol Biol 227: 799-817; Tramontano A et al., (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226, all of which are herein incorporated by reference in their entireties). In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises the Chothia VH CDRs of a VH disclosed in Table 6 herein. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises the Chothia VL CDRs of a VL disclosed in Table 6 herein. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises the Chothia VH CDRs and Chothia VL CDRs of an antibody disclosed in Table 6 herein. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a combination of Kabat CDRs and Chothia CDRs.

[00249] In certain embodiments, the CDRs of the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprise CDRs of an antibody disclosed in Table 6 herein, as determined by the IMGT numbering system, for example, as described in Lefranc M-P (1999) supra and Lefranc M-P et al., (1999) supra.

[00250] In certain embodiments, the CDRs of the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprise CDRs of an antibody disclosed in Table 6 herein as determined by the AbM numbering scheme.

[00251] In certain embodiments, the CDRs of the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprise CDRs of an antibody disclosed in Table 6 herein as determined by the MacCallum numbering scheme.

[00252] Accordingly, in certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region comprising the CDRH1, CDRH2, and CDRH3 region amino acid sequences of a heavy chain variable region set forth in SEQ ID NO: 66, 67, 68, 69, 70, 71, 72, or 73, and a light chain variable region comprising the CDRL1, CDRL2, and CDRL3 region amino acid sequences of

a light chain variable region set forth in SEQ ID NO: 74, wherein each CDR is defined in accordance with the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the IMGT numbering system, the AbM definition, or the contact definition of CDR.

[00253] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises :

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75); and/or

(b) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein X_1 is Y or F; X_2 is K or E; and X_3 is K or M; and/or

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein X_1 is G or V; and X_2 is H or Y; and/or

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83); and/or

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and/or

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[00254] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises:

(a) CDRH1 comprises the amino acid sequence of SYGMH (SEQ ID NO: 75);

(b) CDRH2 comprises the amino acid sequence of VIWX_1DGSNX_2YYADSVX_3G (SEQ ID NO: 86), wherein X_1 is Y or F; X_2 is K or E; and X_3 is K or M;

(c) CDRH3 comprises the amino acid sequence of NX_1DX_2 (SEQ ID NO: 87), wherein X_1 is G or V; and X_2 is H or Y;

(d) CDRL1 comprises the amino acid sequence of RASQSVSSNLA (SEQ ID NO: 83);

(e) CDRL2 comprises the amino acid sequence of GASTRAT (SEQ ID NO: 84); and

(f) CDRL3 comprises the amino acid sequence of QQYNNWPRT (SEQ ID NO: 85).

[00255] In certain embodiments, the CDRH2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 76-79. In certain embodiments, the CDRH3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 80-82. In certain embodiments, CDRH1, CDRH2, and CDRH3 comprise the CDRH1, CDRH2, and CDRH3 amino acid sequences, respectively, of an antibody in Table 7. In certain embodiments, CDRL1, CDRL2, and CDRL3 comprise the CDRL1, CDRL2, and CDRL3 amino acid sequences, respectively, of an antibody in Table 8.

[00256] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region comprising

complementarity determining regions CDRH1, CDRH2 and CDRH3, wherein the CDRH1, CDRH2 and CDRH3 comprise the CDRH1, CDRH2 and CDRH3 amino acid sequences, respectively, set forth in SEQ ID NOs: 75, 76, and 80; 75, 76, and 81; 75, 76, and 82; 75, 77, and 81; 75, 78, and 81; or 75, 79, and 81.

[00257] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein the CDRL1, CDRL2 and CDRL3 comprise the CDRL1, CDRL2 and CDRL3 amino acid sequences, respectively, set forth in SEQ ID NOs: 83, 84, and 85.

[00258] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region comprising complementarity determining regions CDRH1, CDRH2 and CDRH3, and a light chain variable region comprising complementarity determining regions CDRL1, CDRL2 and CDRL3, wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 comprise the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 amino acid sequences, respectively, set forth in SEQ ID NOs: 75, 76, 80, 83, 84, and 85; 75, 76, 81, 83, 84, and 85; 75, 76, 82, 83, 84, and 85; 75, 77, 81, 83, 84, and 85; 75, 78, 81, 83, 84, and 85; or 75, 79, 81, 83, 84, and 85, respectively.

[00259] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region comprising CDRH1, CDRH2, and CDRH3 regions, and a light chain variable region comprising CDRL1, CDRL2, and CDRL3 regions, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences set forth in SEQ ID NOs: 75, 76, 81, 83, 84, and 85, respectively.

[00260] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 88.

[00261] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-73. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 66-

73. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 66. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 67. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 68. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 69. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 70. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 71. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 72. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 73.

[00262] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a light chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence of SEQ ID NO: 74. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a light chain variable region having the amino acid sequence of SEQ ID NO: 74.

[00263] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 66, 67, 68, 69, 70, 71, 72, or 73, and a light chain variable region that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in SEQ ID NO: 74. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 66, 67, 68, 69, 70, 71, 72, or 73, and a light chain variable region set forth in SEQ ID NO: 74. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region and light chain variable region having

the amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67 and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 67 and 74, respectively. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 68 and 74, respectively. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 69 and 74, respectively. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 70 and 74, respectively. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 71 and 74, respectively. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 72 and 74, respectively. In certain embodiments, the second antigen-binding region comprises a heavy chain variable region and light chain variable region having the amino acid sequences set forth in SEQ ID NOs: 73 and 74, respectively.

[00264] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-33 germline sequence (*e.g.*, IGHV3-33*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 89). One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 (*e.g.*, two, three, four or five of these regions) can be derived from a human IGHV3-33 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 are all derived from a human IGHV3-33 germline sequence.

[00265] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a light chain variable region having an amino acid sequence derived from a human IGKV3-15 germline sequence (*e.g.*, IGKV3-15*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 90). One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 (*e.g.*, two, three, four or five

of these regions) can be derived from a human IGKV3-15 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 are all derived from a human IGKV3-15 germline sequence.

[00266] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain variable region having an amino acid sequence derived from a human IGHV3-33 germline sequence (*e.g.*, IGHV3-33*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 89), and a light chain variable region having an amino acid sequence derived from a human IGKV3-15 germline sequence (*e.g.*, IGKV3-15*01, *e.g.*, having the amino acid sequence of SEQ ID NO: 90). One or more regions selected from framework 1, framework 2, framework 3, CDRH1, and CDRH2 of the heavy chain variable region (*e.g.*, two, three, four or five of these regions) can be derived from a human IGHV3-33 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRH1, and CDRH2 are all derived from a human IGHV3-33 germline sequence. One or more regions selected from framework 1, framework 2, framework 3, CDRL1, and CDRL2 of the light chain (*e.g.*, two, three, four or five of these regions) can be derived from a human IGKV3-15 germline sequence. In one embodiment, framework 1, framework 2, framework 3, CDRL1, and CDRL2 are all derived from a human IGKV3-15 germline sequence.

[00267] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 91 and 92. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 91. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain having the amino acid sequence set forth in SEQ ID NO: 92.

[00268] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a light chain having the amino acid sequence of SEQ ID NO: 93.

[00269] In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 or 92, and a light chain comprising the amino acid sequence of SEQ ID NO: 93. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain and light chain having the amino acid sequences set forth in SEQ ID NOs: 91 and 93, respectively. In certain embodiments, the second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1) comprises a heavy chain and

light chain having the amino acid sequences set forth in SEQ ID NOs: 92 and 93, respectively.

[00270] In certain embodiments, the second antigen-binding region cross-competes for binding to PD-1 (*e.g.*, human PD-1) with an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67 and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively. In certain embodiments, the second antigen-binding region cross-competes for binding to PD-1 (*e.g.*, human PD-1), with an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively.

[00271] In certain embodiments, the second antigen-binding region binds to the same epitope on PD-1 (*e.g.*, human PD-1) as an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 66 and 74; 67 and 74; 68 and 74; 69 and 74; 70 and 74; 71 and 74; 72 and 74; or 73 and 74, respectively. In certain embodiments, the second antigen-binding region binds to the same epitope on PD-1 (*e.g.*, human PD-1) as an antibody comprising the heavy and light chain variable region amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively. In certain embodiments, the second antigen-binding region binds to an epitope located within a region of human PD-1 consisting of the amino acid sequence of SEQ ID NO: 103. In certain embodiments, the second antigen-binding region binds to an epitope located within a region of human PD-1 consisting of the amino acid sequence of SEQ ID NO: 104. In certain embodiments, the second antigen-binding region binds to an epitope located within a region of human PD-1 consisting of the amino acid sequence of SEQ ID NO: 105. In certain embodiments, the second antigen-binding region binds to an epitope located within a region of human PD-1 consisting of the amino acid sequence of SEQ ID NO: 106. In certain embodiments, the second antigen-binding region binds to an epitope located within a region of human PD-1 consisting of the amino acid sequence of SEQ ID NO: 107.

[00272] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding region and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding region comprise the amino acid sequences listed in a single row of Table 11. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*,

human PD-1), wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding region and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding region respectively comprise the amino acid sequences set forth in SEQ ID NOs: 20, 22, 24, 27, 30, 36, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 76, 80, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 76, 80, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 76, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 76, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 76, 82, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 76, 82, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 77, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 77, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 78, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 78, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 29, 35,

38, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 79, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 79, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 79, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 79, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 79, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 79, 81, 83, 84, and 85; or 21, 22, 26, 29, 35, 38, 75, 79, 81, 83, 84, and 85.

[00273] In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain variable region and the light chain variable region of the first antigen-binding region and the heavy chain variable region and the light chain variable region of the second antigen-binding region comprise the amino acid sequences listed in a single row of Table 12. In certain embodiments, the instant disclosure provides an isolated multispecific antibody comprising a first antigen-binding region that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain variable region and the light chain variable region of the first antigen-binding region and the heavy chain variable region and the light chain variable region of the second antigen-binding region respectively comprise the amino acid sequences set forth in SEQ ID NOs: 1, 14, 67, and 74; 1, 16, 67, and 74; 1, 17, 67, and 74; 9, 14, 67, and 74; 9, 17, 67, and 74; 10, 15, 67, and 74; 10, 17, 67, and 74; 10, 18, 67, and 74; 10, 19, 67, and 74; 11, 15, 67, and 74; 11, 14, 67, and 74; 11, 16, 67, and 74; 11, 17, 67, and 74; 12, 14, 67, and 74; 12, 16, 67, and 74; 12, 17, 67, and 74; 12, 19, 67, and 74; 13, 15, 67, and 74; 13, 17, 67, and 74; 1, 14, 66, and 74; 1, 16, 66, and 74; 1, 17, 66, and 74; 9, 14, 66, and 74; 9, 17, 66, and 74; 10, 15, 66, and 74; 10, 17, 66, and 74; 10, 18, 66, and 74; 10, 19, 66, and 74; 11, 15, 66, and 74; 11, 14, 66, and 74; 11, 16, 66, and 74; 11, 17, 66, and 74; 12, 14, 66, and 74; 12, 16, 66, and 74; 12, 17, 66, and 74; 12, 19, 66, and 74; 13, 15, 66, and 74; 13, 17, 66, and 74; 1, 14, 68, and 74; 1, 16, 68, and 74; 1, 17, 68, and 74; 9, 14, 68, and 74; 9, 17, 68, and 74; 10, 15, 68, and 74; 10, 17, 68, and 74; 10, 18, 68, and 74; 10, 19, 68, and 74; 11, 15, 68, and 74; 11, 14, 68, and 74; 11, 16, 68, and 74; 11, 17, 68, and 74; 12, 14, 68, and 74; 12, 16, 68, and 74; 12, 17, 68, and 74; 12, 19, 68, and 74; 13, 15, 68, and 74; 13, 17, 68, and 74; 1, 14, 69, and 74; 1, 16, 69, and 74; 1, 17, 69, and 74; 9, 14, 69, and 74; 9, 17, 69, and 74; 10, 15, 69, and 74; 10, 17, 69, and 74; 10, 18, 69, and 74; 10, 19, 69, and 74; 11, 15, 69, and 74; 11, 14, 69, and 74; 11, 16, 69, and 74; 11, 17, 69, and 74; 12, 14, 69, and 74; 12, 16, 69, and 74;

12, 17, 69, and 74; 12, 19, 69, and 74; 13, 15, 69, and 74; 13, 17, 69, and 74; 1, 14, 70, and 74; 1, 16, 70, and 74; 1, 17, 70, and 74; 9, 14, 70, and 74; 9, 17, 70, and 74; 10, 15, 70, and 74; 10, 17, 70, and 74; 10, 18, 70, and 74; 10, 19, 70, and 74; 11, 15, 70, and 74; 11, 14, 70, and 74; 11, 16, 70, and 74; 11, 17, 70, and 74; 12, 14, 70, and 74; 12, 16, 70, and 74; 12, 17, 70, and 74; 12, 19, 70, and 74; 13, 15, 70, and 74; 13, 17, 70, and 74; 1, 14, 71, and 74; 1, 16, 71, and 74; 1, 17, 71, and 74; 9, 14, 71, and 74; 9, 17, 71, and 74; 10, 15, 71, and 74; 10, 17, 71, and 74; 10, 18, 71, and 74; 10, 19, 71, and 74; 11, 15, 71, and 74; 11, 14, 71, and 74; 11, 16, 71, and 74; 11, 17, 71, and 74; 12, 14, 71, and 74; 12, 16, 71, and 74; 12, 17, 71, and 74; 12, 19, 71, and 74; 13, 15, 71, and 74; 13, 17, 71, and 74; 1, 14, 72, and 74; 1, 16, 72, and 74; 1, 17, 72, and 74; 9, 14, 72, and 74; 9, 17, 72, and 74; 10, 15, 72, and 74; 10, 17, 72, and 74; 10, 18, 72, and 74; 10, 19, 72, and 74; 11, 15, 72, and 74; 11, 14, 72, and 74; 11, 16, 72, and 74; 11, 17, 72, and 74; 12, 14, 72, and 74; 12, 16, 72, and 74; 12, 17, 72, and 74; 12, 19, 72, and 74; 13, 15, 72, and 74; 13, 17, 72, and 74; 1, 14, 73, and 74; 1, 16, 73, and 74; 1, 17, 73, and 74; 9, 14, 73, and 74; 9, 17, 73, and 74; 10, 15, 73, and 74; 10, 17, 73, and 74; 10, 18, 73, and 74; 10, 19, 73, and 74; 11, 15, 73, and 74; 11, 14, 73, and 74; 11, 16, 73, and 74; 11, 17, 73, and 74; 12, 14, 73, and 74; 12, 16, 73, and 74; 12, 17, 73, and 74; 12, 19, 73, and 74; 13, 15, 73, and 74; or 13, 17, 73, and 74.

[00274] In certain embodiments, an isolated anti-CTLA-4/PD-1 antibody as provided herein can decreases CTLA-4 and/or PD-1 activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to CTLA-4 and/or PD-1 activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1). In certain embodiments, a multispecific antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and PD-1 (*e.g.*, human PD-1) as provided herein decreases CTLA-4 and/or PD-1 activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to CTLA-4 and/or PD-1 activity without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1). Non-limiting examples of CTLA-4 activity can include CTLA-4 signaling, CTLA-4 binding to CTLA-4 ligand (*e.g.*, CD80 or CD86), inhibition of cytokine production (*e.g.*, IL-2 or IFNγ), and inhibition of T cell proliferation. Non-limiting examples of PD-1 activity can include PD-1 signaling, PD-1 binding to PD-1 ligand (*e.g.*, PD-L1 or PD-L2), inhibition of cytokine production (*e.g.*, IL-2 or

IFNγ), and inhibition of T cell proliferation. In certain embodiments, the instant disclosure provides an isolated antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and PD-1 (*e.g.*, human PD-1), and deactivates, reduces, or inhibits a CTLA-4 and/or PD-1 activity. In specific embodiments, a decrease in a CTLA-4 and/or PD-1 activity is assessed as described in the Examples, *infra*.

[00275] In certain embodiments, an isolated anti-CTLA-4/PD-1 antibody as provided herein can decreases CTLA-4 binding to its ligand (*e.g.*, CD80 or CD86) and/or PD-1 binding to its ligand (*e.g.*, PD-L1 or PD-L2) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to CTLA-4 binding to its ligand (*e.g.*, CD80 or CD86) without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4), and/or relative to PD-1 binding to its ligand (*e.g.*, PD-L1 or PD-L2) without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1). In certain embodiments, an isolated anti-CTLA-4/PD-1 antibody as provided herein can decrease CTLA-4 binding to its ligand (*e.g.*, CD80 or CD86) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to CTLA-4 binding to its ligand (*e.g.*, CD80 or CD86) without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4), and/or can decrease PD-1 binding to its ligand (*e.g.*, PD-L1 or PD-L2) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, relative to PD-1 binding to its ligand (*e.g.*, PD-L1 or PD-L2) without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to PD-1).

[00276] In certain embodiments, an isolated anti-CTLA-4/PD-1 antibody as provided herein can antagonize CTLA-4 and/or PD-1 functions, for example, by stimulating T cell activation. For instance, an isolated anti-CTLA-4/PD-1 antibody comprising a combination of CDR sequences specified herein, a combination of VH and/or VL sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100% sequence identity with a combination of VH and/or VL sequences specified herein, or a combination of heavy and/or light chains specified herein, can stimulate T cell activation, optionally wherein T cell activation is a substantially increasing function of antibody

concentrations.

[00277] In specific embodiments, an isolated anti-CTLA-4/PD-1 antibody as provided herein can increase cytokine production (*e.g.*, IL-2 or IFNγ) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to cytokine production without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1). In specific embodiments, an isolated anti-CTLA-4/PD-1 antibody as provided herein can increase cytokine production (*e.g.*, IL-2 or IFNγ) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to cytokine production without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1).

[00278] In specific embodiments, the instant disclosure provides an isolated anti-CTLA-4/PD-1 antibody that either alone or in combination with an anti-CTLA-4 antibody (*e.g.*, ipilimumab or tremelimumab), an anti-PD-1 antibody (*e.g.*, nivolumab or pembrolizumab), an anti-TIGIT antibody, an anti-CD137 antibody (*e.g.*, urelumab or utomilumab), or an anti-OX40 antibody (*e.g.*, pogalizumab or tavolixizumab) increases IL-2 production in human peripheral blood mononuclear cells (PBMCs) in response to Staphylococcus Enterotoxin A (SEA) stimulation by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to IL-2 production without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1).

[00279] In certain embodiments, human peripheral blood mononuclear cells (PBMCs) stimulated with Staphylococcus Enterotoxin A (SEA) in the presence of an isolated anti-CTLA-4/PD-1 antibody as provided herein, either alone or in combination with an anti-CTLA-4 antibody (*e.g.*, ipilimumab or tremelimumab), an anti-PD-1 antibody (*e.g.*, nivolumab or pembrolizumab), an anti-TIGIT antibody, an anti-CD137 antibody (*e.g.*, urelumab or utomilumab), or an anti-OX40 antibody (*e.g.*, pogalizumab or tavolixizumab), have increased IL-2 production by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold,

40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold relative to PBMCs only stimulated with SEA without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1), as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art.

[00280] In specific embodiments, the instant disclosure provides an isolated anti-CTLA-4/PD-1 antibody that increases IFNγ production of a co-culture of human T cells and allogenic dendritic cells by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to IFNγ production of a co-culture of human T cells and allogenic dendritic cells without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1).

[00281] In certain embodiments, a co-culture of human T cells and allogenic dendritic cells in the presence of an isolated anti-CTLA-4/PD-1 antibody as provided herein has increased IFNγ production by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold relative to a co-culture of human T cells and allogenic dendritic cells without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1), as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art.

[00282] In specific embodiments, the instant disclosure provides an isolated anti-CTLA-4/PD-1 antibody that increases T cell proliferation by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to T cell proliferation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1). In specific embodiments, the instant disclosure provides an isolated anti-CTLA-4/PD-1 antibody that increases T cell proliferation by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to T cell proliferation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1).

[00283] In specific embodiments, the instant disclosure provides an isolated anti-CTLA-

4/PD-1 antibody that increases proliferation of anti-CD3-antibody-stimulated CD4+ or CD8+ T cells co-cultured with ovarian cancer ascites fluid by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*) or known to one of skill in the art, relative to proliferation of anti-CD3-antibody-stimulated CD4+ or CD8+ T cells co-cultured with ovarian cancer ascites fluid without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not specifically bind to CTLA-4 or PD-1).

[00284] A multispecific antibody, *e.g.*, a bispecific antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and/or PD-1 (*e.g.*, human PD-1) as provided herein can be prepared by chemically linking two different monoclonal antibodies or by fusing two hybridoma cell lines to produce a hybrid-hybridoma. Other multivalent formats that can be used include, for example, Kλ-bodies, dAbs, diabodies, TandAbs, nanobodies, SMIPs, DNLs, strand-exchange engineered domain bodies (SEEDbodies), Affibodies, Fynomers, Kunitz Domains, Albu-dabs, DARTs, DVD-IG, Covx-bodies, peptibodies, scFv-Igs, SVD-Igs, dAb-Igs, Knobs-in-Holes, and triomAbs. Exemplary bispecific formats are discussed in Garber *et al.*, *Nature Reviews Drug Discovery 13*:799-801 (2014), which is herein incorporated by reference in its entirety.

[00285] Exemplary bispecific antibody molecules comprise (i) a single antibody that has two arms comprising different antigen-binding regions, one with a specificity to a first antigen such as CTLA-4 (*e.g.*, human CTLA-4) and one with a specificity to a second antigen such as PD-1 (*e.g.*, human PD-1), (ii) a single antibody that has one antigen-binding region or arm specific to a first antigen such as CTLA-4 (*e.g.*, human CTLA-4) and a second antigen-binding region or arm specific to a second antigen such as PD-1 (*e.g.*, human PD-1), (iii) a single chain antibody that has a first specificity to a first antigen such as CTLA-4 (*e.g.*, human CTLA-4) and a second specificity to a second antigen such as PD-1 (*e.g.*, human PD-1), *e.g.*, via two scFvs linked in tandem by an extra peptide linker; (iv) a dual-variable-domain antibody (DVD-Ig), where each light chain and heavy chain contains two variable regions in tandem through a short peptide linkage (Wu et al., Generation and Characterization of a Dual Variable Domain Immunoglobulin (DVD-Ig.TM.) Molecule, In: Antibody Engineering, Springer Berlin Heidelberg (2010)); (v) a chemically-linked bispecific $(Fab')_2$ fragment; (vi) a Tandab, which is a fusion of two single chain diabodies resulting in a tetravalent bispecific antibody that has two binding sites for each of the target antigens; (vii) a flexibody, which is a combination of scFvs with a diabody resulting in a multivalent molecule; (viii) a so called "dock and lock"

molecule, based on the "dimerization and docking domain" in Protein Kinase A, which, when applied to Fabs, can yield a trivalent bispecific binding protein consisting of two identical Fab fragments linked to a different Fab fragment; (ix) a so-called Scorpion molecule, comprising, *e.g.*, two scFvs fused to both termini of a human Fab-arm; and (x) a diabody.

[00286] Examples of different classes of bispecific antibodies include but are not limited to IgG-like molecules with complementary CH3 domains to force heterodimerisation; recombinant IgG-like dual targeting molecules, wherein the two sides of the molecule each contain the Fab fragment or part of the Fab fragment of at least two different antibodies; IgG fusion molecules, wherein full length IgG antibodies are fused to extra Fab fragment or parts of Fab fragment; Fc fusion molecules, wherein single chain Fv molecules or stabilized diabodies are fused to heavy-chain constant-domains, Fc-regions or parts thereof; Fab fusion molecules, wherein different Fab-fragments are fused together; ScFv- and diabody-based and heavy chain antibodies (*e.g.*, domain antibodies, nanobodies) wherein different single chain Fv molecules or different diabodies or different heavy-chain antibodies (*e.g.* domain antibodies, nanobodies) are fused to each other or to another protein or carrier molecule.

[00287] Examples of Fab fusion bispecific antibodies include but are not limited to $F(ab)_2$ (Medarex/AMGEN), Dual-Action or Bis-Fab (Genentech), Dock-and-Lock (DNL) (ImmunoMedics), Bivalent Bispecific (Biotecnol) and Fab-Fv (UCB-Celltech). Examples of ScFv-, diabody-based and domain antibodies include but are not limited to Bispecific T Cell Engager (BITE) (Micromet, Tandem Diabody (Tandab) (Affimed), Dual Affinity Retargeting Technology (DART) (MacroGenics), Single-chain Diabody (Academic), TCR-like Antibodies (AIT, ReceptorLogics), Human Serum Albumin ScFv Fusion (Merrimack) and COMBODY (Epigen Biotech), dual targeting nanobodies (Ablynx), and dual targeting heavy chain only domain antibodies.

6.2.4 Constant regions

[00288] Any heavy chain or light chain constant region can be used in the antibodies (*e.g.*, monospecific or multispecific antibodies) described herein. In certain embodiments, the antibodies (*e.g.*, monospecific or multispecific antibodies) described herein comprise an Ig region that is a human IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule, any class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2), or any subclass (*e.g.*, IgG_{2a} and IgG_{2b}) of immunoglobulin molecule.

[00289] In certain embodiments, the antibodies (*e.g.*, monospecific or multispecific

antibodies) described herein comprise a human IgG heavy chain constant region that is a variant of a wild type human IgG heavy chain constant region, wherein the variant human IgG heavy chain constant region binds to human Fc gamma receptors with higher affinity than the wild type human IgG heavy chain constant region binds to the human Fc gamma receptors.

[00290] In certain embodiments, the variant human IgG heavy chain constant region comprises one or more of the following amino acid mutations, numbered according to the EU numbering system: S239D, A330L, and I332E. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: S239D and I332E. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: S239D and I332E. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: S239D, A330L, and I332E. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: S239D, A330L, and I332E.

[00291] In certain embodiments, the variant human IgG heavy chain constant region comprises one or more of the following amino acid mutations, numbered according to the EU numbering system: L235V, F243L, R292P, Y300L, and P396L. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: L235V, F243L, R292P, Y300L, and P396L. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: L235V, F243L, R292P, Y300L, and P396L.

[00292] In certain embodiments, the variant human IgG heavy chain constant region comprises one or more of the following amino acid mutations, numbered according to the EU numbering system: G236A, S239D, F243L, T256A, K290A, R292P, S298A, Y300L, V305I, A330L, I332E, E333A, K334A, A339T, and P396L. In certain embodiments, the variant human IgG heavy chain constant region comprises a set of amino acid mutations selected from the group consisting of: S239D; T256A; K290A; S298A; I332E; E333A; K334A; A339T; S239D and I332E; S239D, A330L, and I332E; S298A, E333A, and K334A; G236A, S239D, and I332E; and F243L, R292P, Y300L, V305I, and P396L, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant

region comprises S267E or L328F amino acid mutation, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: S267E and L328F. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: S267E and L328F. In certain embodiments, the variant human IgG heavy chain constant region comprises P238D amino acid mutation, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising P238D amino acid mutation, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region comprises one or more of the following amino acid mutations, numbered according to the EU numbering system: P238D, E233D, G237D, H268D, P271G, and A330R. In certain embodiments, the variant human IgG heavy chain constant region comprises the following amino acid mutations, numbered according to the EU numbering system: P238D, E233D, G237D, H268D, P271G, and A330R. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_1 heavy chain constant region comprising the following amino acid mutations, numbered according to the EU numbering system: P238D, E233D, G237D, H268D, P271G, and A330R. In certain embodiments, the variant human IgG heavy chain constant region comprises C127S amino acid mutation, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region is a variant human IgG_2 heavy chain constant region comprising C127S amino acid mutation, numbered according to the EU numbering system.

[00293] In certain embodiments, the antibodies (*e.g.*, monospecific or multispecific antibodies) provided herein comprise an afucosylated Fc region.

[00294] In certain embodiments, the antibodies (*e.g.*, monospecific or multispecific antibodies) described herein comprise a human IgG heavy chain constant region that is a variant of a wild type human IgG heavy chain constant region, wherein the variant human IgG heavy chain constant region binds to human Fc gamma receptors with lower affinity than the wild type human IgG heavy chain constant region binds to the human Fc gamma receptors. In certain embodiments, the variant human IgG heavy chain constant region comprises a mutation selected from the group consisting of N297A, N297Q, D265A, and a combination thereof, numbered according to the EU numbering system. In certain embodiments, the variant human IgG heavy chain constant region comprises a mutation selected from the group consisting of

D265A, P329A, and a combination thereof, numbered according to the EU numbering system.

[00295] In certain embodiments, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein (*e.g.*, CH2 domain (residues 231-340 of human IgG_1) and/or CH3 domain (residues 341-447 of human IgG_1) and/or the hinge region numbered according to the EU numbering system to alter one or more functional properties of the antibody (*e.g.*, a monospecific or multispecific antibody), such as serum half-life, complement fixation, Fc receptor binding and/or antigen-dependent cellular cytotoxicity.

[00296] In certain embodiments, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (*e.g.*, increased or decreased) as described in, *e.g.*, U.S. Patent No. 5,677,425. The number of cysteine residues in the hinge region of the CH1 domain may be altered to, *e.g.*, facilitate assembly of the light and heavy chains, or to alter (*e.g.*, increase or decrease) the stability of the antibody (*e.g.*, a monospecific or multispecific antibody).

[00297] In some embodiments, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein (*e.g.*, CH2 domain (residues 231-340 of human IgG_1) and/or CH3 domain (residues 341-447 of human IgG_1) and/or the hinge region numbered according to the EU numbering system to increase or decrease the affinity of the antibody (*e.g.*, a monospecific or multispecific antibody) for an Fc receptor (*e.g.*, an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region of an antibody (*e.g.*, a monospecific or multispecific antibody) that decrease or increase the affinity of an antibody (*e.g.*, a monospecific or multispecific antibody) for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor of an antibody (*e.g.*, a monospecific or multispecific antibody) that can be made to alter the affinity of the antibody (*e.g.*, a monospecific or multispecific antibody) for an Fc receptor are described in, *e.g.*, Smith P *et al.*, (2012) PNAS 109: 6181-6186, U.S. Patent No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[00298] In a specific embodiment, one, two, or more amino acid mutations (*i.e.,* substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (for example an Fc or hinge-Fc domain fragment) to alter (*e.g.*, decrease or increase) half-life of an antibody (*e.g.*, a monospecific or multispecific antibody)

in vivo. *See, e.g.,* International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Patent Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (*e.g.*, decrease or increase) the half-life of an antibody (*e.g.*, a monospecific or multispecific antibody) *in vivo*. In some embodiments, one, two or more amino acid mutations (*i.e.,* substitutions, insertions, or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (for example an Fc or hinge-Fc domain fragment) to decrease the half-life of the antibody (*e.g.*, a monospecific or multispecific antibody) *in vivo*. In other embodiments, one, two or more amino acid mutations (*i.e.,* substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (for example an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody (*e.g.*, a monospecific or multispecific antibody) *in vivo*. In a specific embodiment, the antibodies (*e.g.*, monospecific or multispecific antibodies) may have one or more amino acid mutations (*e.g.*, substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG_1) and/or the third constant (CH3) domain (residues 341-447 of human IgG_1), numbered according to the EU numbering system. In a specific embodiment, the constant region of the IgG_1 of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU numbering system. *See* U.S. Patent No. 7,658,921, which is incorporated herein by reference. This type of mutant IgG, referred to as "YTE mutant" has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (*see* Dall'Acqua WF *et al.*, (2006) J Biol Chem 281: 23514-24). In certain embodiments, an antibody (*e.g.*, a monospecific or multispecific antibody) comprises an IgG constant domain comprising one, two, three or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU numbering system.

[00299] In certain embodiments, one or more amino acids selected from amino acid residues 329, 331, and 322 in the constant region of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein, numbered according to the EU numbering system, can be replaced with a different amino acid residue such that the antibody (*e.g.*, a monospecific or multispecific antibody) has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent No. 6,194,551 (Idusogie *et al*). In some embodiments, one or more amino acid residues within amino acid positions 231 to 238 in the N-terminal region of the CH2 domain of an antibody (*e.g.*, a

monospecific or multispecific antibody) described herein are altered to thereby alter the ability of the antibody (*e.g.*, a monospecific or multispecific antibody) to fix complement. This approach is described further in International Publication No. WO 94/29351. In certain embodiments, the Fc region of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein is modified to increase the ability of the antibody (*e.g.*, a monospecific or multispecific antibody) to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody (*e.g.*, a monospecific or multispecific antibody) for an Fcγ receptor by mutating one or more amino acids (*e.g.*, introducing amino acid substitutions) at the following positions: 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 328, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438, or 439, numbered according to the EU numbering system. This approach is described further in International Publication No. WO 00/42072.

[00300] In certain embodiments, an antibody (*e.g.*, a monospecific or multispecific antibody) described herein comprises the constant region of an IgG_4 antibody and the serine at amino acid residue 228 of the heavy chain, numbered according to the EU numbering system, is substituted for proline.

[00301] In certain embodiments, an antibody (*e.g.*, a monospecific or multispecific antibody) described herein comprises the constant region of an IgG_2 antibody and the cysteine at amino acid residue 127 of the heavy chain, numbered according to the EU numbering system, is substituted for serine.

[00302] Antibodies with reduced fucose content have been reported to have an increased affinity for Fc receptors, such as, *e.g.*, FcγRIIIa. Accordingly, in certain embodiments, the antibodies (*e.g.*, monospecific or multispecific antibodies) described herein have reduced fucose content or no fucose content. Such antibodies (*e.g.*, monospecific or multispecific antibodies) can be produced using techniques known to one skilled in the art. For example, the antibodies (*e.g.*, monospecific or multispecific antibodies) can be expressed in cells deficient or lacking the ability of fucosylation. In a specific example, cell lines with a knockout of both alleles of α1,6-fucosyltransferase can be used to produce antibodies (*e.g.*, monospecific or multispecific antibodies) with reduced fucose content. The Potelligent® system (Lonza) is an example of such a system that can be used to produce antibodies (*e.g.*, monospecific or multispecific antibodies) with reduced fucose content. Alternatively, antibodies (*e.g.*,

monospecific or multispecific antibodies) with reduced fucose content or no fucose content can be produced by, *e.g.*: (i) culturing cells under conditions which prevent or reduce fucosylation; (ii) posttranslational removal of fucose (*e.g.*, with a fucosidase enzyme); (iii) post-translational addition of the desired carbohydrate, *e.g.*, after recombinant expression of a non-glycosylated glycoprotein; or (iv) purification of the glycoprotein so as to select for antibodies (*e.g.*, monospecific or multispecific antibodies) thereof which are not fucsoylated. *See*, *e.g.*, Longmore GD & Schachter H (1982) Carbohydr Res 100: 365-92 and Imai-Nishiya H *et al.*, (2007) BMC Biotechnol. 7: 84 for methods for producing antibodies (*e.g.*, monospecific or multispecific antibodies) with no fucose content or reduced fucose content.

[00303] Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function. Methods for generating engineered glycoforms in an antibody (*e.g.*, a monospecific or multispecific antibody) described herein include but are not limited to those disclosed, *e.g.*, in Umaña P *et al.*, (1999) Nat Biotechnol 17: 176-180; Davies J *et al.*, (2001) Biotechnol Bioeng 74: 288-294; Shields RL *et al.*, (2002) J Biol Chem 277: 26733-26740; Shinkawa T *et al.*, (2003) J Biol Chem 278: 3466-3473; Niwa R *et al.*, (2004) Clin Cancer Res 1: 6248-6255; Presta LG *et al.*, (2002) Biochem Soc Trans 30: 487-490; Kanda Y *et al.*, (2007) Glycobiology 17: 104-118; U.S. Patent Nos. 6,602,684; 6,946,292; and 7,214,775; U.S. Patent Publication Nos. US 2007/0248600; 2007/0178551; 2008/0060092; and 2006/0253928; International Publication Nos. WO 00/61739; WO 01/292246; WO 02/311140; and WO 02/30954; Potillegent™ technology (Biowa, Inc. Princeton, N.J.); and GlycoMAb® glycosylation engineering technology (Glycart biotechnology AG, Zurich, Switzerland). *See also*, *e.g.*, Ferrara C *et al.*, (2006) Biotechnol Bioeng 93: 851-861; International Publication Nos. WO 07/039818; WO 12/130831; WO 99/054342; WO 03/011878; and WO 04/065540.

[00304] In certain embodiments, the technology used to engineer the Fc domain of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein is the Xmab® Technology of Xencor (Monrovia, CA). *See*, *e.g.*, U.S. Patent Nos. 8,367,805; 8,039,592; 8,124,731; 8,188,231; U.S. Patent Publication No. 2006/0235208; International Publication Nos. WO 05/077981; WO 11/097527; and Richards JO *et al.*, (2008) Mol Cancer Ther 7: 2517-2527.

[00305] In certain embodiments, any of the constant region mutations or modifications described herein can be introduced into one or both heavy chain constant regions of an antibody (*e.g.*, a monospecific or multispecific antibody) described herein having two heavy chain constant regions.

6.3 Pharmaceutical Compositions

[00306] Provided herein are compositions comprising an anti-CTLA-4 antibody, an anti-PD-1 antibody, and/or an anti-CTLA-4/PD-1 antibody described herein having the desired degree of purity in a physiologically acceptable carrier, excipient or stabilizer (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA).

[00307] In certain embodiments, the pharmaceutical composition comprises an anti-CTLA-4 antibody described herein and an anti-PD-1 antibody described herein. The pharmaceutical composition can comprise any combination of an anti-CTLA-4 antibody described herein and an anti-PD-1 antibody described herein. In certain embodiments, the pharmaceutical composition comprises a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antibody and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antibody comprise the amino acid sequences listed in a single row of Table 11. In certain embodiments, the pharmaceutical composition comprises a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain variable region and the light chain variable region of the first antibody and the heavy chain variable region and the light chain variable region of the second antibody comprise the amino acid sequences listed in a single row of Table 12.

[00308] In certain embodiments, the pharmaceutical composition comprises an effective amount of an antibody described herein. In certain embodiments, the pharmaceutical composition comprises an effective amount of an anti-CTLA-4/PD-1 antibody described herein. In certain embodiments, the pharmaceutical composition comprises an effective amount of a therapeutic combination comprising an anti-CTLA-4 antibody described herein and an anti-PD-1 antibody described herein. The effective amount of the anti-CTLA-4 antibody in such therapeutic combination can be lower than, equal to, or higher than the effective amounts of the anti-CTLA-4 antibody when administered alone, and the effective amount of the anti-PD-1 antibody in this therapeutic combination can be lower than, equal to, or higher than the effective amounts of the anti-PD-1 antibody when administered alone. In certain embodiments, the effective amount of the anti-CTLA-4 antibody in this therapeutic combination is lower than the effective amount of the anti-CTLA-4 antibody when administered alone. In certain embodiments, the effective amount of the anti-PD-1 antibody in this therapeutic combination is lower than the effective amount of the anti-PD-1 antibody

when administered alone. In certain embodiments, the effective amount of the anti-CTLA-4 antibody in this therapeutic combination is lower than the effective amount of the anti-CTLA-4 antibody when administered alone, and the effective amount of the anti-PD-1 antibody in this therapeutic combination is lower than the effective amount of the anti-PD-1 antibody when administered alone.

[00309] Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.,* Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[00310] A pharmaceutical composition may be formulated for any route of administration to a subject. Specific examples of routes of administration include intranasal, oral, pulmonary, transdermal, intradermal, and parenteral. Parenteral administration, characterized by either subcutaneous, intramuscular or intravenous injection, is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

[00311] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances. Examples

of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions includes EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[00312] Preparations for parenteral administration of an antibody include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[00313] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[00314] A pharmaceutical composition described herein can be formulated as an aerosol for topical application, such as by inhalation (see, *e.g.,* U.S. Patent Nos. 4,044,126, 4,414,209 and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflations, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in one embodiment, have diameters of less than 50 microns, in one embodiment less than 10 microns.

[00315] A pharmaceutical composition described herein can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for

transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the antibody alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[00316] Topical mixtures comprising an antibody are prepared as described for the local and systemic administration. The resulting mixture can be a solution, suspension, emulsions or the like and can be formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[00317] Transdermal patches, including iontophoretic and electrophoretic devices, are well known to those of skill in the art, and can be used to administer an antibody. For example, such patches are disclosed in U.S. Patent Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024,975, 6,010715, 5,985,317, 5,983,134, 5,948,433, and 5,860,957.

[00318] In certain embodiments, a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof described herein is a lyophilized powder, which can be reconstituted for administration as solutions, emulsions and other mixtures. It may also be reconstituted and formulated as solids or gels. The lyophilized powder is prepared by dissolving an antibody or antigen-binding fragment thereof described herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In some embodiments, the lyophilized powder is sterile. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4°C to room temperature. Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

[00319] A pharmaceutical composition described herein can also be formulated to be

targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, see, *e.g.*, U.S. Patent Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542 and 5,709,874. In a specific embodiment, a pharmaceutical composition described herein is targeted to a tumor.

[00320] In certain embodiments, pharmaceutical compositions comprise an anti-CTLA-4 antibody, an anti-PD-1 antibody, and/or an anti-CTLA-4/PD-1 antibody described herein described herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. In some embodiments, the antibody is the only active ingredient included in the pharmaceutical composition.

[00321] In certain embodiments, pharmaceutical compositions comprise an effective amount of one or more antibodies described herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier.

[00322] The compositions to be used for *in vivo* administration can be sterile. This is readily accomplished by filtration through, *e.g.,* sterile filtration membranes.

6.4 Methods of Use and Uses

[00323] In one aspect, the instant disclosure provides a method of treating a subject using an anti-CTLA-4 antibody, an anti-PD-1 antibody, and/or a multispecific antibody (e.g., an anti-CTLA-4/PD-1 antibody) described herein. In certain embodiments, the instant disclosure provides a method of treating a subject using an anti-CTLA-4/PD-1 antibody described herein. In certain embodiments, the instant disclosure provides a method of treating a subject using a therapeutic combination comprising an anti-CTLA-4 antibody described herein and an anti-PD-1 antibody described herein, optionally in the absence of a concomitant therapy for treating the same disease or disorder. In certain embodiments, the instant disclosure provides a method of treating a subject using an anti-CTLA-4 antibody described herein as a monotherapy. In certain embodiments, the instant disclosure provides a method of treating a subject using an anti-PD-1 antibody described herein as a monotherapy.

[00324] The therapeutic combination can comprise any combination of an anti-CTLA-4 antibody described herein and an anti-PD-1 antibody described herein. In certain embodiments, the therapeutic combination comprises a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antibody that specifically binds to PD-1 (*e.g.*,

human PD-1), wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antibody and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antibody comprise the amino acid sequences listed in a single row of Table 11. In certain embodiments, the therapeutic combination comprises a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antibody and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antibody respectively comprise the amino acid sequences set forth in SEQ ID NOs: 20, 22, 24, 27, 30, 36, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 76, 80, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 76, 80, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 76, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 76, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 76, 82, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 76, 82, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 77, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 77, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 78, 81,

83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 78, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 79, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 79, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 79, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 79, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 79, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 79, 81, 83, 84, and 85; or 21, 22, 26, 29, 35, 38, 75, 79, 81, 83, 84, and 85.

[00325] In certain embodiments, the therapeutic combination comprises a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain variable region and the light chain variable region of the first antibody and the heavy chain variable region and the light chain variable region of the second antibody comprise the amino acid sequences listed in a single row of Table 12. In certain embodiments, the therapeutic combination comprises a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) and a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain variable region and the light chain variable region of the first antibody and the heavy chain variable region and the light chain variable region of the second antibody respectively comprise the amino acid sequences set forth in SEQ ID NOs: 1, 14, 67, and 74; 1, 16, 67, and 74; 1, 17, 67, and 74; 9, 14, 67, and 74; 9, 17, 67, and 74; 10, 15, 67, and 74; 10, 17, 67, and 74; 10, 18, 67, and 74; 10, 19, 67, and 74; 11, 15, 67, and 74; 11, 14, 67, and 74; 11, 16, 67, and 74; 11, 17, 67, and 74; 12, 14, 67, and 74; 12, 16, 67, and 74; 12, 17, 67, and 74; 12, 19, 67, and 74; 13, 15, 67, and 74; 13, 17, 67, and 74; 1, 14, 66, and 74; 1, 16, 66, and 74; 1, 17, 66, and 74; 9, 14, 66, and 74; 9, 17, 66, and 74; 10, 15, 66, and 74; 10, 17, 66, and 74; 10, 18, 66, and 74; 10, 19, 66, and 74; 11, 15, 66, and 74; 11, 14, 66, and 74; 11, 16, 66, and 74; 11, 17, 66, and 74; 12, 14, 66, and 74; 12, 16, 66, and 74; 12, 17, 66, and 74; 12, 19, 66, and 74; 13, 15, 66, and 74; 13, 17, 66, and 74; 1, 14, 68, and 74; 1, 16, 68, and 74; 1, 17, 68, and 74; 9, 14, 68, and 74; 9, 17, 68, and 74; 10, 15, 68, and 74; 10, 17, 68, and 74; 10, 18, 68, and 74; 10, 19, 68, and 74; 11, 15, 68, and 74; 11, 14, 68, and 74; 11, 16, 68, and 74; 11, 17, 68, and 74; 12, 14, 68, and 74; 12, 16, 68, and 74; 12, 17, 68, and 74; 12, 19, 68, and 74; 13, 15, 68, and 74; 13, 17, 68, and 74; 1, 14,

69, and 74; 1, 16, 69, and 74; 1, 17, 69, and 74; 9, 14, 69, and 74; 9, 17, 69, and 74; 10, 15, 69, and 74; 10, 17, 69, and 74; 10, 18, 69, and 74; 10, 19, 69, and 74; 11, 15, 69, and 74; 11, 14, 69, and 74; 11, 16, 69, and 74; 11, 17, 69, and 74; 12, 14, 69, and 74; 12, 16, 69, and 74; 12, 17, 69, and 74; 12, 19, 69, and 74; 13, 15, 69, and 74; 13, 17, 69, and 74; 1, 14, 70, and 74; 1, 16, 70, and 74; 1, 17, 70, and 74; 9, 14, 70, and 74; 9, 17, 70, and 74; 10, 15, 70, and 74; 10, 17, 70, and 74; 10, 18, 70, and 74; 10, 19, 70, and 74; 11, 15, 70, and 74; 11, 14, 70, and 74; 11, 16, 70, and 74; 11, 17, 70, and 74; 12, 14, 70, and 74; 12, 16, 70, and 74; 12, 17, 70, and 74; 12, 19, 70, and 74; 13, 15, 70, and 74; 13, 17, 70, and 74; 1, 14, 71, and 74; 1, 16, 71, and 74; 1, 17, 71, and 74; 9, 14, 71, and 74; 9, 17, 71, and 74; 10, 15, 71, and 74; 10, 17, 71, and 74; 10, 18, 71, and 74; 10, 19, 71, and 74; 11, 15, 71, and 74; 11, 14, 71, and 74; 11, 16, 71, and 74; 11, 17, 71, and 74; 12, 14, 71, and 74; 12, 16, 71, and 74; 12, 17, 71, and 74; 12, 19, 71, and 74; 13, 15, 71, and 74; 13, 17, 71, and 74; 1, 14, 72, and 74; 1, 16, 72, and 74; 1, 17, 72, and 74; 9, 14, 72, and 74; 9, 17, 72, and 74; 10, 15, 72, and 74; 10, 17, 72, and 74; 10, 18, 72, and 74; 10, 19, 72, and 74; 11, 15, 72, and 74; 11, 14, 72, and 74; 11, 16, 72, and 74; 11, 17, 72, and 74; 12, 14, 72, and 74; 12, 16, 72, and 74; 12, 17, 72, and 74; 12, 19, 72, and 74; 13, 15, 72, and 74; 13, 17, 72, and 74; 1, 14, 73, and 74; 1, 16, 73, and 74; 1, 17, 73, and 74; 9, 14, 73, and 74; 9, 17, 73, and 74; 10, 15, 73, and 74; 10, 17, 73, and 74; 10, 18, 73, and 74; 10, 19, 73, and 74; 11, 15, 73, and 74; 11, 14, 73, and 74; 11, 16, 73, and 74; 11, 17, 73, and 74; 12, 14, 73, and 74; 12, 16, 73, and 74; 12, 17, 73, and 74; 12, 19, 73, and 74; 13, 15, 73, and 74; or 13, 17, 73, and 74.

[00326] In certain embodiments, the instant disclosure provides a method of treating a subject using a therapeutic combination comprising an anti-CTLA-4 antibody described herein (e.g., AGEN1884 (IgG_1)) and an anti-PD-1 antibody (e.g., an antagonistic anti-PD-1 antibody), optionally in the absence of a concomitant therapy for treating the same disease or disorder. In certain embodiments, the anti-PD-1 antibody is nivolumab, also known as BMS-936558 or MDX1106, developed by Bristol-Myers Squibb. In certain embodiments, the anti-PD-1 antibody is pembrolizumab, also known as lambrolizumab or MK-3475, developed by Merck & Co. In certain embodiments, the anti-PD-1 antibody is pidilizumab, also known as CT-011, developed by CureTech. In certain embodiments, the anti-PD-1 antibody is MEDI0680, also known as AMP-514, developed by Medimmune. In certain embodiments, the anti-PD-1 antibody is PDR001 developed by Novartis Pharmaceuticals. In certain embodiments, the anti-PD-1 antibody is REGN2810 developed by Regeneron Pharmaceuticals. In certain embodiments, the anti-PD-1 antibody is PF-06801591 developed by Pfizer. In certain embodiments, the anti-PD-1 antibody is BGB-A317 developed by BeiGene. In certain

embodiments, the anti-PD-1 antibody is TSR-042 developed by AnaptysBio and Tesaro. In certain embodiments, the anti-PD-1 antibody is SHR-1210 developed by Hengrui. In certain embodiments, the anti-CTLA-4 is AGEN1884 (IgG_1) and the anti- PD-1 antibody is pembrolizumab.

[00327] Further non-limiting examples of anti-PD-1 antibodies that may be used in treatment methods described herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entireties for all purposes: U.S. Patent No. 6,808,710; U.S. Patent No. 7,332,582; U.S. Patent No. 7,488,802; U.S. Patent No. 8,008,449; U.S. Patent No. 8,114,845; U.S. Patent No. 8,168,757; U.S. Patent No. 8,354,509; U.S. Patent No. 8,686,119; U.S. Patent No. 8,735,553; U.S. Patent No. 8,747,847; U.S. Patent No. 8,779,105; U.S. Patent No. 8,927,697; U.S. Patent No. 8,993,731; U.S. Patent No. 9,102,727; U.S. Patent No. 9,205,148; U.S. Publication No. US 2013/0202623 A1; U.S. Publication No. US 2013/0291136 A1; U.S. Publication No. US 2014/0044738 A1; U.S. Publication No. US 2014/0356363 A1; U.S. Publication No. US 2016/0075783 A1; and PCT Publication No. WO 2013/033091 A1; PCT Publication No. WO 2015/036394 A1; PCT Publication No. WO 2014/179664 A2; PCT Publication No. WO 2014/209804 A1; PCT Publication No. WO 2014/206107 A1; PCT Publication No. WO 2015/058573 A1; PCT Publication No. WO 2015/085847 A1; PCT Publication No. WO 2015/200119 A1; PCT Publication No. WO 2016/015685 A1; and PCT Publication No. WO 2016/020856 A1.

[00328] In certain embodiments, the instant disclosure provides a method of treating a subject using a therapeutic combination comprising an anti-PD-1 antibody described herein (e.g., AGEN2034 (IgG_4 S228P)) and an anti-CTLA-4 antibody (e.g., an antagonistic anti-CTLA-4 antibody), optionally in the absence of a concomitant therapy for treating the same disease or disorder. In certain embodiments, the anti-CTLA-4 antibody is ipilimumab. In certain embodiments, the anti-CTLA-4 antibody is tremelimumab.

[00329] Any disease or disorder in a subject that would benefit from inhibition of CTLA-4 and/or PD-1 function can be treated using the antibodies, therapeutic combinations, or pharmaceutical composition described herein. The antibodies, or therapeutic combinations or pharmaceutical compositions described herein are particularly useful for inhibiting immune system tolerance to tumors, and accordingly can be used as an immunotherapy for subjects with cancer. For example, in certain embodiments, the instant disclosure provides a method of increasing T-cell activation in response to an antigen in a subject, the method comprising administering to the subject an effective amount of an antibody, therapeutic combination, or pharmaceutical composition as described herein. In certain embodiments, the instant

disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of an antibody, therapeutic combination, or pharmaceutical composition as described herein.

[00330] Cancers that can be treated with the antibodies, therapeutic combinations, or pharmaceutical compositions described herein include, without limitation, solid cancer (*e.g.*, relapsed or refractory solid cancer, and advanced or metastatic solid cancer), carcinoma, sarcoma, melanoma (*e.g.*, stage III or stage IV melanoma), small cell lung cancer, non-small cell lung cancer, urothelial cancer, ovarian cancer, prostate cancer (*e.g.*, metastatic hormone-refractory prostate cancer and progressive metastatic prostate cancer), pancreatic cancer, breast cancer (*e.g.*, $HER2^+$ breast cancer (*e.g.*, relapsed/refractory HER2+ breast cancer)), head and neck cancer (*e.g.*, relapsed/refractory head and neck squamous cell carcinoma (HNSCC)), glioma, malignant glioma, glioblastoma multiforme, brain metastasis, merkel cancer, gastric cancer, gastroesophageal cancer, renal cell carcinoma, uveal melanoma, colon cancer, cervical cancer, lymphoma (*e.g.*, relapsed or refractory lymphoma), non-Hodgkin's lymphoma, Hodgkin's lymphoma, leukemia, and multiple myeloma. In certain embodiments, the cancer is treated with intratumoral administration of an antibody, therapeutic combination, or pharmaceutical composition described herein. Cancers that can be treated with intratumoral administration of the antibodies, therapeutic combinations, or pharmaceutical compositions described herein include, without limitation, solid tumors (*e.g.*, advanced or metastatic solid tumors), head and neck cancer (*e.g.*, relapsed/refractory head and neck squamous cell carcinoma (HNSCC)), and breast cancer (*e.g.*, $HER2^+$ breast cancer (*e.g.*, relapsed/refractory $HER2^+$ breast cancer)).

[00331] In certain embodiments, the cancer treated in accordance with the methods described herein is a metastatic or locally advanced cancer (e.g., solid tumor). In certain embodiments, the cancer is treated in accordance with a method described herein as a first cancer therapy after diagnosis of the metastatic or locally advanced tumor (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis). In certain embodiments, the cancer is treated in accordance with a method described herein as the first cancer therapy after diagnosis of tumor progression (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of tumor progression) that has occurred despite previous treatment of the tumor with a different cancer therapy, optionally wherein the method described herein is provided as the second cancer therapy administered. In certain embodiments, the cancer is treated in accordance with a method described herein as the first cancer therapy after diagnosis of toxicity of a different

cancer therapy (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of toxicity of the different cancer therapy), optionally wherein the method described herein is provided as the second cancer therapy administered. In certain embodiments, the cancer treated in accordance with the methods described herein is a metastatic or locally advanced cancer (e.g., solid tumor) for which no standard therapy is available. In other embodiments, the cancer treated in accordance with the methods described herein is a metastatic or locally advanced cancer (e.g., solid tumor) for which a standard therapy has failed (*i.e.*, the cancer has progressed after the standard therapy). In certain embodiments, a therapy fails if the cancer is refractory to the therapy. In certain embodiments, a therapy fails if the cancer relapses after responding, fully or partially, to the therapy. In certain embodiments, metastatic or locally advanced cancer (e.g., solid tumor) has been confirmed histologically or cytologically.

[00332] In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer (e.g., solid tumor) expresses PD-L1. In certain embodiments, the percentage of tumor cells in a sample of the cancer (e.g., solid tumor) that exhibit detectable expression (e.g., partial or complete expression) of PD-L1 is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%). In certain embodiments, the percentage of tumor cells in a sample of the cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%). In certain embodiments, the percentage of tumor cells in a sample of the cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1%. In certain embodiments, the percentage of tumor cells in a sample of the cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 5%. In certain embodiments, the percentage of tumor cells in a sample of the cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 25%. In certain embodiments, the percentage of tumor cells in a sample of the cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 50%. Expression (e.g., membrane expression) of PD-L1 can be detected by any method well known in the art, including but not limited to immunohistochemistry. Exemplary immunohistochemistry assays for measuring PD-L1 expression in tumor cells are provided in Hirsch et al. (2017, J. Thoracic Oncol. 12(2): 208-222), Rimm et al. (2017, JAMA Oncol. 3(8): 1051-1058), and Diggs and Hsueh (2017,

Biomarker Res. 5:12), which are incorporated by reference herein in their entirety.

[00333] In certain embodiments, the metastatic or locally advanced cancer (e.g., solid tumor) expresses PD-L1. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced cancer (e.g., solid tumor) that exhibit detectable expression (e.g., partial or complete expression) of PD-L1 is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%). In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%). In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1%. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 5%. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 25%. In certain embodiments, the percentage of tumor cells in a sample of the metastatic or locally advanced cancer (e.g., solid tumor) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 50%. Expression (e.g., membrane expression) of PD-L1 can be detected by any method well known in the art, including but not limited to immunohistochemistry. Exemplary immunohistochemistry assays for measuring PD-L1 expression in tumor cells are provided in Hirsch et al. (2017, J. Thoracic Oncol. 12(2): 208-222), Rimm et al. (2017, JAMA Oncol. 3(8): 1051-1058), and Diggs and Hsueh (2017, Biomarker Res. 5:12), which are incorporated by reference herein in their entirety.

[00334] In certain embodiments, the cancer treated in accordance with a method described herein is a non-small cell lung cancer (NSCLC). In certain embodiments, the cancer treated in accordance with a method described herein is a metastatic or locally advanced non-small cell lung cancer (NSCLC). In certain embodiments, the cancer treated in accordance with a method described herein is a Stage IV, metastatic, or locally advanced NSCLC. In certain embodiments, the cancer treated in accordance with a method described herein is a Stage IV NSCLC. In certain embodiments, the method comprises treating a subject using a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein (e.g., AGEN1884

(IgG_1)) or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) an anti-PD-1 antibody described herein (e.g., AGEN2034 (IgG_4 S228P)) or pharmaceutical composition comprising such anti-PD-1 antibody. In certain embodiments, the anti-CTLA-4 antibody is AGEN1884 (IgG_1) and the anti-PD-1 antibody is AGEN2034 (IgG_4 S228P). In certain embodiments, the anti-CTLA-4 antibody is AGEN1884 (IgG_1) and the anti-PD-1 antibody is pembrolizumab. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) that exhibit detectable expression (e.g., partial or complete expression) of PD-L1 is at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 1%. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 5%. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 25%. In certain embodiments, the percentage of tumor cells in a sample of the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) that exhibit detectable membrane expression (e.g., partial or complete membrane expression) of PD-L1 is at least 50%. In certain embodiments, the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) has no EGFR or ALK genomic tumor aberrations. In certain embodiments, the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) has no EGFR sensitizing mutation (e.g., mutation that is amenable to treatment with a tyrosine kinase inhibitor including erlotinib, gefitinib, or afatanib) or ALK translocation. In certain embodiments, the subject having the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) has received no prior systemic chemotherapy treatment for the NSCLC. In certain embodiments, the NSCLC (e.g., the Stage IV, metastatic, or locally advanced NSCLC) is treated in accordance with a method described herein as a first cancer therapy after diagnosis (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months

after diagnosis) of the NSCLC. In certain embodiments, the method comprises treating a subject having NSCLC (e.g., Stage IV, metastatic, or locally advanced NSCLC) using a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) an anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody, wherein the percentage of tumor cells in a sample of the NSCLC that exhibit detectable expression (e.g., membrane expression, partial or complete membrane expression) of PD-L1 is at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%, and wherein the method is provided as a first cancer therapy after diagnosis (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis) of the NSCLC. In certain embodiments, the method comprises treating a subject having NSCLC (e.g., Stage IV, metastatic, or locally advanced NSCLC) using a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) pembrolizumab or pharmaceutical composition comprising pembrolizumab, wherein the percentage of tumor cells in a sample of the NSCLC that exhibit detectable expression (e.g., membrane expression, partial or complete membrane expression) of PD-L1 is at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%, and wherein the method is provided as a first cancer therapy after diagnosis (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis) of the NSCLC.

[00335] In certain embodiments, the cancer treated in accordance with the methods described herein is a cervical cancer. In certain embodiments, the cancer treated in accordance with the methods described herein is a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix. In certain embodiments, the cancer treated in accordance with the methods described herein is an unresectable or metastatic cervical cancer. In certain embodiments, the cervical cancer has progressed after a standard therapy (e.g., has relapsed after the standard therapy, or is refractory to the standard therapy). In certain embodiments, the standard therapy comprises a platinum-containing chemotherapy. In certain embodiments, the platinum-containing chemotherapy is selected from the group consisting of cisplatin, carboplatin, oxaliplatin, nedaplatin, satraplatin, picoplatin, triplatin, phenanthriplatin, iproplatin, lobapatin, heptaplatin, lipoplatin, and a combination thereof. In certain embodiments, the standard therapy further comprises a second chemotherapy. In certain embodiments, the second chemotherapy is selected from the group

consisting of a nucleotide analog (e.g., gemcitabine), a folate antimetabolite (e.g., pemetrexed), a taxane (e.g., paclitaxel). In certain embodiments, the standard therapy is any platinum-based doublet chemotherapy (PT-DC) (also known as platinum-containing doublet) known in the art. In certain embodiments, the PT-DC comprises cisplatin and gemcitabine, cisplatin and pemetrexed, cisplatin and paclitaxel, carboplatin and paclitaxel, or cisplatin and topotecan. The standard therapy (e.g., one comprising a PT-DC) can optionally further comprise one or more additional therapies, such as bevacizumab. In certain embodiments, the standard therapy comprises paclitaxel and topotecan. In certain embodiments, the cervical cancer is HPV positive. In certain embodiments, the cervical cancer is associated with microsatellite instability. In certain embodiments, the cancer treated in accordance with the methods described herein is a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix that has relapsed after a platinum-containing doublet administered for treatment of advanced (recurrent, unresectable, or metastatic) disease. In certain embodiments, the cancer of the cervix is treated in accordance with a method described herein as a first cancer therapy after diagnosis of the cervical cancer (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis). In certain embodiments, the cancer of the cervix is treated in accordance with a method described herein as the first cancer therapy after diagnosis of tumor progression (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of tumor progression) that has occurred despite previous treatment of the cancer of the cervix with a different cancer therapy, optionally wherein the method described herein is provided as the second cancer therapy administered. In certain embodiments, the cancer of the cervix is treated in accordance with a method described herein as the first cancer therapy after diagnosis of toxicity of a different cancer therapy (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of toxicity of the different cancer therapy), optionally wherein the method described herein is provided as the second cancer therapy administered. In certain embodiments, the method comprises treating a subject having cervical cancer (e.g., a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix) using a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) an anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody, wherein the method is provided as a first cancer therapy after diagnosis of the cervical cancer (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2,

3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis). In certain embodiments, the method comprises treating a subject having cervical cancer (e.g., a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix) using a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) an anti-PD-1 antibody described herein, e.g., AGEN2034 (IgG_4 S228P), or pharmaceutical composition comprising such anti-PD-1 antibody, wherein the method is provided after diagnosis of tumor progression (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of tumor progression) that has occurred despite previous treatment of the cervical cancer with a different cancer therapy, or provided after diagnosis of toxicity of a different cancer therapy (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of toxicity of the different cancer therapy), and wherein the method described herein is provided as the second cancer therapy administered. In certain embodiments, the method comprises treating a subject having cervical cancer (e.g., a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix) using a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody, and (b) pembrolizumab or pharmaceutical composition comprising pembrolizumab, wherein the method is provided as a first cancer therapy after diagnosis of the cervical cancer (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis). In certain embodiments, the method comprises treating a subject having cervical cancer (e.g., a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix) using a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein, e.g., AGEN1884 (IgG_1), or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) pembrolizumab or pharmaceutical composition comprising pembrolizumab, wherein the method is provided after diagnosis of tumor progression (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of tumor progression) that has occurred despite previous treatment of the cervical cancer with a different cancer therapy, or provided after diagnosis of toxicity of a different cancer therapy (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of toxicity of the different cancer therapy), and wherein the method described herein is provided as the second cancer therapy

administered.

[00336] In certain embodiments, the cancer treated in accordance with the methods described herein is a cutaneous squamous-cell carcinoma (cSCC). In certain embodiments, the cancer treated in accordance with the methods described herein is a Stage IV cutaneous squamous-cell carcinoma (cSCC). In certain embodiments, the cSCC (e.g., Stage IV cSCC) is not curable with radiation therapy. In certain embodiments, the Stage IV cSCC is diagnosed histologically or cytologically according to the eighth edition of the American Joint Committee on Cancer staging manual (AJCC-8). In certain embodiments, the method comprises treating a subject using a therapeutic combination comprising (a) an anti-CTLA-4 antibody described herein (e.g., AGEN1884 (IgG_1)) or pharmaceutical composition comprising such anti-CTLA-4 antibody; and (b) an anti-PD-1 antibody described herein (e.g., AGEN2034 (IgG_4 S228P)) or pharmaceutical composition comprising such anti-PD-1 antibody. In certain embodiments, the method comprises treating a subject using an anti-PD-1 antibody described herein (e.g., AGEN2034 (IgG_4 S228P)) or pharmaceutical composition comprising such anti-PD-1 antibody as a monotherapy. In certain embodiments, the cSCC (e.g., Stage IV cSCC) is treated in accordance with a method described herein as a first cancer therapy after diagnosis of the cSCC (e.g., Stage IV cSCC) (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis).. In certain embodiments, the cSCC (e.g., Stage IV cSCC) is treated in accordance with a method described herein as the first cancer therapy after diagnosis of tumor progression (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of tumor progression) that has occurred despite previous treatment of the cSCC (e.g., Stage IV cSCC) with a different cancer therapy, optionally wherein the method described herein is provided as the second cancer therapy administered. In certain embodiments, the cSCC (e.g., Stage IV cSCC) is treated in according with a method described herein as the first cancer therapy after diagnosis of toxicity of a different cancer therapy (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of toxicity of the different cancer therapy), optionally wherein the method described herein is provided as the second cancer therapy administered. In certain embodiments, the method comprises treating a subject having cSCC (e.g., Stage IV cSCC) using an anti-PD-1 antibody described herein (e.g., AGEN2034 (IgG_4 S228P)) or pharmaceutical composition comprising such anti-PD-1 antibody as a monotherapy, wherein the method is provided after diagnosis of tumor progression (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of tumor progression) that has occurred despite previous treatment of the cervical

cancer with a different cancer therapy, or provided after diagnosis of toxicity of a different cancer therapy (e.g., within 1, 2, 3, 4, 5, or 6 days; 1, 2, 3, 4, 6, 8, or 12 weeks; or, 1, 2, 3, 4, 6, 8, or 12 months after diagnosis of toxicity of the different cancer therapy), and wherein the method described herein is provided as the second cancer therapy administered.

[00337] In certain embodiments, the cancer treated in accordance with the methods described herein is B cell lymphoma (*e.g.*, B cell chronic lymphocytic leukemia, B cell non-Hodgkin lymphoma, cutaneous B cell lymphoma, diffuse large B cell lymphoma), basal cell carcinoma, bladder cancer, blastoma, brain metastasis, breast cancer, Burkitt lymphoma, carcinoma (*e.g.*, adenocarcinoma (*e.g.*, of the gastroesophageal junction)), cervical cancer, colon cancer, colorectal cancer (colon cancer and rectal cancer), endometrial carcinoma, esophageal cancer, Ewing sarcoma, follicular lymphoma, gastric cancer, gastroesophageal junction carcinoma, gastrointestinal cancer, glioblastoma (*e.g.*, glioblastoma multiforme, *e.g.*, newly diagnosed or recurrent), glioma, head and neck cancer (*e.g.*, head and neck squamous cell carcinoma), hepatic metastasis, Hodgkin's and non-Hodgkin's lymphoma, kidney cancer (*e.g.*, renal cell carcinoma and Wilms' tumors), laryngeal cancer, leukemia (*e.g.*, chronic myelocytic leukemia, hairy cell leukemia), liver cancer (*e.g.*, hepatic carcinoma and hepatoma), lung cancer (*e.g.*, non-small cell lung cancer and small-cell lung cancer), lymphoblastic lymphoma, lymphoma, mantle cell lymphoma, metastatic brain tumor, metastatic cancer, myeloma (*e.g.*, multiple myeloma), neuroblastoma, ocular melanoma, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer (*e.g.*, pancreatic ductal adenocarcinoma), prostate cancer (*e.g.*, hormone refractory (*e.g.*, castration resistant), metastatic, metastatic hormone refractory (*e.g.*, castration resistant, androgen independent)), renal cell carcinoma (*e.g.*, metastatic), salivary gland carcinoma, sarcoma (*e.g.*, rhabdomyosarcoma), skin cancer (*e.g.*, melanoma (*e.g.*, metastatic melanoma)), soft tissue sarcoma, solid tumor, squamous cell carcinoma, synovia sarcoma, testicular cancer, thyroid cancer, transitional cell cancer (urothelial cell cancer), uveal melanoma (*e.g.*, metastatic), verrucous carcinoma, vulval cancer, and Waldenstrom macroglobulinemia.

[00338] In certain embodiments, the cancer treated in accordance with the methods described herein is human sarcoma or carcinoma, *e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma,

papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma (*e.g.*, metastatic), hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, glioblastoma multiforme, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, or retinoblastoma.

[00339] In certain embodiments, the cancer treated in accordance with the methods described herein is an acute lymphocytic leukemia or acute myelocytic leukemia (*e.g.*, myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia or chronic lymphocytic leukemia); Hodgkin's disease; non-Hodgkin's disease; acute myeloid leukemia; B-cell lymphoma; T-cell lymphoma; anaplastic large cell lymphoma; intraocular lymphoma; follicular lymphoma; small intestine lymphoma; or splenic marginal zone lymphoma.

[00340] In certain embodiments, the cancer treated in accordance with the methods described herein is multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, gastrointestinal stromal tumors, head and/or neck cancer (*e.g.*, squamous cell carcinoma of the hypopharynx, squamous cell carcinoma of the larynx, cell carcinoma of the oropharynx, or verrucous carcinoma of the larynx), endometrial stromal sarcoma, mast cell sarcoma, adult soft tissue sarcoma, uterine sarcoma, merkel cell carcinoma, urothelial carcinoma, melanoma with brain metastases, uveal melanoma, uveal melanoma with liver metastases, non-small cell lung cancer, rectal cancer, or myelodysplastic syndrome. In some embodiments, the cancer treated in accordance with the methods is metastatic.

[00341] In certain embodiments, the cancer treated in accordance with the methods described herein is prostate cancer, breast cancer, lung cancer, colorectal cancer, melanoma, bronchial cancer, bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, non-Hodgkin's lymphoma, thyroid cancer, kidney cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, squamous cell cancer, mesothelioma, osteocarcinoma, thyoma/thymic carcinoma, glioblastoma, myelodysplastic syndrome, soft tissue sarcoma, DIPG, adenocarcinoma, osteosarcoma, chondrosarcoma, leukemia, or pancreatic cancer. In some embodiments, the cancer treated in accordance with the methods described herein includes a carcinoma (*e.g.*, an adenocarcinoma), lymphoma, blastoma, melanoma, sarcoma, or leukemia.

[00342] In certain embodiments, the cancer treated in accordance with the methods described herein is squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer (*e.g.*, hepatic carcinoma and hepatoma), bladder cancer, breast cancer, inflammatory breast cancer, Merkel cell carcinoma, colon cancer, colorectal cancer, stomach cancer, urinary bladder cancer, endometrial carcinoma, myeloma (*e.g.*, multiple myeloma), salivary gland, carcinoma, kidney cancer (*e.g.*, renal cell carcinoma and Wilms' tumors), basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, serous adenocarcinoma or various types of head and neck cancer. In certain embodiments, the cancer treated in accordance with the methods described herein includes desmoplastic melanoma, inflammatory breast cancer, thymoma, rectal cancer, anal cancer, or surgically treatable or non-surgically treatable brain stem glioma. In a specific embodiment, the cancer is a solid tumor. In another specific embodiment, the cancer is glioblastoma multiforme. In some embodiments, the glioblastoma multiforme is recurrent. In some embodiments, the glioblastoma multiforme is newly diagnosed. In some embodiments, the glioblastoma multiforme is in a subject having non-methylated MGMT promoters. In some embodiments, the glioblastoma multiforme is refractory to Bevacizumab therapy. In some embodiments, the glioblastoma multiforme is in a subject that has not received Bevacizumab therapy.

[00343] In certain embodiments, the cancer treated in accordance with the methods described herein is metastatic melanoma (*e.g.*, resistant metastatic melanoma), metastatic ovarian cancer, or metastatic renal cell carcinoma. In certain embodiments, the cancer treated in accordance with the methods described herein is melanoma that is resistant to ipilimumab. In some embodiments, the cancer treated in accordance with the methods described herein is melanoma that is resistant to nivolumab or pembrolizumab. In some embodiments, the cancer treated in accordance with the methods described herein is melanoma that is resistant to ipilimumab and nivolumab or pembrolizumab.

[00344] In certain embodiments, the cancer treated in accordance with the methods described herein is breast cancer (*e.g.*, herceptin resistant breast cancer and trastuzumab-DM1 (T-DM1) resistant breast cancer), prostate cancer, glioblastoma multiforme, colorectal cancer, sarcoma, bladder cancer, cervical cancer, HPV-associated cancers, cancers of the vagina, cancers of the vulva, cancers of the penis, cancer of the anus, cancer of the rectum, cancer of the oropharynx, multiple myeloma, renal cell carcinoma, ovarian cancer, hepatocellular cancer, endometrial cancer, pancreatic cancer, lymphoma, and leukemia (*e.g.*, elderly leukemia, acute

myeloid leukemia (AML), and elderly AML).

[00345] In certain embodiments, the cancer treated in accordance with the methods described herein is metastatic malignant melanoma (*e.g.*, cutaneous or intraocular malignant melanoma), renal cancer (*e.g.*, clear cell carcinoma), prostate cancer (*e.g.*, hormone refractory prostate adenocarcinoma), breast cancer, colon cancer, lung cancer (*e.g.*, non-small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, esophageal cancer, liver cancer, refractory or recurrent malignancies, metastatic cancers, cancers that express PD-L1, and combinations of said cancers.

[00346] In certain embodiments, the subject has previously received an immunotherapy. In certain embodiments, the subject has not previously received any immunotherapy. In certain embodiments, the cancer is an advanced or metastatic cancer.

[00347] In certain embodiments, the instant disclosure provides a method of preventing or treating an infectious disease in a subject, the method comprising administering to the subject an effective amount of an antibody, therapeutic combination, or pharmaceutical composition described herein. In one embodiment, provided herein are methods for preventing and/or treating an infection (*e.g.*, a viral infection, a bacterial infection, a fungal infection, a protozoal infection, or a parasitic infection). The infection prevented and/or treated in accordance with the methods can be caused by an infectious agent identified herein. In a specific embodiment, an antibody, therapeutic combination, or pharmaceutical composition described herein is the only active agent administered to a subject. In some embodiments, an antibody, therapeutic combination, or pharmaceutical composition as described herein is used in combination with anti-infective interventions (*e.g.*, antivirals, antibacterials, antifungals, or anti-helminthics) for

the treatment of infectious diseases.

[00348] Infectious diseases that can be treated and/or prevented by antibodies, therapeutic combinations, or pharmaceutical compositions as described herein are caused by infectious agents including but not limited to bacteria, parasites, fungi, protozoa, and viruses. In a specific embodiment, the infectious disease treated and/or prevented by antibodies, therapeutic combinations, or pharmaceutical compositions as described herein is caused by a virus. Viral diseases or viral infections that can be prevented and/or treated in accordance with the methods described herein include, but are not limited to, those caused by hepatitis type A, hepatitis type B, hepatitis type C, influenza (*e.g.*, influenza A or influenza B), varicella, adenovirus, herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), rinderpest, rhinovirus, echovirus, rotavirus, respiratory syncytial virus, papilloma virus, papova virus, cytomegalovirus, echinovirus, arbovirus, huntavirus, coxsackie virus, mumps virus, measles virus, rubella virus, polio virus, small pox, Epstein Barr virus, human immunodeficiency virus type I (HIV-I), human immunodeficiency virus type II (HIV-II), and agents of viral diseases such as viral meningitis, encephalitis, dengue or small pox.

[00349] Bacterial infections that can be prevented and/or treated include infections caused by Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Enterococcus faecalis, Proteus vulgaris, Staphylococcus viridans, and Pseudomonas aeruginosa. Bacterial diseases caused by bacteria (*e.g.*, Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Enterococcus faecalis, Proteus vulgaris, Staphylococcus viridans, and Pseudomonas aeruginosa) that can be prevented and/or treated in accordance with the methods described herein include, but are not limited to, Mycobacteria rickettsia, Mycoplasma, Neisseria, S. pneumonia, Borrelia burgdorferi (Lyme disease), Bacillus antracis (anthrax), tetanus, Streptococcus, Staphylococcus, mycobacterium, pertussis, cholera, plague, diptheria, chlamydia, S. aureus and legionella.

[00350] Protozoal diseases or protozoal infections caused by protozoa that can be prevented and/or treated in accordance with the methods described herein include, but are not limited to, leishmania, coccidiosis, trypanosoma schistosoma or malaria. Parasitic diseases or parasitic infections caused by parasites that can be prevented and/or treated in accordance with the methods described herein include, but are not limited to, chlamydia and rickettsia.

[00351] Fungal diseases or fungal infections that can be prevented and/or treated in accordance with the methods described herein include, but are not limited to, those caused by *Candida* infections, zygomycosis, *Candida* mastitis, progressive disseminated trichosporonosis with latent trichosporonemia, disseminated candidiasis, pulmonary

paracoccidioidomycosis, pulmonary aspergillosis, *Pneumocystis carinii* pneumonia, cryptococcal meningitis, *coccidioidal* meningoencephalitis and cerebrospinal vasculitis, *Aspergillus niger* infection, *Fusarium keratitis*, paranasal sinus mycoses, *Aspergillus fumigatus* endocarditis, tibial dyschondroplasia, *Candida glabrata* vaginitis, oropharyngeal candidiasis, X-linked chronic granulomatous disease, tinea pedis, cutaneous candidiasis, mycotic placentitis, disseminated trichosporonosis, allergic bronchopulmonary aspergillosis, mycotic keratitis, *Cryptococcus neoformans* infection, fungal peritonitis, *Curvularia geniculata* infection, staphylococcal endophthalmitis, sporotrichosis, and dermatophytosis.

[00352] In certain embodiments, the infectious disease is acute. In certain embodiments, the infectious disease is chronic. In certain embodiments, the infectious disease is caused by flavivirus, *e.g.*, West Nile virus, Saint Louis encephalitis virus, Powassan virus, tick-borne encephalitis virus, dengue virus, zika virus, Kyasanur Forest disease virus, yellow fever virus, and chikungunya virus. In certain embodiments, the infectious disease is caused by Ebola virus. In certain embodiments, the infectious disease is caused by influenza virus. In certain embodiments, the infectious disease is caused by Human Immunodeficiency Virus (HIV), Hepatitis B virus (HBV) or Hepatitis C virus (HCV). In certain embodiments, the antibodies, therapeutic combinations, or pharmaceutical compositions described herein promote viral control. In certain embodiments, the antibodies, therapeutic combinations, or pharmaceutical compositions described herein promote eliminates viral reservoirs.

[00353] In certain embodiments, these methods further comprise administering an additional therapeutic agent to the subject. In certain embodiments, the additional therapeutic agent is a chemotherapeutic, radiotherapeutic, or a checkpoint targeting agent. In certain embodiments, the chemotherapeutic agent is a hypomethylating agent (*e.g.*, azacitidine). In certain embodiments, the checkpoint targeting agent is selected from the group consisting of an antagonist anti-CTLA-4 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, an antagonist anti-PD-1 antibody, an antagonist anti-TIM-3 antibody, an antagonist anti-LAG-3 antibody, an antagonist anti-CEACAM1 antibody, an agonist anti-GITR antibody, and an agonist anti-OX40 antibody.

[00354] In certain embodiments, an anti-PD-1 antibody is used in methods described herein. In certain embodiments, the anti-PD-1 antibody is nivolumab, also known as BMS-936558 or MDX1106, developed by Bristol-Myers Squibb. In certain embodiments, the anti-PD-1 antibody is pembrolizumab, also known as lambrolizumab or MK-3475, developed by Merck & Co. In certain embodiments, the anti-PD-1 antibody is pidilizumab, also known as CT-011, developed by CureTech. In certain embodiments, the anti-PD-1 antibody is MEDI0680, also

known as AMP-514, developed by Medimmune. In certain embodiments, the anti-PD-1 antibody is PDR001 developed by Novartis Pharmaceuticals. In certain embodiments, the anti-PD-1 antibody is REGN2810 developed by Regeneron Pharmaceuticals. In certain embodiments, the anti-PD-1 antibody is PF-06801591 developed by Pfizer. In certain embodiments, the anti-PD-1 antibody is BGB-A317 developed by BeiGene. In certain embodiments, the anti-PD-1 antibody is TSR-042 developed by AnaptysBio and Tesaro. In certain embodiments, the anti-PD-1 antibody is SHR-1210 developed by Hengrui.

[00355] Further non-limiting examples of anti-PD-1 antibodies that may be used in treatment methods described herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entireties for all purposes: U.S. Patent No. 6,808,710; U.S. Patent No. 7,332,582; U.S. Patent No. 7,488,802; U.S. Patent No. 8,008,449; U.S. Patent No. 8,114,845; U.S. Patent No. 8,168,757; U.S. Patent No. 8,354,509; U.S. Patent No. 8,686,119; U.S. Patent No. 8,735,553; U.S. Patent No. 8,747,847; U.S. Patent No. 8,779,105; U.S. Patent No. 8,927,697; U.S. Patent No. 8,993,731; U.S. Patent No. 9,102,727; U.S. Patent No. 9,205,148; U.S. Publication No. US 2013/0202623 A1; U.S. Publication No. US 2013/0291136 A1; U.S. Publication No. US 2014/0044738 A1; U.S. Publication No. US 2014/0356363 A1; U.S. Publication No. US 2016/0075783 A1; and PCT Publication No. WO 2013/033091 A1; PCT Publication No. WO 2015/036394 A1; PCT Publication No. WO 2014/179664 A2; PCT Publication No. WO 2014/209804 A1; PCT Publication No. WO 2014/206107 A1; PCT Publication No. WO 2015/058573 A1; PCT Publication No. WO 2015/085847 A1; PCT Publication No. WO 2015/200119 A1; PCT Publication No. WO 2016/015685 A1; and PCT Publication No. WO 2016/020856 A1.

[00356] In certain embodiments, an anti-PD-L1 antibody is used in methods described herein. In certain embodiments, the anti-PD-L1 antibody is atezolizumab developed by Genentech. In certain embodiments, the anti-PD-L1 antibody is durvalumab developed by AstraZeneca, Celgene and Medimmune. In certain embodiments, the anti-PD-L1 antibody is avelumab, also known as MSB0010718C, developed by Merck Serono and Pfizer. In certain embodiments, the anti-PD-L1 antibody is MDX-1105 developed by Bristol-Myers Squibb. In certain embodiments, the anti-PD-L1 antibody is AMP-224 developed by Amplimmune and GSK.

[00357] Non-limiting examples of anti-PD-L1 antibodies that may be used in treatment methods described herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entireties for all purposes: US Patent No. 7,943,743; US Patent No. 8,168,179; US Patent No. 8,217,149; U.S. Patent No. 8,552,154;

U.S. Patent No. 8,779,108; U.S. Patent No. 8,981,063; U.S. Patent No. 9,175,082; U.S. Publication No. US 2010/0203056 A1; U.S. Publication No. US 2003/0232323 A1; U.S. Publication No. US 2013/0323249 A1; U.S. Publication No. US 2014/0341917 A1; U.S. Publication No. US 2014/0044738 A1; U.S. Publication No. US 2015/0203580 A1; U.S. Publication No. US 2015/0225483 A1; U.S. Publication No. US 2015/0346208 A1; U.S. Publication No. US 2015/0355184 A1; and PCT Publication No. WO 2014/100079 A1; PCT Publication No. WO 2014/022758 A1; PCT Publication No. WO 2014/055897 A2; PCT Publication No. WO 2015/061668 A1; PCT Publication No. WO 2015/109124 A1; PCT Publication No. WO 2015/195163 A1; PCT Publication No. WO 2016/000619 A1; and PCT Publication No. WO 2016/030350 A1.

[00358] In certain embodiments, an antibody, therapeutic combination, or pharmaceutical composition described herein is administered to a subject in combination with a compound that targets an immunomodulatory enzyme(s) such as IDO (indoleamine-(2,3)-dioxygenase) and/or TDO (tryptophan 2,3-dioxygenase). In certain embodiments, such compound is selected from the group consisting of epacadostat (Incyte Corp; see, *e.g.*, WO 2010/005958 which is incorporated by reference herein in its entirety), F001287 (Flexus Biosciences/Bristol-Myers Squibb), indoximod (NewLink Genetics), and NLG919 (NewLink Genetics). In one embodiment, the compound is epacadostat. In another embodiment, the compound is F001287. In another embodiment, the compound is indoximod. In another embodiment, the compound is NLG919. In a specific embodiment, an antibody, therapeutic combination, or pharmaceutical composition described herein is administered to a subject in combination with an IDO inhibitor for treating cancer. The IDO inhibitor as described herein for use in treating cancer is present in a solid dosage form of a pharmaceutical composition such as a tablet, a pill or a capsule, wherein the pharmaceutical composition includes an IDO inhibitor and a pharmaceutically acceptable excipient. As such, the antibody as described herein and the IDO inhibitor as described herein can be administered separately, sequentially or concurrently as separate dosage forms. In one embodiment, the antibody is administered parenterally, and the IDO inhibitor is administered orally. In particular embodiments, the inhibitor is selected from the group consisting of epacadostat (Incyte Corporation), F001287 (Flexus Biosciences/Bristol-Myers Squibb), indoximod (NewLink Genetics), and NLG919 (NewLink Genetics). Epacadostat has been described in PCT Publication No. WO 2010/005958, which is incorporated herein by reference in its entirety for all purposes. In one embodiment, the inhibitor is epacadostat. In another embodiment, the inhibitor is F001287. In another embodiment, the inhibitor is indoximod. In another embodiment, the inhibitor is NLG919.

[00359] In certain embodiments, an antibody, therapeutic combination, or pharmaceutical composition described herein is administered to a subject in combination with a vaccine. In certain embodiments, the vaccine is a heat shock protein based tumor vaccine or a heat shock protein based pathogen vaccine. In a specific embodiment, an antibody, therapeutic combination, or pharmaceutical composition described herein is administered to a subject in combination with a heat shock protein based tumor-vaccine. Heat shock proteins (HSPs) are a family of highly conserved proteins found ubiquitously across all species. Their expression can be powerfully induced to much higher levels as a result of heat shock or other forms of stress, including exposure to toxins, oxidative stress or glucose deprivation. Five families have been classified according to molecular weight: HSP-110, -90, -70, -60 and -28. HSPs deliver immunogenic peptides through the cross-presentation pathway in antigen presenting cells (APCs) such as macrophages and dendritic cells (DCs), leading to T cell activation. HSPs function as chaperone carriers of tumor-associated antigenic peptides forming complexes able to induce tumor-specific immunity. Upon release from dying tumor cells, the HSP-antigen complexes are taken up by antigen-presenting cells (APCs) wherein the antigens are processed into peptides that bind MHC class I and class II molecules leading to the activation of anti-tumor CD8+ and CD4+ T cells. The immunity elicited by HSP complexes derived from tumor preparations is specifically directed against the unique antigenic peptide repertoire expressed by the cancer of each subject.

[00360] A heat shock protein peptide complex (HSPPC) is a protein peptide complex consisting of a heat shock protein non-covalently complexed with antigenic peptides. HSPPCs elicit both innate and adaptive immune responses. In a specific embodiment, the antigenic peptide(s) displays antigenicity for the cancer being treated. HSPPCs are efficiently seized by APCs via membrane receptors (mainly CD91) or by binding to Toll-like receptors. HSPPC internalization results in functional maturation of the APCs with chemokine and cytokine production leading to activation of natural killer cells (NK), monocytes and Th1 and Th-2-mediated immune responses. In certain embodiments, HSPPCs used in methods described herein comprise one or more heat shock proteins from the hsp60, hsp70, or hsp90 family of stress proteins complexed with antigenic peptides. In certain embodiments, HSPPCs comprise hsc70, hsp70, hsp90, hsp110, grp170, gp96, calreticulin, or combinations of two or more thereof.

[00361] In a specific embodiment, an antibody, therapeutic combination, or pharmaceutical composition described herein is administered to a subject in combination with a heat shock protein peptide complex (HSPPC), *e.g.*, heat shock protein peptide complex-96 (HSPPC-96),

to treat cancer. HSPPC-96 comprises a 96 kDa heat shock protein (Hsp), gp96, complexed to antigenic peptides. HSPPC-96 is a cancer immunotherapy manufactured from a subject's tumor and contains the cancer's antigenic "fingerprint." In certain embodiments, this fingerprint contains unique antigens that are present only in that particular subject's specific cancer cells and injection of the vaccine is intended to stimulate the subject's immune system to recognize and attack any cells with the specific cancer fingerprint.

[00362] In certain embodiments, the HSPPC, *e.g.*, HSPPC-96, is produced from the tumor tissue of a subject. In a specific embodiment, the HSPPC (*e.g.*, HSPPC-96) is produced from a tumor of the type of cancer or metastasis thereof being treated. In another specific embodiment, the HSPPC (*e.g.*, HSPPC-96) is autologous to the subject being treated. In certain embodiments, the tumor tissue is non-necrotic tumor tissue. In certain embodiments, at least 1 gram (*e.g.*, at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 grams) of non-necrotic tumor tissue is used to produce a vaccine regimen. In certain embodiments, after surgical resection, non-necrotic tumor tissue is frozen prior to use in vaccine preparation. In some embodiments, the HSPPC, *e.g.*, HSPPC-96, is isolated from the tumor tissue by purification techniques, filtered and prepared for an injectable vaccine. In certain embodiments, a subject is administered 6-12 doses of the HSPPC, *e.g.*, HSPCC-96. In such embodiments, the HSPPC, *e.g.*, HSPPC-96, doses may be administered weekly for the first 4 doses and then biweekly for the 2-8 additional doses.

[00363] Further examples of HSPPCs that may be used in accordance with the methods described herein are disclosed in the following patents and patent applications, which are incorporated herein by reference herein in their entireties, U.S. Patent Nos. 6,391,306, 6,383,492, 6,403,095, 6,410,026, 6,436,404, 6,447,780, 6,447,781 and 6,610,659.

[00364] The antibody, therapeutic combination, or pharmaceutical composition and the additional therapeutic agent (*e.g.*, chemotherapeutic, radiotherapeutic, checkpoint targeting agent, IDO inhibitor, and/or vaccine) can be administered separately, sequentially or concurrently as separate dosage forms. In one embodiment, an antibody, therapeutic combination, or pharmaceutical composition described herein is administered parenterally, and an IDO inhibitor is administered orally.

[00365] An antibody, therapeutic combination, or pharmaceutical composition described herein may be delivered to a subject by a variety of routes. These include, but are not limited to, parenteral, intranasal, intratracheal, oral, intradermal, topical, intramuscular, intraperitoneal, transdermal, intravenous, intratumoral, conjunctival and subcutaneous routes. Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and

formulation with an aerosolizing agent for use as a spray. In certain embodiments, the antibody, therapeutic combination, or pharmaceutical composition described herein is delivered subcutaneously or intravenously. In certain embodiments, the antibody, therapeutic combination, or pharmaceutical composition described herein is delivered intratumorally. In certain embodiments, the antibody, therapeutic combination, or pharmaceutical composition described herein is delivered into a tumor draining lymph node. In certain embodiments, the antibody, therapeutic combination, or pharmaceutical composition described herein is delivered via a localized administration (*e.g.*, subcutaneous administration). In certain embodiments, the antibody, therapeutic combination, or pharmaceutical composition described herein is delivered systemically. In certain embodiments, the antibody, therapeutic combination, or pharmaceutical composition described herein is delivered locally. In certain embodiments, the therapeutic combination comprises a first antibody and a second antibody, wherein the first antibody and the second antibody are delivered via the same route (*e.g.*, intravenously, subcutaneously, or intratumorally). In certain embodiments, the therapeutic combination comprises a first antibody and a second antibody, wherein the first antibody and the second antibody are delivered via different routes.

[00366] The amount of an antibody, therapeutic combination, or pharmaceutical composition which will be effective in the treatment and/or prevention of a condition will depend on the nature of the disease, and can be determined by standard clinical techniques.

[00367] The precise dose to be employed in a composition will also depend on the route of administration, and the seriousness of the infection or disease caused by it, and should be decided according to the judgment of the practitioner and each subject's circumstances. For example, effective doses may also vary depending upon means of administration, target site, physiological state of the patient (including age, body weight and health), whether the patient is human or an animal, other medications administered, or whether treatment is prophylactic or therapeutic. Usually, the patient is a human but non-human mammals including transgenic mammals can also be treated. Treatment dosages are optimally titrated to optimize safety and efficacy.

[00368] In certain embodiments, an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-CTLA-4/PD-1 antibody, and/or a pharmaceutical composition described herein is administered to a subject (*e.g.*, intravenously, intratumorally, or subcutaneously) at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.01 mg/kg, about 0.03 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks.

[00369] In one aspect, provided herein is an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-CTLA-4/PD-1 antibody, and/or a pharmaceutical composition, and optionally an additional therapeutic agent, for use in a method for treating cancer, for enhancing or inducing an immune response, or for treating an infectious disease, wherein the antibody and/or pharmaceutical composition is administered to a subject at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks.

[00370] In one aspect, provided herein is a use of a therapeutic combination, a multispecific antibody, a kit, and/or a pharmaceutical composition described herein in the preparation of a medicament, for treating cancer, for enhancing or inducing an immune response, or for treating an infectious disease. Alternatively, the use of a therapeutic combination and/or a multispecific antibody for preparing a medicament, pharmaceutical composition or kit is provided. For example, the use of an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-CTLA-4/PD-1 antibody, and optionally an additional therapeutic agent, for preparing a pharmaceutical composition, medicament or kit for treating cancer, for enhancing or inducing an immune response, or for treating an infectious disease is provided herein.

[00371] In certain embodiments, an antibody or pharmaceutical composition described herein is administered to a subject (*e.g.*, via intravenous injection or via intratumoral injection) at 0.01 mg/kg or about 0.01 mg/kg, optionally every one, two or three weeks. In certain embodiments, an antibody or pharmaceutical composition described herein is administered to a subject (*e.g.*, intravenously, intratumorally, or subcutaneously) at 0.03 mg/kg or about 0.03 mg/kg, optionally every one, two or three weeks. In certain embodiments, an antibody or pharmaceutical composition described herein is administered to a subject (*e.g.*, intravenously, intratumorally, or subcutaneously) at 0.1 mg/kg or about 0.1 mg/kg, optionally every one, two or three weeks. In certain embodiments, an antibody or pharmaceutical composition described herein is administered to a subject (*e.g.*, intravenously, intratumorally, or subcutaneously) at 0.3 mg/kg or about 0.3 mg/kg, optionally every one, two or three weeks. In certain embodiments, an antibody or pharmaceutical composition described herein is administered to a subject (*e.g.*, intravenously, intratumorally, or subcutaneously) at 1 mg/kg or about 1 mg/kg, optionally every one, two or three weeks. In certain embodiments, an antibody or pharmaceutical composition described herein is administered to a subject (*e.g.*, intravenously, intratumorally, or subcutaneously) at 3 mg/kg or about 3 mg/kg, optionally every one, two or three weeks. In certain embodiments, an antibody or pharmaceutical composition described

herein is administered to a subject (*e.g.*, intravenously, intratumorally, or subcutaneously) at 6 mg/kg or about 6 mg/kg, optionally every one, two or three weeks. In certain embodiments, an antibody or pharmaceutical composition described herein is administered to a subject (*e.g.*, intravenously, intratumorally, or subcutaneously) at 10 mg/kg or about 10 mg/kg, optionally every one, two or three weeks.

[00372] The effective amount of a therapeutic combination of a first therapy and a second therapy includes a first amount of the first therapy and a second amount of the second therapy, wherein the administration of the therapeutic combination achieves a desired prophylactic or therapeutic effect. The first amount can be lower than, equal to, or higher than the effective amount of the first therapy when administered alone, and the second amount can be lower than, equal to, or higher than the effective amount of the second therapy when administered alone. In certain embodiments, the first amount is lower than the effective amount of the first therapy when administered alone. In certain embodiments, the second amount is lower than the effective amount of second first therapy when administered alone. In certain embodiments, the first amount is lower than the effective amount of the first therapy when administered alone, and the second amount is lower than the effective amount of the second therapy when administered alone.

[00373] For example, where a therapeutic combination comprises an anti-CTLA-4 antibody described herein and an anti-PD-1 antibody described herein, the effective amount of the anti-CTLA-4 antibody in this therapeutic combination can be lower than, equal to, or higher than the effective amounts of the anti-CTLA-4 antibody when administered alone, and/or the effective amount of the anti-PD-1 antibody in this therapeutic combination can be lower than, equal to, or higher than the effective amounts of the anti-PD-1 antibody when administered alone. In certain embodiments, the effective amount of the anti-CTLA-4 antibody in this therapeutic combination is lower than the effective amount of the anti-CTLA-4 antibody when administered alone. In certain embodiments, the effective amount of the anti-PD-1 antibody in this therapeutic combination is lower than the effective amount of the anti-PD-1 antibody when administered alone. In certain embodiments, the effective amount of the anti-CTLA-4 antibody in this therapeutic combination is lower than the effective amount of the anti-CTLA-4 antibody when administered alone, and the effective amount of the anti-PD-1 antibody in this therapeutic combination is lower than the effective amount of the anti-PD-1 antibody when administered alone.

[00374] In certain embodiments, the therapeutic combination comprises an anti-CTLA-4 antibody described herein administered at a first frequency and an anti-PD-1 antibody

described herein administered at a second frequency. The first and second frequencies can be independently selected from every week, every two weeks, every three weeks, every four weeks, every six weeks, every eight weeks, every twelve weeks, every month, every two months, every three months, every four months, every five months, every six months, every eight months, and every year. In certain embodiments, the first and second frequencies are the same. In certain embodiments, the first and second frequencies are different. In certain embodiments, the anti-CTLA-4 antibody described is administered every three weeks and the anti-PD-1 antibody is administered every two weeks.

[00375] The anti-CTLA-4 antibody and the anti-PD-1 antibody in a therapeutic combination can be administered simultaneously or sequentially. In certain embodiments, the anti-CTLA-4 antibody and the anti-PD-1 antibody are administered simultaneously. In certain embodiments, the anti-CTLA-4 antibody and the anti-PD-1 antibody are administered in the same pharmaceutical composition (*e.g.*, provided as one pharmaceutical composition, or provided as separate pharmaceutical compositions and mixed completely or partially right before or during administration). In certain embodiments, the anti-CTLA-4 antibody and the anti-PD-1 antibody are administered sequentially. In certain embodiments, the anti-CTLA-4 antibody and the anti-PD-1 antibody are administered in separate pharmaceutical compositions, wherein the anti-CTLA-4 antibody is administered after (*e.g.*, about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, or 14 days after) the administration of the anti-PD-1 antibody. In certain embodiments, the anti-CTLA-4 antibody and the anti-PD-1 antibody are administered in separate pharmaceutical compositions, wherein the anti-PD-1 antibody is administered after (*e.g.*, about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, or 14 days after) the administration of the anti-CTLA-4 antibody.

[00376] In certain embodiments, the therapeutic combination comprises an anti-CTLA-4 antibody described herein administered (*e.g.*, intravenously) about every six weeks, and an anti-PD-1 antibody described herein administered (*e.g.*, intravenously) about every two weeks. In certain embodiments, the therapeutic combination comprises an anti-CTLA-4 antibody described herein administered (*e.g.*, intravenously) every six weeks, and an anti-PD-1 antibody described herein administered (*e.g.*, intravenously) every two weeks. In certain embodiments, the therapeutic combination comprises an anti-CTLA-4 antibody described herein administered (*e.g.*, intravenously) about every six weeks, and an anti-PD-1 antibody described herein administered (*e.g.*, intravenously) about every three weeks. In certain embodiments, the therapeutic combination comprises an anti-CTLA-4 antibody described herein administered (*e.g.*, intravenously) every six weeks, and an anti-PD-1 antibody described herein administered

(*e.g.*, intravenously) every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered on the same day as the anti-PD-1 antibody. In certain embodiments, each administration of the anti-CTLA-4 antibody is conducted on the same day as the anti-PD-1 antibody. In certain embodiments, the anti-CTLA-4 antibody is administered within 30 minutes or 1 hour after the completion of administration of the anti-PD-1 antibody.

[00377] In certain embodiments, the anti-CTLA-4 antibody is administered at 0.01 mg/kg or about 0.01 mg/kg and the anti-PD-1 antibody is administered at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered at 0.03 mg/kg or about 0.03 mg/kg and the anti-PD-1 antibody is administered at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered at 0.1 mg/kg or about 0.1 mg/kg and the anti-PD-1 antibody is administered at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered at 0.3 mg/kg or about 0.3 mg/kg and the anti-PD-1 antibody is administered at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered at 1 mg/kg or about 1 mg/kg and the anti-PD-1 antibody is administered at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered at 3 mg/kg or about 3 mg/kg and the anti-PD-1 antibody is administered at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered at 6 mg/kg or about 6 mg/kg and the anti-PD-1 antibody is administered at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks. In certain embodiments, the anti-CTLA-4 antibody

is administered at 10 mg/kg or about 10 mg/kg and the anti-PD-1 antibody is administered at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks. The anti-CTLA-4 antibody and the anti-PD-1 antibody can be administered simultaneously or sequentially by the same or different routes of administration (*e.g.*, as described herein). In certain embodiments, the anti-CTLA-4 antibody and the anti-PD-1 antibody are administered simultaneously via intravenous injection (*e.g.*, intravenous infusion). In certain embodiments, the anti-CTLA-4 antibody and the anti-PD-1 antibody are both administered sequentially via intravenous injection (*e.g.*, intravenous infusion). In certain embodiments, the anti-CTLA-4 antibody is administered intravenously at 0.1 mg/kg and the anti-PD-1 antibody is administered intravenously at 3 mg/kg, optionally every one, two or three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered every three weeks and the anti-PD-1 antibody is administered every two weeks.

[00378] In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 0.3 mg/kg or 1 mg/kg, and the anti-PD-1 antibody is administered (e.g., intravenously) at about 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 0.3 mg/kg and the anti-PD-1 antibody is administered (e.g., intravenously) at about 1 mg/kg. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 1 mg/kg and the anti-PD-1 antibody is administered (e.g., intravenously) at about 1 mg/kg. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 1 mg/kg and the anti-PD-1 antibody is administered (e.g., intravenously) at about 3 mg/kg. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 1 mg/kg and the anti-PD-1 antibody is administered (e.g., intravenously) at about 6 mg/kg. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 0.3 mg/kg or 1 mg/kg, and the anti-PD-1 antibody is administered (e.g., intravenously) at 1 mg/kg or 3 mg/kg. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 0.3 mg/kg and the anti-PD-1 antibody is administered (e.g., intravenously) at 1 mg/kg. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 1 mg/kg and the anti-PD-1 antibody is administered (e.g., intravenously) at 1 mg/kg. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 1 mg/kg and the anti-PD-1 antibody is administered (e.g., intravenously) at 3 mg/kg. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 1 mg/kg and the anti-PD-1 antibody is administered (e.g., intravenously) at 6 mg/kg. In certain

embodiments, the anti-CTLA-4 antibody is administered on the same day as the anti-PD-1 antibody. In certain embodiments, each administration of the anti-CTLA-4 antibody is conducted on the same day as the anti-PD-1 antibody. In certain embodiments, the anti-CTLA-4 antibody is administered within 30 minutes or 1 hour after the completion of administration of the anti-PD-1 antibody.

[00379] In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), and the anti-PD-1 antibody, e.g., AGEN2034 (IgG_4 S228P), are each administered at the dosage and at the frequency shown in a single row of Table 13 below. In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), and the anti-PD-1 antibody, e.g., AGEN2034 (IgG_4 S228P), are each administered at about the dosage and at the frequency shown in a single row of Table 13 below. In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), and the anti-PD-1 antibody, e.g., AGEN2034 (IgG_4 S228P), are each administered at the dosage and at about the frequency shown in a single row of Table 13 below. In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), and the anti-PD-1 antibody, e.g., AGEN2034 (IgG_4 S228P), are each administered at about the dosage and at about the frequency shown in a single row of Table 13 below. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 0.3 mg/kg or 1 mg/kg about every six weeks, and the anti-PD-1 antibody is administered (e.g., intravenously) at about 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg about every two weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 0.3 mg/kg or 1 mg/kg about every six weeks, and the anti-PD-1 antibody is administered (e.g., intravenously) at about 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg about every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 0.3 mg/kg about every six weeks and the anti-PD-1 antibody is administered (e.g., intravenously) at about 1 mg/kg about every two weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 1 mg/kg about every six weeks and the anti-PD-1 antibody is administered (e.g., intravenously) at about 1 mg/kg about every two weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 1 mg/kg about every six weeks and the anti-PD-1 antibody is administered (e.g., intravenously) at about 3 mg/kg about every two weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 1 mg/kg about every six weeks and the anti-PD-1 antibody is administered (e.g., intravenously) at about 6 mg/kg about every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 0.3 mg/kg or 1 mg/kg every six weeks, and the anti-PD-1 antibody is administered (e.g.,

intravenously) at 1 mg/kg or 3 mg/kg every two weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 0.3 mg/kg every six weeks and the anti-PD-1 antibody is administered (e.g., intravenously) at 1 mg/kg every two weeks. In certain embodiments, the anti-CTLA-4 is administered (e.g., intravenously) at antibody 1 mg/kg every six weeks and the anti-PD-1 antibody is administered (e.g., intravenously) at 1 mg/kg about every two weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 1 mg/kg every six weeks and the anti-PD-1 antibody is administered (e.g., intravenously) at 3 mg/kg every two weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 1 mg/kg about every six weeks and the anti-PD-1 antibody is administered (e.g., intravenously) at 6 mg/kg about every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) on the same day as the anti-PD-1 antibody. In certain embodiments, each administration of the anti-CTLA-4 antibody is conducted on the same day as the anti-PD-1 antibody. In certain embodiments, the anti-CTLA-4 antibody is administered within 30 minutes or 1 hour after the completion of administration of the anti-PD-1 antibody. In certain embodiments, the anti-CTLA-4 antibody is administered on the same day as the anti-PD-1 antibody. In certain embodiments, each administration of the anti-CTLA-4 antibody is conducted on the same day as the anti-PD-1 antibody. In certain embodiments, the anti-CTLA-4 antibody is administered within 30 minutes or 1 hour after the completion of administration of the anti-PD-1 antibody. In certain embodiments, the therapeutic combination is administered to a subject for at least 3, 6, 9, 12, 18, or 24 months. In certain embodiments, the therapeutic combination is administered to a subject for up to 3, 6, 9, 12, 18, or 24 months.

Table 13. Dosage and frequency of administration of an anti-CTLA-4 antibody and an anti-PD-1 antibody in combination.

Anti-CTLA-4 antibody		**Anti-PD-1 antibody**	
Dosage (mg/kg)	**Frequency**	**Dosage (mg/kg)**	**Frequency**
0.3	every 4 weeks	1	every 2 weeks
0.3	every 4 weeks	1	every 3 weeks
0.3	every 4 weeks	3	every 2 weeks
0.3	every 4 weeks	3	every 3 weeks
0.3	every 4 weeks	6	every 2 weeks
0.3	every 4 weeks	6	every 3 weeks
0.3	every 4 weeks	10	every 2 weeks

Anti-CTLA-4 antibody		Anti-PD-1 antibody	
Dosage (mg/kg)	**Frequency**	**Dosage (mg/kg)**	**Frequency**
0.3	every 4 weeks	10	every 3 weeks
0.3	every 6 weeks	1	every 2 weeks
0.3	every 6 weeks	1	every 3 weeks
0.3	every 6 weeks	3	every 2 weeks
0.3	every 6 weeks	3	every 3 weeks
0.3	every 6 weeks	6	every 2 weeks
0.3	every 6 weeks	6	every 3 weeks
0.3	every 6 weeks	10	every 2 weeks
0.3	every 6 weeks	10	every 3 weeks
0.3	every 12 weeks	1	every 2 weeks
0.3	every 12 weeks	1	every 3 weeks
0.3	every 12 weeks	3	every 2 weeks
0.3	every 12 weeks	3	every 3 weeks
0.3	every 12 weeks	6	every 2 weeks
0.3	every 12 weeks	6	every 3 weeks
0.3	every 12 weeks	10	every 2 weeks
0.3	every 12 weeks	10	every 3 weeks
1	every 4 weeks	1	every 2 weeks
1	every 4 weeks	1	every 3 weeks
1	every 4 weeks	3	every 2 weeks
1	every 4 weeks	3	every 3 weeks
1	every 4 weeks	6	every 2 weeks
1	every 4 weeks	6	every 3 weeks
1	every 4 weeks	10	every 2 weeks
1	every 4 weeks	10	every 3 weeks
1	every 6 weeks	1	every 2 weeks
1	every 6 weeks	1	every 3 weeks
1	every 6 weeks	3	every 2 weeks
1	every 6 weeks	3	every 3 weeks
1	every 6 weeks	6	every 2 weeks

Anti-CTLA-4 antibody		Anti-PD-1 antibody	
Dosage (mg/kg)	**Frequency**	**Dosage (mg/kg)**	**Frequency**
1	every 6 weeks	6	every 3 weeks
1	every 6 weeks	10	every 2 weeks
1	every 6 weeks	10	every 3 weeks
1	every 12 weeks	1	every 2 weeks
1	every 12 weeks	1	every 3 weeks
1	every 12 weeks	3	every 2 weeks
1	every 12 weeks	3	every 3 weeks
1	every 12 weeks	6	every 2 weeks
1	every 12 weeks	6	every 3 weeks
1	every 12 weeks	10	every 2 weeks
1	every 12 weeks	10	every 3 weeks
3	every 4 weeks	1	every 2 weeks
3	every 4 weeks	1	every 3 weeks
3	every 4 weeks	3	every 2 weeks
3	every 4 weeks	3	every 3 weeks
3	every 4 weeks	6	every 2 weeks
3	every 4 weeks	6	every 3 weeks
3	every 4 weeks	10	every 2 weeks
3	every 4 weeks	10	every 3 weeks
3	every 6 weeks	1	every 2 weeks
3	every 6 weeks	1	every 3 weeks
3	every 6 weeks	3	every 2 weeks
3	every 6 weeks	3	every 3 weeks
3	every 6 weeks	6	every 2 weeks
3	every 6 weeks	6	every 3 weeks
3	every 6 weeks	10	every 2 weeks
3	every 6 weeks	10	every 3 weeks
3	every 12 weeks	1	every 2 weeks
3	every 12 weeks	1	every 3 weeks
3	every 12 weeks	3	every 2 weeks

Anti-CTLA-4 antibody		Anti-PD-1 antibody	
Dosage (mg/kg)	**Frequency**	**Dosage (mg/kg)**	**Frequency**
3	every 12 weeks	3	every 3 weeks
3	every 12 weeks	6	every 2 weeks
3	every 12 weeks	6	every 3 weeks
3	every 12 weeks	10	every 2 weeks
3	every 12 weeks	10	every 3 weeks

[00380] In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), is administered, optionally as a monotherapy, at the dosage and at the frequency shown in a single row of Table 13. In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), is administered, optionally as a monotherapy, at about the dosage and at the frequency shown in a single row of Table 13. In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), is administered, optionally as a monotherapy, at the dosage and at about the frequency shown in a single row of Table 13. In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), is administered, optionally as a monotherapy, at about the dosage and at about the frequency shown in a single row of Table 13. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously), optionally as a monotherapy, at about 0.3 mg/kg, 1 mg/kg, or 3 mg/kg about every four weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously), optionally as a monotherapy, at about 0.3 mg/kg, 1 mg/kg, or 3 mg/kg about every six weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously), optionally as a monotherapy, at about 0.3 mg/kg, 1 mg/kg, or 3 mg/kg about every twelve weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously), optionally as a monotherapy, at 0.3 mg/kg, 1 mg/kg, or 3 mg/kg every four weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously), optionally as a monotherapy, at 0.3 mg/kg, 1 mg/kg, or 3 mg/kg every six weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously), optionally as a monotherapy, at 0.3 mg/kg, 1 mg/kg, or 3 mg/kg every twelve weeks. In certain embodiments, the anti-CTLA-4 antibody is administered to a subject for at least 3, 6, 9, 12, 18, or 24 months. In certain embodiments, the anti-CTLA-4 antibody is administered to a subject for up to 3, 6, 9, 12, 18, or 24 months.

[00381] In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), is administered at the dosage and at the frequency shown in a single row of Table 13, in

combination with pembrolizumab administered at 200 mg every three weeks. In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), is administered at about the dosage and at the frequency shown in a single row of Table 13, in combination with pembrolizumab administered at about 200 mg every three weeks. In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), is administered at the dosage and at about the frequency shown in a single row of Table 13, in combination with pembrolizumab administered at 200 mg about every three weeks. In certain embodiments, the anti-CTLA-4 antibody, e.g., AGEN1884 (IgG_1), is administered at about the dosage and at about the frequency shown in a single row of Table 13, in combination with pembrolizumab administered at about 200 mg about every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 0.3 mg/kg, 1 mg/kg, or 3 mg/kg about every four weeks, in combination with pembrolizumab administered (e.g., intravenously) at about 200 mg about every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 0.3 mg/kg, 1 mg/kg, or 3 mg/kg about every six weeks, in combination with pembrolizumab administered (e.g., intravenously) at about 200 mg about every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at about 0.3 mg/kg, 1 mg/kg, or 3 mg/kg about every twelve weeks, in combination with pembrolizumab administered (e.g., intravenously) at about 200 mg about every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 0.3 mg/kg, 1 mg/kg, or 3 mg/kg every four weeks, in combination with pembrolizumab administered (e.g., intravenously) at 200 mg every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 0.3 mg/kg, 1 mg/kg, or 3 mg/kg every six weeks, in combination with pembrolizumab administered (e.g., intravenously) at 200 mg every three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (e.g., intravenously) at 0.3 mg/kg, 1 mg/kg, or 3 mg/kg every twelve weeks, in combination with pembrolizumab administered (e.g., intravenously) at 200 mg every three weeks. In certain embodiments, the anti-CTLA-4 antibody and pembrolizumab are administered to a subject for at least 3, 6, 9, 12, 18, or 24 months. In certain embodiments, the anti-CTLA-4 antibody and pembrolizumab are administered to a subject for up to 3, 6, 9, 12, 18, or 24 months.

[00382] In certain embodiments, the anti-PD-1 antibody, e.g., AGEN2034 (IgG_4 S228P), is administered, optionally as a monotherapy, at the dosage and at the frequency shown in a single row of Table 13. In certain embodiments, the anti-PD-1 antibody, e.g., AGEN2034 (IgG_4 S228P), is administered, optionally as a monotherapy, at about the dosage and at the frequency

shown in a single row of Table 13. In certain embodiments, the anti-PD-1 antibody, e.g., AGEN2034 (IgG_4 S228P), is administered, optionally as a monotherapy, at the dosage and at about the frequency shown in a single row of Table 13. In certain embodiments, the anti-PD-1 antibody, e.g., AGEN2034 (IgG_4 S228P), is administered, optionally as a monotherapy, at about the dosage and at about the frequency shown in a single row of Table 13. In certain embodiments, the anti-PD-1 antibody is administered (e.g., intravenously), optionally as a monotherapy, at about 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg about every two weeks. In certain embodiments, the anti-PD-1 antibody is administered (e.g., intravenously), optionally as a monotherapy, at about 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg about every three weeks. In certain embodiments, the anti-PD-1 antibody is administered (e.g., intravenously), optionally as a monotherapy, at 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg every two weeks. In certain embodiments, the anti-PD-1 antibody is administered (e.g., intravenously), optionally as a monotherapy at 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg every three weeks. In certain embodiments, the anti-PD-1 antibody is administered to a subject for at least 3, 6, 9, 12, 18, or 24 months. In certain embodiments, the anti-PD-1 antibody is administered to a subject for up to 3, 6, 9, 12, 18, or 24 months.

[00383] In certain embodiments, the instant disclosure provides a method of treating a subject having angiosarcoma, the method comprising administering to the subject (*e.g.*, intravenously, intratumorally, or subcutaneously) an effective amount of a therapeutic combination and/or multispecific antibody as described herein. In certain embodiments, the subject is administered a therapeutic combination comprising an anti-CTLA-4 antibody described herein and an anti-PD-1 antibody described herein. In certain embodiments, the effective amount of the anti-CTLA-4 antibody in this therapeutic combination is lower than the effective amount of the anti-CTLA-4 antibody when administered alone. In certain embodiments, the anti-CTLA-4 antibody is administered (*e.g.*, intravenously, intratumorally, or subcutaneously) at 0.1 mg/kg and the anti-PD-1 antibody is administered (*e.g.*, intravenously, intratumorally, or subcutaneously) at 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg, about 0.1 mg/kg, about 0.3 mg/kg, about 1 mg/kg, about 3 mg/kg, about 6 mg/kg, or about 10 mg/kg, optionally every one, two or three weeks. In certain embodiments, the anti-CTLA-4 antibody is administered (*e.g.*, intravenously) at 0.1 mg/kg and the anti-PD-1 antibody is administered (*e.g.*, intravenously) at 3 mg/kg, optionally every one, two or three weeks.

6.5 Antibody Production

[00384] Antibodies, including monospecific or multispecific (*e.g.*, bispecific) antibodies, that specifically bind to CTLA-4 and/or PD-1, (*e.g.*, human CTLA-4 and/or PD-1) can be produced by any method known in the art for the synthesis of antibodies, for example, by chemical synthesis or by recombinant expression techniques. The methods described herein employ, unless otherwise indicated, conventional techniques in molecular biology, microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described, for example, in the references cited herein and are fully explained in the literature. *See*, *e.g.,* Maniatis T *et al.*, (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (1989), Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel FM *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons (1987 and annual updates); Current Protocols in Immunology, John Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein (ed.) (1991) Oligonucleotides and Analogues: A Practical Approach, IRL Press; Birren B *et al.*, (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

[00385] In a specific embodiment, an antibody described herein is an antibody (*e.g.*, a recombinant antibody) prepared, expressed, created or isolated by any means that involves creation, *e.g.*, via synthesis, genetic engineering of DNA sequences. In certain embodiments, such antibody comprises sequences (*e.g.*, DNA sequences or amino acid sequences) that do not naturally exist within the antibody germline repertoire of an animal or mammal (*e.g.*, human) *in vivo*.

[00386] In a certain aspect, provided herein is a method of making an antibody which specifically binds to CTLA-4 and/or PD-1 (including, *e.g.*, monospecific or multispecific antibodies that bind to human CTLA-4 and/or human PD-1) comprising culturing a cell or host cell described herein. In a certain aspect, provided herein is a method of making an antibody which specifically binds to CTLA-4 and/or PD-1 (including, *e.g.*, monospecific or multispecific antibodies that bind to human CTLA-4 and/or PD-1) comprising expressing (*e.g.*, recombinantly expressing) the antibody using a cell or host cell described herein (*e.g.*, a cell or a host cell comprising polynucleotides encoding an antibody described herein). In a particular

embodiment, the cell is an isolated cell. In a particular embodiment, the exogenous polynucleotides have been introduced into the cell. In a particular embodiment, the method further comprises the step of purifying the antibody obtained from the cell or host cell.

[00387] Methods for producing polyclonal antibodies are known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM *et al.,* eds., John Wiley and Sons, New York).

[00388] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow E & Lane D, Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling GJ *et al.,* in: Monoclonal Antibodies and T-Cell Hybridomas 563 681 (Elsevier, N.Y., 1981). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. For example, monoclonal antibodies can be produced recombinantly from host cells exogenously expressing an antibody described herein.

[00389] In specific embodiments, a "monoclonal antibody," as used herein, is an antibody produced by a single cell (*e.g.*, hybridoma or host cell producing a recombinant antibody), wherein the antibody specifically binds to CTLA-4 and/or PD-1 (including, *e.g.*, monospecific or multispecific antibodies that bind to human CTLA-4 and/or PD-1) as determined, *e.g.,* by ELISA or other antigen-binding or competitive binding assay known in the art or in the Examples provided herein. In particular embodiments, a monoclonal antibody can be a chimeric antibody or a humanized antibody. In certain embodiments, a monoclonal antibody is a monovalent antibody or multivalent (*e.g.*, bivalent) antibody. In certain embodiments, a monoclonal antibody can be a Fab fragment or a $F(ab')_2$ fragment. Monoclonal antibodies described herein can, for example, be made by the hybridoma method as described in Kohler G & Milstein C (1975) Nature 256: 495 or can, *e.g.*, be isolated from phage libraries using the techniques as described herein, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies expressed thereby are well known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM *et al., supra*).

[00390] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. For example, in the hybridoma method, a mouse or other appropriate host animal, such as a sheep, goat, rabbit, rat, hamster or macaque monkey, is immunized to elicit lymphocytes that produce or are capable of producing

antibodies that will specifically bind to the protein (*e.g.*, CTLA-4 or PD-1 (*e.g.*, human CTLA-4 or PD-1)) used for immunization. Alternatively, lymphocytes can be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding JW (Ed), Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986)). Additionally, a RIMMS (repetitive immunization multiple sites) technique can be used to immunize an animal (Kilpatrick KE *et al.,* (1997) Hybridoma 16:381-9, incorporated by reference in its entirety).

[00391] In some embodiments, mice (or other animals, such as rats, monkeys, donkeys, pigs, sheep, hamster, or dogs) can be immunized with an antigen (*e.g.*, CTLA-4 or PD-1 (*e.g.*, human CTLA-4 or PD-1)) and once an immune response is detected, *e.g.,* antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well-known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the American Type Culture Collection (ATCC®) (Manassas, VA), to form hybridomas. Hybridomas are selected and cloned by limited dilution. In certain embodiments, lymph nodes of the immunized mice are harvested and fused with NS0 myeloma cells.

[00392] The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that optionally contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[00393] Specific embodiments employ myeloma cells that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these myeloma cell lines are murine myeloma lines, such as NS0 cell line or those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, CA, USA, and SP-2 or X63-Ag8.653 cells available from the American Type Culture Collection, Rockville, MD, USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor D (1984) J Immunol 133: 3001-5; Brodeur *et al.,* Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

[00394] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against CTLA-4 and/or PD-1 (*e.g.*, human CTLA-4 and/or PD-

1). The binding specificity of monoclonal antibodies produced by hybridoma cells is determined by methods known in the art, for example, immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

[00395] After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding JW (Ed), Monoclonal Antibodies: Principles and Practice, *supra*). Suitable culture media for this purpose include, for example, D-MEM or RPMI 1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

[00396] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

[00397] Antibodies described herein can be generated by any technique known to those of skill in the art. For example, Fab and $F(ab')_2$ fragments described herein can be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce $F(ab')_2$ fragments). A Fab fragment corresponds to one of the two identical arms of a tetrameric antibody molecule and contains the complete light chain paired with the VH and CH1 domains of the heavy chain. A $F(ab')_2$ fragment contains the two antigen-binding arms of a tetrameric antibody molecule linked by disulfide bonds in the hinge region.

[00398] Further, the antibodies or antigen-binding fragments described herein can also be generated using various phage display methods known in the art. In phage display methods, proteins are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding heavy and light chain variable regions are amplified from animal cDNA libraries (*e.g.,* human or murine cDNA libraries of affected tissues). The DNA encoding the heavy and light chain variable regions are recombined together with a scFv linker by PCR and cloned into a phagemid vector. The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13, and the heavy and light chain variable regions are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antibody that binds to a particular antigen can be selected or identified with antigen, *e.g.,* using labeled antigen or antigen bound or captured to a solid surface or bead.

Examples of phage display methods that can be used to make the antibodies described herein include those disclosed in Brinkman U *et al.,* (1995) J Immunol Methods 182: 41-50; Ames RS *et al.,* (1995) J Immunol Methods 184: 177-186; Kettleborough CA *et al.,* (1994) Eur J Immunol 24: 952-958; Persic L *et al.,* (1997) Gene 187: 9-18; Burton DR & Barbas CF (1994) Advan Immunol 57: 191-280; PCT Application No. PCT/GB91/001134; International Publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO 97/13844; and U.S. Patent Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743, and 5,969,108.

[00399] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate antibodies, including human antibodies, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.,* as described below. Techniques to recombinantly produce antibodies such as Fab, Fab' and $F(ab')_2$ fragments can also be employed using methods known in the art such as those disclosed in PCT publication No. WO 92/22324; Mullinax RL *et al.,* (1992) BioTechniques 12(6): 864-9; Sawai H *et al.,* (1995) Am J Reprod Immunol 34: 26-34; and Better M *et al.,* (1988) Science 240: 1041-1043.

[00400] In one aspect, to generate antibodies, PCR primers including heavy or light chain variable region nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the heavy or light chain variable region sequences from a template, *e.g.*, scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified heavy chain variable regions can be cloned into vectors expressing a heavy chain constant region, and the PCR amplified light chain variable regions can be cloned into vectors expressing a light chain constant region, *e.g.,* human kappa or lambda constant regions. The heavy and light chain variable regions can also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express antibodies, *e.g.,* IgG, using techniques known to those of skill in the art.

[00401] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules. For example, a chimeric antibody can contain a variable region of a mouse or rat monoclonal antibody fused to a constant region of a human antibody. Methods for producing chimeric antibodies are known in the art. *See, e.g.,* Morrison SL (1985) Science 229: 1202-7; Oi VT & Morrison SL (1986) BioTechniques 4: 214-221; Gillies SD *et al.,* (1989) J Immunol Methods 125: 191-202; and U.S. Patent Nos.

5,807,715, 4,816,567, 4,816,397, and 6,331,415.

[00402] A humanized antibody is capable of binding to a predetermined antigen and which comprises a framework region having substantially the amino acid sequence of a human immunoglobulin and CDRs having substantially the amino acid sequence of a non-human immunoglobulin (*e.g.*, a murine immunoglobulin). In particular embodiments, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The antibody also can include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. A humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG_1, IgG_2, IgG_3 and IgG_4. Humanized antibodies can be produced using a variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239400; International Publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592106 and EP 519596; Padlan EA (1991) Mol Immunol 28(4/5): 489-498; Studnicka GM *et al.,* (1994) Prot Engineering 7(6): 805-814; and Roguska MA *et al.,* (1994) PNAS 91: 969-973), chain shuffling (U.S. Patent No. 5,565,332), and techniques disclosed in, *e.g.,* U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, International Publication No. WO 93/17105; Tan P *et al.,* (2002) J Immunol 169: 1119-25; Caldas C *et al.,* (2000) Protein Eng. 13(5): 353-60; Morea V *et al.,* (2000) Methods 20(3): 267-79; Baca M *et al.,* (1997) J Biol Chem 272(16): 10678-84; Roguska MA *et al.,* (1996) Protein Eng 9(10): 895 904; Couto JR *et al.,* (1995) Cancer Res. 55 (23 Supp): 5973s-5977s; Couto JR *et al.,* (1995) Cancer Res 55(8): 1717-22; Sandhu JS (1994) Gene 150(2): 409-10 and Pedersen JT *et al.,* (1994) J Mol Biol 235(3): 959-73. See also U.S. Application Publication No. US 2005/0042664 A1 (Feb. 24, 2005), which is incorporated by reference herein in its entirety.

[00403] Single domain antibodies, for example, antibodies lacking the light chains, can be produced by methods well known in the art. See Riechmann L & Muyldermans S (1999) J Immunol 231: 25-38; Nuttall SD *et al.,* (2000) Curr Pharm Biotechnol 1(3): 253-263; Muyldermans S, (2001) J Biotechnol 74(4): 277-302; U.S. Patent No. 6,005,079; and International Publication Nos. WO 94/04678, WO 94/25591 and WO 01/44301.

[00404] Further, antibodies that specifically bind to a CTLA-4 and/or PD-1 antigen can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" an antigen using techniques well known to those skilled in the art. (See, *e.g.,* Greenspan NS & Bona CA (1989) FASEB J 7(5): 437-444; and Nissinoff A (1991) J Immunol 147(8): 2429-2438).

[00405] In particular embodiments, an antibody or antigen-binding fragment thereof described herein, which binds to the same epitope of CTLA-4 and/or PD-1 (*e.g.*, human CTLA-

4 and/or PD-1) as an anti-CTLA-4 or anti-PD-1 antibody or antigen-binding fragment thereof described herein, is a human antibody. In particular embodiments, an antibody described herein, which competitively blocks (*e.g.*, in a dose-dependent manner) any one of the antibodies described herein, from binding to CTLA-4 or PD-1 (*e.g.*, human CTLA-4 or PD-1), is a human antibody. Human antibodies can be produced using any method known in the art. For example, transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes, can be used. In particular, the human heavy and light chain immunoglobulin gene complexes can be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region can be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes can be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J_H region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.,* all or a portion of an antigen (*e.g.*, CTLA-4 or PD-1). Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg N & Huszar D (1995) Int Rev Immunol 13:65-93. For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, *see*, *e.g.,* International Publication Nos. WO 98/24893, WO 96/34096 and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318 and 5,939,598. Examples of mice capable of producing human antibodies include the Xenomouse™ (Abgenix, Inc.; U.S. Patent Nos. 6,075,181 and 6,150,184), the HuAb-Mouse™ (Mederex, Inc./Gen Pharm; U.S. Patent Nos. 5,545,806 and 5,569, 825), the Trans Chromo Mouse™ (Kirin) and the KM Mouse™ (Medarex/Kirin).

[00406] Human antibodies or antigen-binding fragments which specifically bind to CTLA-4 and/or PD-1 (including, *e.g.*, monospecific or multispecific antibodies that bind to human

CTLA-4 and/or PD-1) can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. *See* also U.S. Patent Nos. 4,444,887, 4,716,111, and 5,885,793; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741.

[00407] In some embodiments, human antibodies can be produced using mouse–human hybridomas. For example, human peripheral blood lymphocytes transformed with Epstein-Barr virus (EBV) can be fused with mouse myeloma cells to produce mouse–human hybridomas secreting human monoclonal antibodies, and these mouse–human hybridomas can be screened to determine ones which secrete human monoclonal antibodies that specifically bind to a target antigen (*e.g.*, CTLA-4 or PD-1, *e.g.*, human CTLA-4 or PD-1). Such methods are known and are described in the art, see, *e.g.*, Shinmoto H *et al.,* (2004) Cytotechnology 46: 19-23; Naganawa Y *et al.,* (2005) Human Antibodies 14: 27-31.

[00408] Bispecific, bivalent antibodies, and methods of making them, are described, for instance in U.S. Pat. Nos. 5,731,168, 5,807,706, 5,821,333, and U.S. Appl. Publ. Nos. 2003/020734 and 2002/0155537; each of which is herein incorporated by reference in its entirety. Bispecific tetravalent antibodies, and methods of making them are described, for instance, in Int. Appl. Publ. Nos. WO02/096948 and WO00/44788, the disclosures of both of which are herein incorporated by reference in its entirety. See generally, Int. Appl. Publ. Nos. WO93/17715, WO92/08802, WO91/00360, and WO92/05793; Tutt *et al.*, J. Immunol. 147:60-69 (1991); U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; and 5,601,819; and Kostelny *et al.*, J. Immunol. 148:1547-1553 (1992); each of which is herein incorporated by reference in its entirety.

[00409] One method for generating bispecific antibodies has been termed the "knobs-into-holes" strategy (see, *e.g.,* Intl. Publ. WO2006/028936). The mispairing of Ig heavy chains is reduced in this technology by mutating selected amino acids forming the interface of the CH3 domains in IgG. At positions within the CH3 domain at which the two heavy chains interact directly, an amino acid with a small side chain (hole) is introduced into the sequence of one heavy chain and an amino acid with a large side chain (knob) into the counterpart interacting residue location on the other heavy chain. In some embodiments, the compositions described herein have immunoglobulin chains in which the CH3 domains have been modified by mutating selected amino acids that interact at the interface between two polypeptides to form a bispecific antibody. The bispecific antibodies can be composed of immunoglobulin chains of the same subclass (*e.g.,*IgG1 or IgG3) or different subclasses (*e.g.,* IgG1 and IgG3, or IgG3

and IgG4)

[00410] In one embodiment, a bispecific antibody that binds to CTLA-4 and/or PD-1 comprises a T366W mutation in the "knobs chain" and T366S, L368A, Y407V mutations in the "hole chain," and optionally an additional interchain disulfide bridge between the CH3 domains by, *e.g.,* introducing a Y349C mutation into the "knobs chain" and a E356C mutation or a S354C mutation into the "hole chain;" R409D, K370E mutations in the "knobs chain" and D399K, E357K mutations in the "hole chain;" R409D, K370E mutations in the "knobs chain" and D399K, E357K mutations in the "hole chain;" a T366W mutation in the "knobs chain" and T366S, L368A, Y407V mutations in the "hole chain;" R409D, K370E mutations in the "knobs chain" and D399K, E357K mutations in the "hole chain;" Y349C, T366W mutations in one of the chains and E356C, T366S, L368A, Y407V mutations in the counterpart chain; Y349C, T366W mutations in one chain and S354C, T366S, L368A, Y407V mutations in the counterpart chain; Y349C, T366W mutations in one chain and S354C, T366S, L368A, Y407V mutations in the counterpart chain; and Y349C, T366W mutations in one chain and S354C, T366S, L368A, Y407V mutations in the counterpart chain, numbering according to the EU numbering system.

[00411] Bispecific antibodies that bind to CTLA-4 and/or PD-1 can, in some instances contain, IgG4 and IgG1, IgG4 and IgG2, IgG4 and IgG2, IgG4 and IgG3, or IgG1 and IgG3 chain heterodimers. Such heterodimeric heavy chain antibodies, can routinely be engineered by, for example, modifying selected amino acids forming the interface of the CH3 domains in human IgG4 and the IgG1 or IgG3 so as to favor heterodimeric heavy chain formation.

In particular embodiments, a multispecific (*e.g.*, bispecific) antibody can be a chimeric antibody or a humanized antibody. In certain embodiments, a multispecific (*e.g.*, bispecific) antibody can be a $F(ab')_2$ fragment. A $F(ab')_2$ fragment contains the two antigen-binding arms of a tetrameric antibody molecule linked by disulfide bonds in the hinge region.

[00412] Multispecific (*e.g.*, bispecific) antibodies described herein can be generated by any technique known to those of skill in the art. For example, $F(ab')_2$ fragments described herein can be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as pepsin.

6.6 Kits

[00413] Also provided are kits comprising one or more antibodies described herein, or therapeutic combination, pharmaceutical composition, or conjugates thereof. In a specific embodiment, provided herein is a pharmaceutical pack or kit comprising one or more

containers filled with one or more of the ingredients of the pharmaceutical compositions described herein, such as one or more antibodies provided herein. In some embodiments, the kits contain one or more pharmaceutical compositions described herein and any prophylactic or therapeutic agent, such as those described herein. In certain embodiments, the kits may contain a T cell mitogen, such as, *e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00414] In certain embodiments, the kit comprises a container filled with a pharmaceutical composition comprising an anti-CTLA-4/PD-1 antibody described herein. In certain embodiments, the kit comprises a container filled with a pharmaceutical composition comprising an effective amount of an anti-CTLA-4/PD-1 antibody described herein.

[00415] In certain embodiments, the kit comprises a first container filled with a pharmaceutical composition comprising an anti-CTLA-4 antibody and a second container filled with a pharmaceutical composition comprising an anti-PD-1 antibody. The combination of the anti-CTLA-4 antibody and anti-PD-1 antibody can be any combination of an anti-CTLA-4 antibody described herein and an anti-PD-1 antibody described herein. In certain embodiments, the kit comprises a first container filled with a pharmaceutical composition comprising a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), and a second container filled with a pharmaceutical composition comprising a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antibody and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antibody comprise the amino acid sequences listed in a single row of Table 11. In certain embodiments, the kit comprises a first container filled with a pharmaceutical composition comprising a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), and a second container filled with a pharmaceutical composition comprising a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antibody and CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antibody respectively comprise the amino acid sequences set forth in SEQ ID NOs: 20, 22, 24, 27, 30, 36, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 76, 80, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 76, 80, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 76, 80,

83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 76, 80, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 76, 80, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 76, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 76, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 76, 81, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 76, 81, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 76, 82, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 76, 82, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 76, 82, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 76, 82, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 77, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 77, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 77, 81, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 77, 81, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 78, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 78, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 29, 33, 38, 75, 78, 81, 83, 84, and 85; 21, 22, 26, 29, 35, 38, 75, 78, 81, 83, 84, and 85; 20, 22, 24, 27, 30, 36, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 32, 37, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 33, 38, 75, 79, 81, 83, 84, and 85; 21, 22, 24, 27, 30, 36, 75, 79, 81, 83, 84, and 85; 21, 22, 24, 29, 33, 38, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 28, 31, 36, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 34, 36, 75, 79, 81, 83, 84, and 85; 20, 22, 24, 29, 35, 38, 75, 79, 81, 83, 84, and 85; 21, 22, 26, 27, 30, 36, 75, 79, 81, 83, 84, and 85; 21, 22, 26, 29, 32, 37, 75, 79, 81, 83, 84, and 85; 21,

22, 26, 29, 33, 38, 75, 79, 81, 83, 84, and 85; or 21, 22, 26, 29, 35, 38, 75, 79, 81, 83, 84, and 85.

[00416] In certain embodiments, the kit comprises a first container filled with a pharmaceutical composition comprising a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), and a second container filled with a pharmaceutical composition comprising a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain variable region and the light chain variable region of the first antibody and the heavy chain variable region and the light chain variable region of the second antibody comprise the amino acid sequences listed in a single row of Table 12. In certain embodiments, the kit comprises a first container filled with a pharmaceutical composition comprising a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4), and a second container filled with a pharmaceutical composition comprising a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1), wherein the heavy chain variable region and the light chain variable region of the first antibody and the heavy chain variable region and the light chain variable region of the second antibody respectively comprise the amino acid sequences set forth in SEQ ID NOs: 1, 14, 67, and 74; 1, 16, 67, and 74; 1, 17, 67, and 74; 9, 14, 67, and 74; 9, 17, 67, and 74; 10, 15, 67, and 74; 10, 17, 67, and 74; 10, 18, 67, and 74; 10, 19, 67, and 74; 11, 15, 67, and 74; 11, 14, 67, and 74; 11, 16, 67, and 74; 11, 17, 67, and 74; 12, 14, 67, and 74; 12, 16, 67, and 74; 12, 17, 67, and 74; 12, 19, 67, and 74; 13, 15, 67, and 74; 13, 17, 67, and 74; 1, 14, 66, and 74; 1, 16, 66, and 74; 1, 17, 66, and 74; 9, 14, 66, and 74; 9, 17, 66, and 74; 10, 15, 66, and 74; 10, 17, 66, and 74; 10, 18, 66, and 74; 10, 19, 66, and 74; 11, 15, 66, and 74; 11, 14, 66, and 74; 11, 16, 66, and 74; 11, 17, 66, and 74; 12, 14, 66, and 74; 12, 16, 66, and 74; 12, 17, 66, and 74; 12, 19, 66, and 74; 13, 15, 66, and 74; 13, 17, 66, and 74; 1, 14, 68, and 74; 1, 16, 68, and 74; 1, 17, 68, and 74; 9, 14, 68, and 74; 9, 17, 68, and 74; 10, 15, 68, and 74; 10, 17, 68, and 74; 10, 18, 68, and 74; 10, 19, 68, and 74; 11, 15, 68, and 74; 11, 14, 68, and 74; 11, 16, 68, and 74; 11, 17, 68, and 74; 12, 14, 68, and 74; 12, 16, 68, and 74; 12, 17, 68, and 74; 12, 19, 68, and 74; 13, 15, 68, and 74; 13, 17, 68, and 74; 1, 14, 69, and 74; 1, 16, 69, and 74; 1, 17, 69, and 74; 9, 14, 69, and 74; 9, 17, 69, and 74; 10, 15, 69, and 74; 10, 17, 69, and 74; 10, 18, 69, and 74; 10, 19, 69, and 74; 11, 15, 69, and 74; 11, 14, 69, and 74; 11, 16, 69, and 74; 11, 17, 69, and 74; 12, 14, 69, and 74; 12, 16, 69, and 74; 12, 17, 69, and 74; 12, 19, 69, and 74; 13, 15, 69, and 74; 13, 17, 69, and 74; 1, 14, 70, and 74; 1, 16, 70, and 74; 1, 17, 70, and 74; 9, 14, 70, and 74; 9, 17, 70, and 74; 10, 15, 70, and 74; 10, 17, 70, and 74; 10, 18, 70, and 74; 10, 19, 70, and 74; 11, 15, 70, and 74; 11, 14, 70, and 74; 11, 16, 70, and 74; 11, 17, 70, and 74; 12, 14, 70, and 74; 12, 16, 70, and 74; 12, 17, 70, and 74; 12, 19, 70, and 74; 13, 15, 70, and

74; 13, 17, 70, and 74; 1, 14, 71, and 74; 1, 16, 71, and 74; 1, 17, 71, and 74; 9, 14, 71, and 74; 9, 17, 71, and 74; 10, 15, 71, and 74; 10, 17, 71, and 74; 10, 18, 71, and 74; 10, 19, 71, and 74; 11, 15, 71, and 74; 11, 14, 71, and 74; 11, 16, 71, and 74; 11, 17, 71, and 74; 12, 14, 71, and 74; 12, 16, 71, and 74; 12, 17, 71, and 74; 12, 19, 71, and 74; 13, 15, 71, and 74; 13, 17, 71, and 74; 1, 14, 72, and 74; 1, 16, 72, and 74; 1, 17, 72, and 74; 9, 14, 72, and 74; 9, 17, 72, and 74; 10, 15, 72, and 74; 10, 17, 72, and 74; 10, 18, 72, and 74; 10, 19, 72, and 74; 11, 15, 72, and 74; 11, 14, 72, and 74; 11, 16, 72, and 74; 11, 17, 72, and 74; 12, 14, 72, and 74; 12, 16, 72, and 74; 12, 17, 72, and 74; 12, 19, 72, and 74; 13, 15, 72, and 74; 13, 17, 72, and 74; 1, 14, 73, and 74; 1, 16, 73, and 74; 1, 17, 73, and 74; 9, 14, 73, and 74; 9, 17, 73, and 74; 10, 15, 73, and 74; 10, 17, 73, and 74; 10, 18, 73, and 74; 10, 19, 73, and 74; 11, 15, 73, and 74; 11, 14, 73, and 74; 11, 16, 73, and 74; 11, 17, 73, and 74; 12, 14, 73, and 74; 12, 16, 73, and 74; 12, 17, 73, and 74; 12, 19, 73, and 74; 13, 15, 73, and 74; or 13, 17, 73, and 74.

[00417] In certain embodiments, the kit comprises a first container filled with a pharmaceutical composition comprising a first antibody that specifically binds to CTLA-4 (*e.g.*, human CTLA-4) described herein, and a second container filled with a pharmaceutical composition comprising a second antibody that specifically binds to PD-1 (*e.g.*, human PD-1) described herein, wherein a therapeutic combination of the first antibody and the second antibody is in an effective amount. The amount of the anti-CTLA-4 antibody in this kit can be lower than, equal to, or higher than the effective amounts of the anti-CTLA-4 antibody when administered alone, and the amount of the anti-PD-1 antibody in this kit can be lower than, equal to, or higher than the effective amounts of the anti-PD-1 antibody when administered alone. In certain embodiments, the amount of the anti-CTLA-4 antibody in this kit is lower than the effective amount of the anti-CTLA-4 antibody when administered alone. In certain embodiments, the amount of the anti-PD-1 antibody in this kit is lower than the effective amount of the anti-PD-1 antibody when administered alone. In certain embodiments, the amount of the anti-CTLA-4 antibody in this kit is lower than the effective amount of the anti-CTLA-4 antibody when administered alone, and the amount of the anti-PD-1 antibody in this kit is lower than the effective amount of the anti-PD-1 antibody alone.

7. EXAMPLES

[00418] The examples in this Section (*i.e.*, Section 6) are offered by way of illustration, and not by way of limitation.

7.1 Example 1: Combination of anti-CTLA-4 antibody and anti-PD-1 antibody

[00419] This example characterizes the functional activity of combining an anti-CTLA-4

antagonist antibody with an anti-PD-1 antagonist antibody. The full length sequences of the antibodies tested are shown in Table 14.

Table 14. Full length sequences of anti-CTLA-4 antibody and anti-PD-1 antibody.

Antibody	Heavy chain SEQ ID NO	Light chain SEQ ID NO
AGEN1884 (IgG_1)	51	59
AGEN2034 (IgG_4 S228P)	91	93

7.1.1 Dosage titrations of anti-CTLA-4 antibody in combination with anti-PD-1 antibody

[00420] In a series of experiments, the functional activity of the anti-CTLA-4 antibody AGEN1884 (IgG_1) administered at varying concentrations, in combination with a fixed concentration of the anti-PD-1 antibody AGEN2034 (IgG_4 S228P), was tested in human peripheral blood mononuclear cells (PBMCs).

[00421] In a first experiment, human peripheral blood mononuclear cells (PBMCs) were stimulated with a sub-optimal concentration (100 ng/ml) of the Staphylococcal Enterotoxin A (SEA) superantigen (Toxin Technologies, Cat# at101red) in the presence of a dose titration of an anti-CTLA-4 antibody AGEN1884 (IgG_1) or an isotype control antibody (IgG_1) in combination with 10 µg/ml of an anti-PD-1 antibody AGEN2034 (IgG_4 S228P) or an isotype control antibody (IgG_4 S228P) for 5 days at 37°C and 5% CO_2. IL-2 concentrations in the culture supernatant were analyzed by AlphaLISA (Perkin Elmer, Cat# AL221F). PBMCs from two different donors were tested.

[00422] As shown in Figures 1A and 1B, the anti-CTLA-4 antibody AGEN1884 (IgG_1) stimulated IL-2 production in a dose dependent manner. Combination with the anti-PD-1 antibody AGEN2034 (IgG_4 S228P) further enhanced the secretion of IL-2 induced by the anti-CTLA-4 antibody alone.

[00423] In a second experiment, cryopreserved human PBMCs were plated at 10^5 cells/well in medium (RPMI1640 supplemented with Normocin™ (Invivogen #ant-nr) and 10% heat-inactivated FBS (Gibco, Invitrogen Corporation)). Cells were stimulated with a sub-optimal concentration (100 ng/ml) of the SEA superantigen (Toxin Technologies, Cat# at101red) in the presence of a dose range (100 - 0.001 µg/mL) of anti-CTLA-4 antibody AGEN1884 (IgG_1) in combination with a fixed antibody concentration of 20 µg/ml of either (i) anti-PD-1 antibody AGEN2034 (IgG_4 S228P), or (ii) an isotype control antibody (IgG_4 S228P). Cells were then incubated for 5 days at 37°C in 5% CO_2. IL-2 concentrations in the culture supernatant were analyzed by AlphaLISA (Perkin Elmer, Cat# AL221F). PBMCs from two different donors

were tested.

[00424] As shown in Figures 2A and 2B, the combination of AGEN1884 (IgG_1) and AGEN2034 (IgG_4 S228P) enhanced the secretion of IL-2 by stimulated PBMCs relative to AGEN1884 (IgG_1) and isotype control. This effect was observed in PBMCs from both donors.

7.1.2 Functional activity of anti-CTLA-4 antibody and anti-PD-1 antibody at fixed concentrations

[00425] In each of two experiments, the functional activity of fixed concentrations of the anti-CTLA-4 antibody AGEN1884 (IgG_1) and the anti-PD-1 antibody AGEN2034 (IgG_4 S228P) was tested in PBMCs from six different human donors. Five of the six donors were the same between the two experiments (donors 5, 7, 8, 9, and 10). The remaining donors were different between the two experiments (donors 6 and 11, as shown in Figures 3 and 4, respectively).

[00426] In each experiment, cryopreserved human PBMCs from six healthy donors were plated at 10^5 cells/well in medium (RPMI1640 supplemented with Normocin™ (Invivogen #ant-nr) and 10% heat-inactivated FBS (Gibco, Invitrogen Corporation)). PBMCs were stimulated with a sub-optimal concentration (100 ng/ml) of the SEA superantigen (Toxin Technologies, Cat# at101red) in the presence of 10 μg/mL of either (i) anti-CTLA-4 antibody AGEN1884 (IgG_1) or (ii) an isotype control antibody (IgG_1), in combination with 10 μg/ml of either (i) anti-PD-1 antibody AGEN2034 (IgG_4 S228P) or (ii) an isotype control antibody (IgG_4 S228P). Cells were then incubated for 5 days at 37°C in 5% CO_2. Clarified supernatants were collected and stored at -80°C until analysis. IL-2 concentrations in the culture supernatant were analyzed by AlphaLISA (Perkin Elmer, Cat# AL221F).

[00427] As shown in Figures 3 and 4, anti-PD-1 AGEN2034 antibody (IgG_4 S228P) and anti-CTLA-4 antibody AGEN1884 (IgG_1) consistently combined to enhance IL-2 secretion in cultures of activated human PBMCs above levels observed for each of these antibodies alone. This enhancement was observed in PBMCs obtained from seven different human donors.

7.1.3 Anti-CTLA-4 antibody and anti-PD-1 antibody combine to enhance central memory T cell activation and proliferation in a non-human primate

[00428] In this example, cynomolgus monkeys were administered anti-CTLA-4 antibody AGEN1884 (IgG_1) in combination with anti-PD-1 antibody AGEN2034 (IgG_4 S228P) and assessed for change in central memory T cell activation and proliferation three days after treatment.

[00429] Four cynomolgus monkeys were treated with AGEN1884 (IgG_1) in combination with AGEN2034 (IgG_4 S228P). For each monkey, 10 mg/kg of AGEN1884 (IgG_1) was

administered first intravenously (slow bolus) with an unprimed stopcock, immediately followed by 3 mg/kg AGEN2034 (IgG_4 S228P) administered in the same fashion. Following antibody administration, a 3mL saline flush was run through the bolus and stopcock to ensure that the correct and full amount of test material was administered. The dose volume for each animal was based on its most recent body weight measurement. Animals were temporarily restrained for dose administration and were not sedated. The first day of dosing was designated as Day 1. Blood samples (2mL) were collected for PBMC isolation and flow cytometry analysis prior to dosing on Day -14 (3 animals) or Day -7 (1 animal), as well as three days after dosing. Figure 5A shows the gating strategy for defining each of the T cell populations measured – i.e., CD4 naïve T cells (CD3+, CD4+, CD28+, CD95-), CD8 naïve T cells (CD3+, CD8+, CD28+, CD95-), CD4 central memory T cells (CD3+, CD4+, CD28+, CD95+), CD8 central memory T cells (CD3+, CD8+, CD28+, CD95+), CD4 effector memory T cells (CD3+, CD4+, CD28-, CD95+), and CD8 effector memory T cells (CD3+, CD8+, CD28-, CD95+). Shown in Figures 5B and 5C are representative flow cytometry data for Ki67 and ICOS expression in CD4+ and CD8+ central memory T cells, in pre-dose samples (Day -14) and at three days after antibody administration for one animal in the study. T cell activation and proliferation were found to be elevated in both CD4+ and CD8+ central memory T cell populations three days after antibody treatment, relative to pre-dose levels.

[00430] As shown in Figures 6A-6D, cynomolgus monkeys administered the anti-CTLA-4 antibody AGEN1884 (IgG_1) and anti-PD-1 antibody AGEN2034 (IgG_4 S228P) exhibited a substantial increase in ICOS+ and Ki67+ central memory T cells three days after antibody administration, relative to pre-dose samples. These results include the data shown in Figure 5 for one of the animals in the study. A statistically significant increase in activated and proliferating populations was observed for CD8+ central memory T cells (Figures 6C and 6D). These data show that AGEN1884 (IgG_1) and AGEN2034 (IgG_4 S228P) combination treatment increased central memory T cell activation and proliferation.

7.2 Example 2: Epitope mapping of anti-CTLA-4 antibody

[00431] The interaction of the Fab fragment of AGEN1884 (AGEN1884-Fab) with the extracellular domain of human CTLA-4 was studied by hydrogen-deuterium exchange (HDX) mass spectrometry. CTLA-4 extracellular domain alone or in combination with AGEN1884-Fab, in phosphate buffered saline solution at pH 7.4, was diluted with a ten-fold volume of deuterium oxide labeling buffer and incubated for varying periods of time (0, 60, 300, 1800, and 7200 seconds) at room temperature. Exchange of deuterium for hydrogen was quenched

by adding one volume of 4 M guanidine hydrochloride, 0.85 M TCEP (tris(2-carboxyethyl)phosphine) buffer and the final pH was 2.5. Samples were then subjected to on-column pepsin/protease type XIII digestion and LC-MS analysis. Mass spectra were recorded in MS only mode. For the calculation of deuterium incorporation, the mass spectra for a given peptide were combined across the extracted ion chromatogram peak and the weighted average m/z was calculated. The mass increase from the mass of the native peptide (0 minute) to the weighted averaged mass corresponds to the level of deuterium incorporation. The deuterium buildup curves over exchange time for all the peptides were plotted for further analysis and were compared with HDExaminer software.

[00432] Most of the CTLA-4 peptides displayed identical or similar deuterium levels with and without the anti-human CTLA-4 Fab present. Several peptide segments, however, were found to have significantly decreased deuterium incorporation upon Fab binding. All the residues in this paragraph are numbered according to SEQ ID NO: 96. Two regions, residues 80-82 (QVT, SEQ ID NO: 102) and residues 135-149 (YPPPYYLGIGNGTQI, SEQ ID NO: 100), experienced strong deuterium protection when human CTLA-4 was bound to Fab. The strongest decrease in deuterium uptake was observed at residues 140-141 (YL) which thus appeared to be a main feature of the epitope of AGEN1884 on CTLA-4. Inspection of the sequences of human and cynomolgus monkey CTLA-4, both of which AGEN1884 binds strongly (data not shown), reveals almost complete sequence identity in the two regions described above, except for a methionine substitution for leucine at position 141 (Figure 7A). In contrast, AGEN1884 does not bind to any significant extent to either mouse or rat CTLA-4 (data not shown) which differ from human CTLA-4 at residues 140-143 (YLGI, SEQ ID NO: 97) at three out of four positions (Figure 7A). Further selectivity data show that AGEN1884 binds with high specificity to human and cynolmolgus monkey CTLA-4 and not to other related CD28 family members including CD28, ICOS, BTLA, and PD-1 (data not shown). Sequence comparison among these related proteins shows that the non-CTLA-4 proteins all differ at residues 140-143 (YLGI, SEQ ID NO: 97) (Figure 7B), further supporting the importance of this epitope to the binding of AGEN1884.

7.3 Example 3: Epitope mapping of anti-PD-1 antibody

[00433] The epitope of the anti-PD-1 antibody AGEN2034 was characterized using hydrogen-deuterium exchange (HDX) mass spectrometry and a Pepscan analysis.

7.3.1 Epitope mapping of anti-PD-1 Fab using hydrogen-deuterium exchange (HDX) mass spectrometry

[00434] The interaction of a Fab fragment of AGEN2034 (AGEN2034-Fab) with the extracellular domain of human PD-1 was studied by hydrogen-deuterium exchange (HDX) mass spectrometry.

[00435] Recombinant His-tagged human PD-1 was obtained from Sino Biological Inc (Cat# 10377-H08H). When used, deglycosylated PD-1 was prepared from 300 µg of recombinant His-tagged human PD-1 protein incubated with 6 µl of PNGase F at 37°C for 4 hours. Fab fragment of an anti-PD-1 antibody was prepared from AGEN2034 by protease treatment.

[00436] For pepsin/protease XVIII digestion, 4.0 µg of native or deglycosylated human PD-1 in 125 µl control buffer (50 mM phosphate, 100 mM sodium chloride at pH 7.4) was denatured by adding 135 µl of 4 M guanidine hydrochloride, 0.85 M TCEP buffer (final pH is 2.5), and incubating the mixture for 3 minutes at 11°C. Then, the mixture was subjected to on-column pepsin/protease XVIII digestion using an in-house packed pepsin/protease XVIII column and the resultant peptides were analyzed using a UPLC-MS system comprised of a Waters Acquity UPLC coupled to a Q Exactive™ Hybrid Quadrupole-Orbitrap Mass Spectrometer (Thermo). The peptides were separated on a 50 mm × 1 mm C8 column with a 19 min gradient from 2-27% solvent B (0.2% formic acid in acetonitrile). Peptide identification was done through searching MS/MS data against the human PD-1 sequence with Mascot. The mass tolerance for the precursor and product ions was 10 ppm and 0.05 Da, respectively.

[00437] 10 µl human PD-1 (4.0 µg) or 10 µl human PD-1 and Fab mixture (4.0 µg: 4.0 µg) was incubated with 125 µl deuterium oxide labeling buffer (50 mM sodium phosphate, 100 mM sodium chloride at pD 7.4) for 0 second, 60 seconds, 600 seconds, and 3600 seconds at 11°C. Hydrogen/deuterium exchange was quenched by adding 135 µl of 4 M guanidine hydrochloride, 0.85 M TCEP buffer and the final pH was 2.5. Subsequently, the quenched samples were subjected to on column pepsin/protease XVIII digestion and LC-MS analysis as described above. The mass spectra were recorded in MS only mode.

[00438] Raw MS data was processed using HDX WorkBench, software for the analysis of H/D exchange MS data (J. Am. Soc. Mass Spectrom. 2012, 23 (9), 1512-1521, incorporated herein by reference in its entirety). The deuterium levels were calculated using the average mass difference between the deuteriated peptide and its native form (t_0).

[00439] Sequence coverage of 85.4% was achieved for deglycosylated human PD-1 without His-tag. Most PD-1 peptides displayed identical or similar deuterium levels with and without the anti-human PD-1 Fab present. Several peptide segments, however, were found to have

significantly decreased deuterium incorporation upon Fab binding. All the residues in this paragraph are numbered according to SEQ ID NO: 96. Deglycosylated human PD-1 showed strong reduction in deuterium uptake upon binding to anti-human PD-1 Fab at residues 127-142 (SLAPKAQIKESLRAEL, SEQ ID NO: 103). In addition, a decrease in deuterium uptake was observed at residues 25-42 (LDSPDRPWNPPTFSPALL) (SEQ ID NO: 104) upon binding to anti-human PD-1 Fab.

7.3.2 Epitope mapping of anti-PD-1 antibody using a Pepscan analysis

[00440] The binding of the anti-PD-1 antibody AGEN2034 was measured against synthesized PD-1 peptide fragments prepared as a chip-bound peptide array. Analysis was performed by Pepscan Presto BV, Lelystad, the Netherlands. Briefly, to reconstruct epitopes of human PD-1, a library of peptides was synthesized. An amino functionalized polypropylene support was obtained by grafting with a proprietary hydrophilic polymer formulation, followed by reaction with t-butyloxycarbonyl-hexamethylenediamine (BocHMDA) using dicyclohexylcarbodiimide (DCC) with Nhydroxybenzotriazole (HOBt) and subsequent cleavage of the Boc-groups using trifluoroacetic acid (TFA). Standard Fmoc-peptide synthesis was used to synthesize peptides on the amino-functionalized solid support by custom modified JANUS liquid handling stations (Perkin Elmer). Synthesis of structural mimics was conducted using Pepscan's proprietary Chemically Linked Peptides on Scaffolds (CLIPS) technology. CLIPS technology allows to structure peptides into single loops, double loops, triple loops, sheet-like folds, helix-like folds and combinations thereof. The binding of antibody to each of the synthesized peptides was tested in a PEPSCAN-based ELISA. The peptide arrays were incubated with primary antibody solution overnight at 4°C. After washing, the peptide arrays were incubated with a goat anti-human HRP conjugate (Southern Biotech, Cat# 2010-05) for one hour at 25°C. After washing, the peroxidase substrate 2,2'-azino-di-3-ethylbenzthiazoline sulfonate (ABTS) and 20 µl/ml of 3% H_2O_2 were added. After one hour, the color development was measured and quantified with a charge coupled device (CCD) - camera and an image processing system.

[00441] The Pepscan study showed that the anti-PD-1 antibody AGEN2034 recognized stretches of human PD-1 including residues 26-35 (DSPDRPWNPP, SEQ ID NO: 105), residues 150-158 (EVPTAHPSP, SEQ ID NO: 106), and residues 126-133 (ISLAPKAQ, SEQ ID NO: 107), numbered according to SEQ ID NO: 96.

* * *

[00442] The invention is not to be limited in scope by the specific embodiments described

herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[00443] All references (*e.g.*, publications or patents or patent applications) cited herein are incorporated herein by reference in their entireties and for all purposes to the same extent as if each individual reference (*e.g.*, publication or patent or patent application) was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[00444] Other embodiments are within the following claims.

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WHAT IS CLAIMED:

1. A pharmaceutical composition comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

2. The composition of claim 1, wherein:

the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first isolated antibody comprises the amino acid sequences of SEQ ID NO: 20, 22, 24, 27, 30, and 36, respectively;

the heavy chain variable region and the light chain variable region of the first isolated antibody comprises the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively;

the first isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 59;

the first isolated antibody is antagonistic to human CTLA-4;

the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second isolated antibody comprises the amino acid sequences of SEQ ID NO: 75, 76, 81, 83, 84, and 85, respectively;

the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively;

the second isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 93; and/or

the second isolated antibody is antagonistic to human PD-1.

3. The composition of claim 1 or 2, wherein:

the first isolated antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively, and the second isolated antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively; and/or

the first isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 59, and the second isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 93.

4. A multispecific antibody comprising a first antigen-binding region that specifically binds to human CTLA-4 and a second antigen-binding region that specifically binds to human PD-1, wherein:

(a) the first antigen-binding region comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second antigen-binding region comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

5. The multispecific antibody of claim 4, wherein:

the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first antigen-binding region comprise the amino acid sequences of SEQ ID NO: 20, 22, 24, 27, 30, and 36, respectively;

the heavy chain variable region and the light chain variable region of the first antigen-binding region comprise the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively;

the first antigen-binding region comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 59;

the first antigen-binding region is antagonistic to human CTLA-4;

the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second antigen-binding region comprise the amino acid sequences of SEQ ID NO: 75, 76, 81, 83, 84, and 85, respectively;

the heavy chain variable region and the light chain variable region of the second antigen-binding region comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively;

the second antigen-binding region comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 93; and/or

the second antigen-binding region is antagonistic to human PD-1.

6. The multispecific antibody of claim 4 or 5, wherein:

the first antigen-binding region comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively, and the second antigen-binding region comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively; and/or

the first antigen-binding region comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 59, and the second antigen-binding region comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 93.

7. A kit comprising a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(c) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(d) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

8. The kit of claim 7, wherein:

the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first isolated antibody comprises the amino acid sequences of SEQ ID NO: 20, 22, 24, 27, 30, and 36, respectively;

the heavy chain variable region and the light chain variable region of the first isolated antibody comprises the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively;

the first isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 59;

the first isolated antibody is antagonistic to human CTLA-4;

the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second isolated antibody comprises the amino acid sequences of SEQ ID NO: 75, 76, 81, 83, 84, and 85, respectively;

the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively;

the second isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 93; and/or

the second isolated antibody is antagonistic to human PD-1.

9. The kit of claim 7 or 8, wherein:

the first isolated antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively, and the second isolated antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively; and/or

the first isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 59, and the second isolated antibody comprises a heavy chain comprising

the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 93.

10. A method of enhancing T cell activation and/or proliferation in a subject, the method comprising administering to the subject an effective amount of a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

11. A method of treating a cancer in a subject, the method comprising administering to the subject an effective amount of a first isolated antibody that specifically binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

12. A method of treating an infectious disease in a subject, the method comprising administering to the subject an effective amount of a first isolated antibody that specifically

binds to human CTLA-4 and a second isolated antibody that specifically binds to human PD-1, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

13. Use of a first isolated antibody that specifically binds to human CTLA-4 in combination with a second isolated antibody that specifically binds to human PD-1 in a method of enhancing T cell activation and/or proliferation in a subject, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and

(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

14. Use of a first isolated antibody that specifically binds to human CTLA-4 in combination with a second isolated antibody that specifically binds to human PD-1 in a method of treating an infectious disease in a subject, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid

sequence set forth in SEQ ID NO: 14; and
(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

15. Use of a first isolated antibody that specifically binds to human CTLA-4 in combination with a second isolated antibody that specifically binds to human PD-1 in a method of treating a cancer in a subject, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and
(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

16. Use of a first isolated antibody that specifically binds to human CTLA-4 in combination with a second isolated antibody that specifically binds to human PD-1 in the manufacture of a medicament for treating a cancer in a subject, wherein:

(a) the first isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2, and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 1, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2, and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 14; and
(b) the second isolated antibody comprises a heavy chain variable region (VH) comprising the complementarity determining regions CDRH1, CDRH2 and CDRH3 of the VH amino acid sequence set forth in SEQ ID NO: 66, and a light chain variable region (VL) comprising the complementarity determining regions CDRL1, CDRL2 and CDRL3 of the VL amino acid sequence set forth in SEQ ID NO: 74.

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17. The method or use of any one of claims 10-16, wherein:

the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the first isolated antibody comprises the amino acid sequences of SEQ ID NO: 20, 22, 24, 27, 30, and 36, respectively;

the heavy chain variable region and the light chain variable region of the first isolated antibody comprises the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively;

the first isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 59;

the first isolated antibody is antagonistic to human CTLA-4;

the amino acid sequences of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of the second isolated antibody comprises the amino acid sequences of SEQ ID NO: 75, 76, 81, 83, 84, and 85, respectively;

the heavy chain variable region and the light chain variable region of the second isolated antibody comprise the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively;

the second isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 93; and/or

the second isolated antibody is antagonistic to human PD-1.

18. The method or use of any one of claims 10-17, wherein:

the first isolated antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 14, respectively, and the second isolated antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences set forth in SEQ ID NOs: 66 and 74, respectively; and/or

the first isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 51 and a light chain comprising the amino acid sequence of SEQ ID NO: 59, and the second isolated antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 93.

19. The method or use of any one of claims 10-18, wherein:

the first isolated antibody and the second isolated antibody are administered to the subject separately;

the first isolated antibody is administered at 0.3 mg/kg or 1 mg/kg;

the second isolated antibody is administered at 1 mg/kg, 3 mg/kg, or 6 mg/kg;

the second isolated antibody is administered at the dose of 200 mg;

the first isolated antibody is administered at 0.3 mg/kg, and the second isolated antibody is administered at 1 mg/kg;

the first isolated antibody is administered at 1 mg/kg, and the second isolated antibody is administered at 1 mg/kg;

the first isolated antibody is administered at 1 mg/kg, and the second isolated antibody is administered at 3 mg/kg;

the first isolated antibody is administered at 1 mg/kg, and the second isolated antibody is administered at 6 mg/kg;

the first isolated antibody is administered every six weeks;

the second isolated antibody is administered every two weeks or every three weeks;

the first isolated antibody is administered intravenously; and/or

the second isolated antibody is administered intravenously.

20. A method of enhancing T cell activation and/or proliferation in a subject, treating an infectious disease in a subject, or treating a cancer in a subject, the method comprising administering to the subject an effective amount of the composition of any one of claims 1-3, or the multispecific antibody of any one of claims 4-6.

21. Use of the composition of any one of claims 1-3, the multispecific antibody of any one of claims 4-6, or the kit of any one of claims 7-9, for enhancing T cell activation and/or proliferation, for treating an infectious disease, or for treating a cancer in subject.

22. Use of the composition of any one of claims 1-3, the multispecific antibody of any one of claims 4-6, or the kit of any one of claims 7-9, in the manufacture of a medicament for treating a cancer in a subject.

23. The method or use of any one of claims 10-22, wherein the subject has a metastatic or locally advanced solid tumor; and/or a metastatic or locally advanced, unresectable squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.

24. The method or use of claim 23, wherein the first and second isolated antibody is

administered as a first cancer therapy after diagnosis of the cancer, optionally wherein the first and second isolated antibodies are administered as the first cancer therapy after:

(a) diagnosis of tumor progression that has occurred despite previous treatment of the cancer with a different cancer therapy; or

(b) diagnosis of toxicity of a different cancer therapy, and

optionally wherein the first and/or second isolated antibodies are the second cancer therapy administered to the subject.

25. The method or use of claim 24, wherein:

no standard therapy is available for the cancer; or

the cancer is refractory to a standard therapy, or the cancer has relapsed after a standard therapy, optionally wherein:

the standard therapy comprises a platinum-containing chemotherapy;

the standard therapy is a platinum-containing doublet; and/or

the cancer is HPV positive.

26. The method or use of claim 25, wherein the cancer is a non-small cell lung cancer (NSCLC), optionally wherein:

the NSCLC is a Stage IV, metastatic, or locally advanced NSCLC;

the NSCLC has no EGFR or ALK genomic tumor aberrations;

the NSCLC has no EGFR sensitizing mutation or ALK translocation; and/or

the subject has received no prior systemic chemotherapy treatment for the NSCLC.

27. The method or use of claim 25, wherein the cancer is a cutaneous squamous-cell carcinoma (cSCC), optionally wherein:

the cSCC is a Stage IV, metastatic, or locally advanced cSCC.;

the cSCC is diagnosed histologically or cytologically according to the eighth edition of the American Joint Committee on Cancer staging manual; and/or

the cSCC is not curable with radiation therapy.

28. The method or use of any one of claims 24-27, wherein the percentage of tumor cells in a sample of the cancer that exhibit detectable membrane expression of PD-L1 is at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or 90%.

29. The method or use of any one of claims 24-28, wherein:

the composition or multispecific antibody is administered intravenously; and/or

the composition or multispecific antibody is administered as a first cancer therapy after diagnosis of the cancer, optionally wherein the first and second isolated antibodies are administered as the first cancer therapy after:

(a) diagnosis of tumor progression that has occurred despite previous treatment of the cancer with a different cancer therapy; or

(b) diagnosis of toxicity of a different cancer therapy, and

optionally wherein the first and/or second isolated antibodies are the second cancer therapy administered to the subject.

Figure 1A

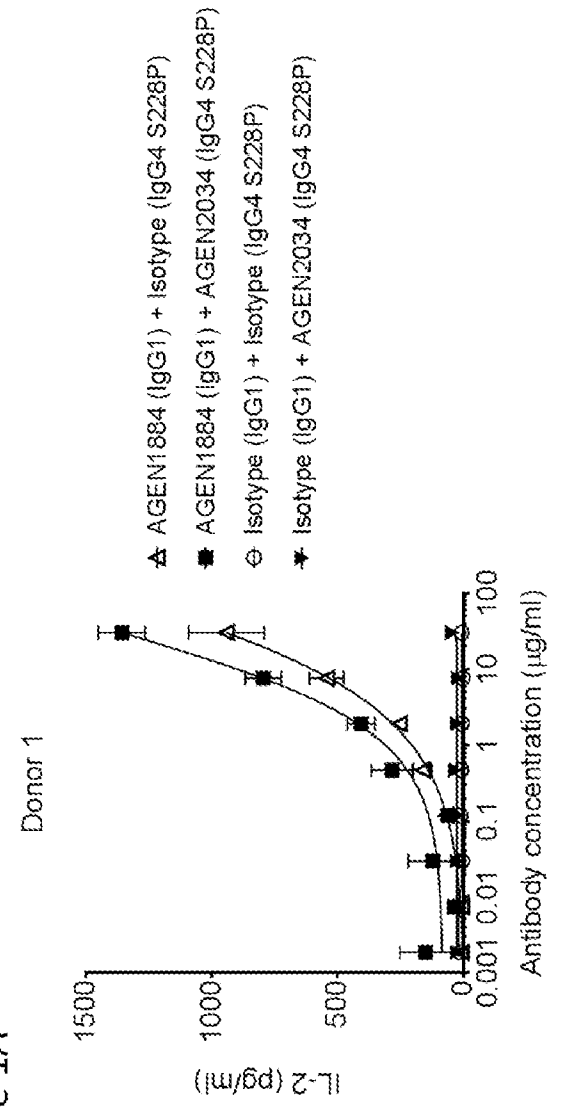
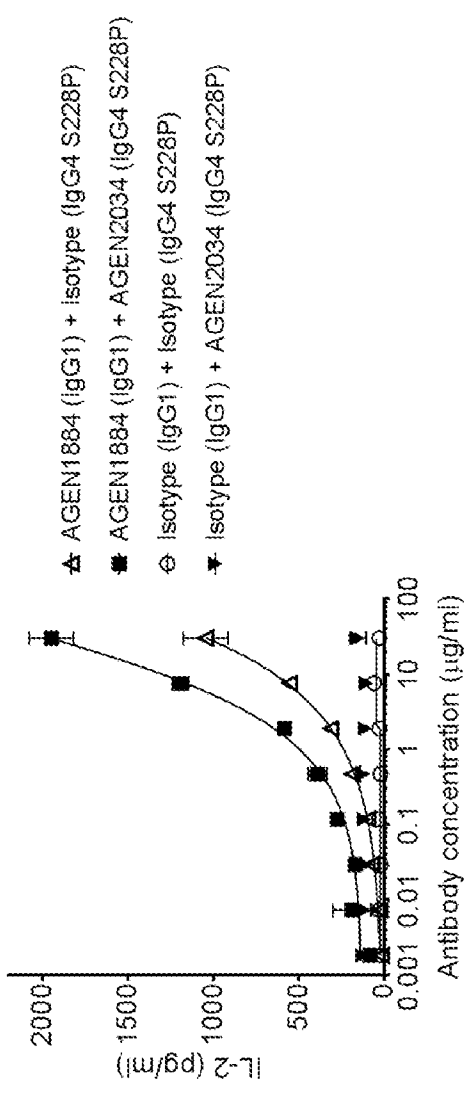


Figure 1B



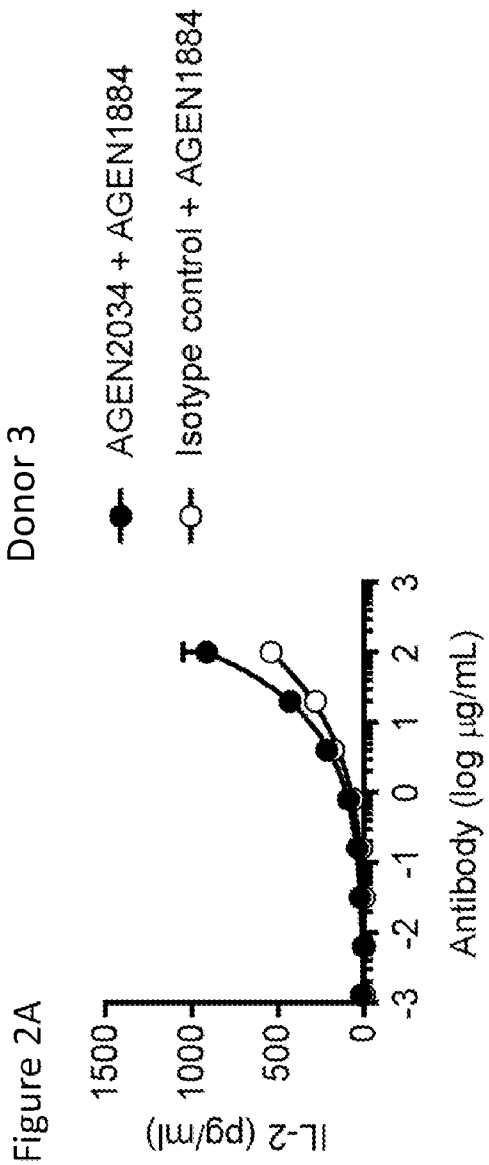


Figure 2A

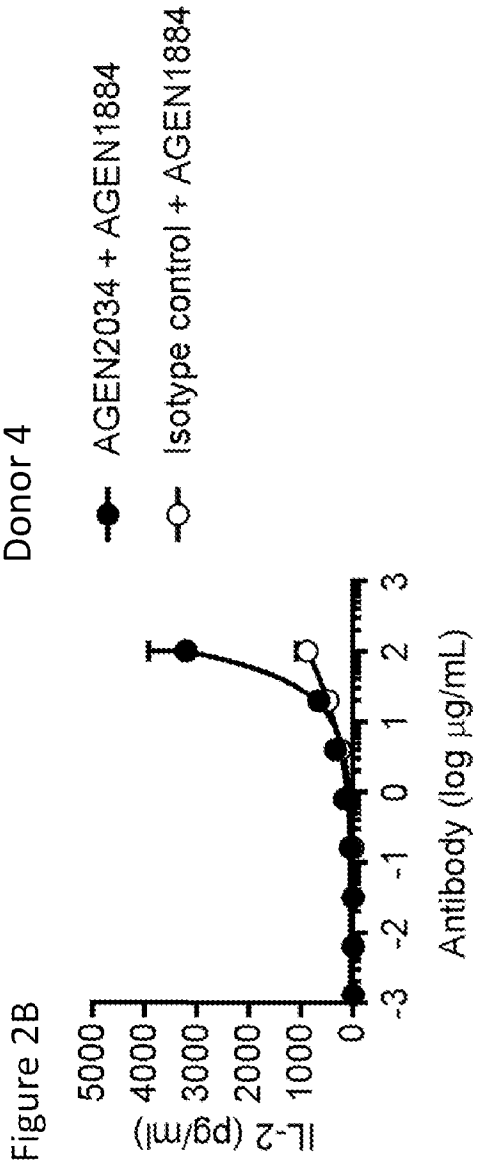
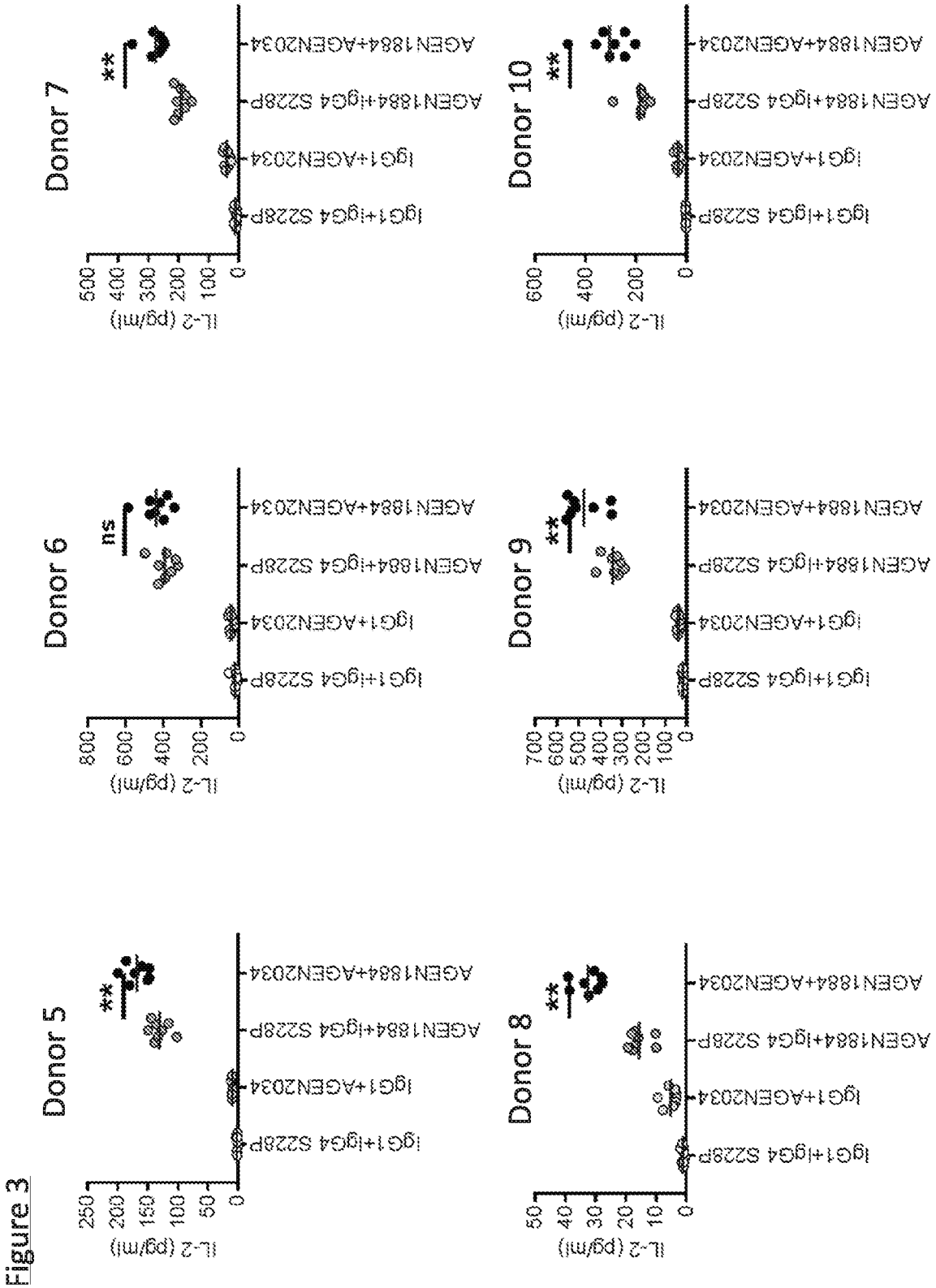


Figure 2B

Figure 3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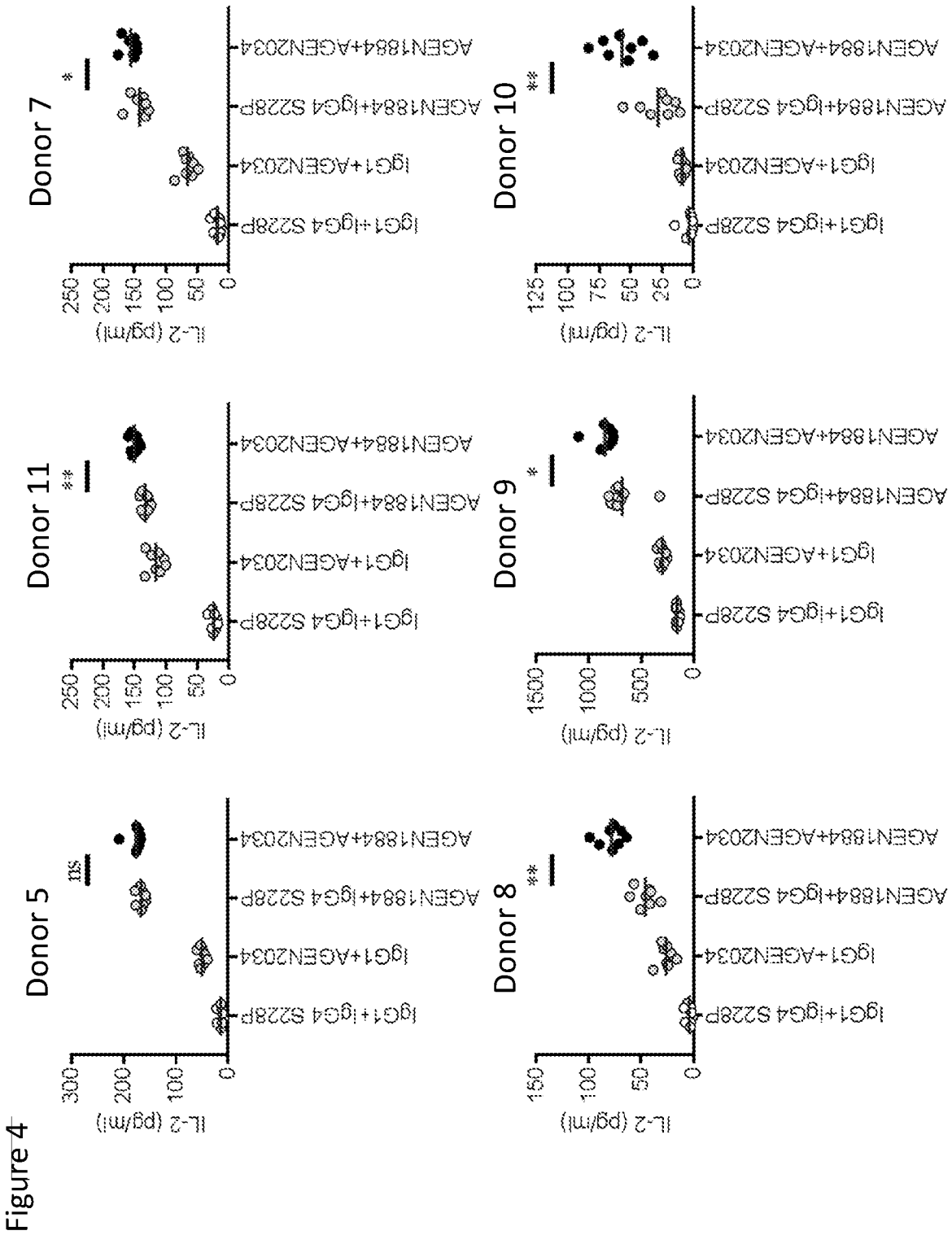
IL-2 (pg/ml)
0
50
100
150
200
250
**
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 8
IL-2 (pg/ml)
0
10
20
30
40
50
**
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 6
IL-2 (pg/ml)
0
200
400
600
800
ns
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 9
IL-2 (pg/ml)
0
100
200
300
400
500
600
700
**
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 7
IL-2 (pg/ml)
0
100
200
300
400
500
**
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 10
IL-2 (pg/ml)
0
200
400
600
**
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034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IL-2 (pg/ml)
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0
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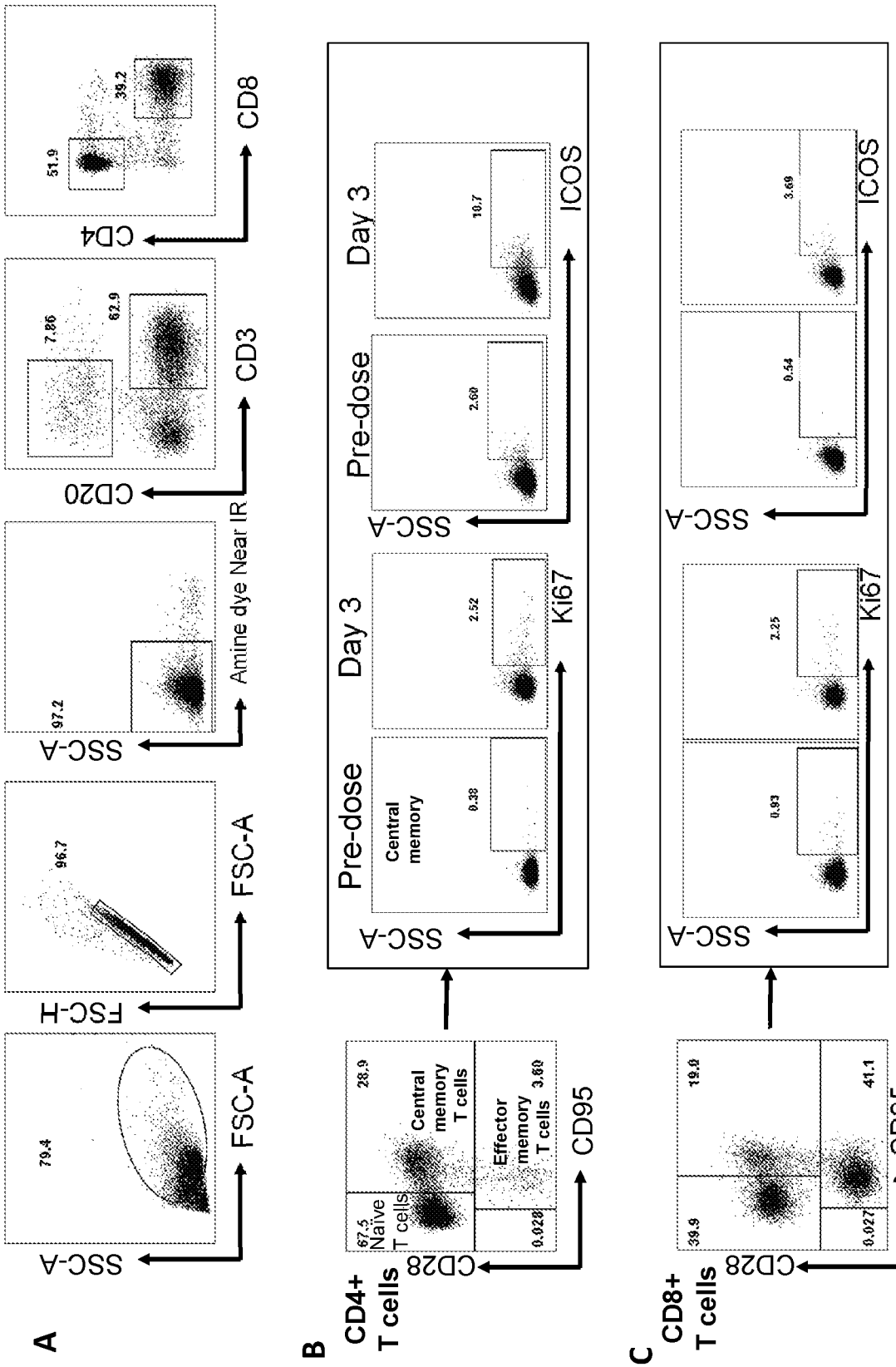
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 7
*
IL-2 (pg/ml)
250
200
150
100
50
0
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 8
**
IL-2 (pg/ml)
150
100
50
0
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 9
*
IL-2 (pg/ml)
1500
1000
500
0
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 10
**
IL-2 (pg/ml)
125
100
75
50
25
0
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034
Donor 11
**
IL-2 (pg/ml)
250
200
150
100
50
0
IgG1+IgG4 S228P
IgG1+AGEN2034
AGEN1884+IgG4 S228P
AGEN1884+AGEN2034

Figure 4

Figures 5A-5C



Figures 6A-6D

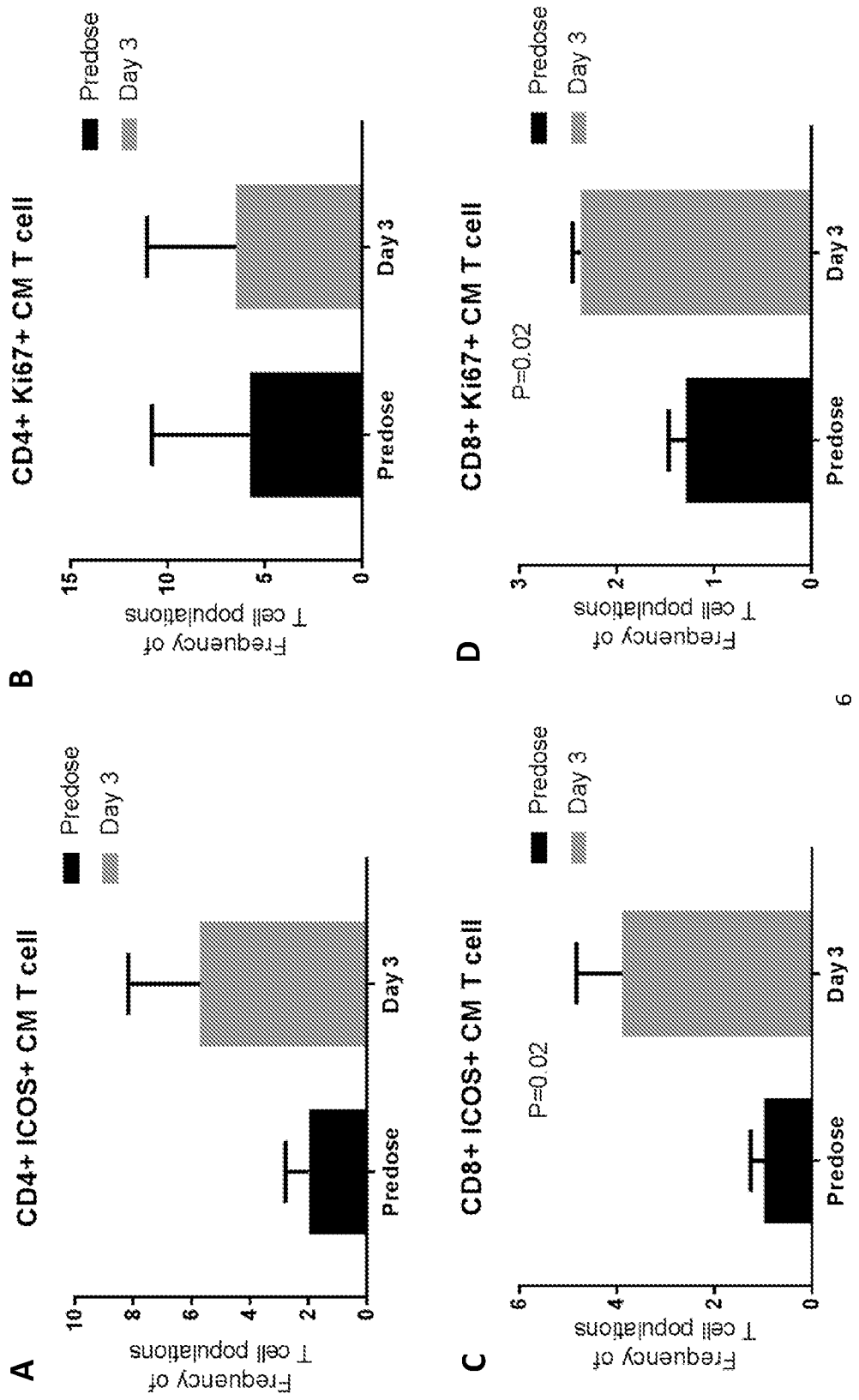


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Figure 7A

```
P16410 CTLA4_HUMAN  1   MACLGFQRHKAQLNLATRTWPCTLLFFLLFIPVFCKAMHVAQPAVVLASSRGIASFVCEY   60
G7PL88 CTLA4_MACFA  1   ...........R.......R.Y....S.......S............N...........   60
P09793 CTLA4_MOUSE  1   .....LR.Y....Q.PS....FVA.LT.......SE.IQ.T..S......H.V...P...   60
Q62859 CTLA4_RAT    1   .....L..Y.TH.Q.PS....FGV.LS.....I.SE.IQ.T..S......H.V...P...   60
                        *****::*:*::*:* :** *   *: *****:*.:*::*:**:****.*:*:*** ***

P16410 CTLA4_HUMAN  61  ASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQGLR   120
G7PL88 CTLA4_MACFA  61  ............................................................   120
P09793 CTLA4_MOUSE  61  SPSHNTD.........TND.M.....T.FTEK.TVG...YPF.S..FNESR.........   120
Q62859 CTLA4_RAT    61  ..SHNTD.........TND.......T.FTVK.T.G....PF.S..FNESR.........   120
                        :   :: *********::.*:*****:*:   * : ***  :*:** . .:*********

P16410 CTLA4_HUMAN  121 AMDTGLYICKVELMYPPPYYLGIGNGTQIYVIDPEPCPDSDFLLWILAAVSSGLFFYSFL   180
G7PL88 CTLA4_MACFA  121 ......................M.....................................   180
P09793 CTLA4_MOUSE  121 .V.....L...........FV.M.........................V...L........   180
Q62859 CTLA4_RAT    121 .A.....F...........FV.M.....................................   180
                        * *****:***********::*:************************.*** ********

P16410 CTLA4_HUMAN  181 LTAVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPIN                    223
G7PL88 CTLA4_MACFA  181 ........................................                      223
P09793 CTLA4_MOUSE  181 VS......................................                      223
Q62859 CTLA4_RAT    181 V.....NRT...................................                  223
                        ::****.: **********************************
```

Figure 7B

```
SP|P16410|CTLA4_HUMAN  MACLGFQRHKAQLNLATRTWPCTLLFFLLFIP--VFC-------KAMHVAQPAVVLA--- 48
TR|G7PL88|G7PL88_MACFA MACLGFQRHKARLNLATRTRPYTLLFSLLFIP--VFS-------KAMHVAQPAVVLA--- 48
SP|P10747|CD28_HUMAN   ----------------------MLRLLLALN--LFPS-IQVTGNKILVKQSP-MLV--- 30
SP|Q9Y6W8|ICOS_HUMAN   --------------MKSGLWY---------FF--LFCLRIKVLTGEINGSANYEMFI--- 32
SP|Q7Z6A9|BTLA_HUMAN   ----------------MKTLPAMLGTGKLFWV---FFLIPYLDIWNIHGKESCDVQLYIK 41
SP|Q15116|PDCD1_HUMAN  ------------MQIPQAPWPVVWAVLQLGWRPGWFLDSPD-RPWNPPTFSPALLVV--- 44
                                                       *                 :

SP|P16410|CTLA4_HUMAN  -------SSRGIASFVCEYASPGKA---TEVRVTVLRQADSQVTEVCAATYMMGNE--LT 96
TR|G7PL88|G7PL88_MACFA -------NSRGIASFVCEYASPGKA---TEVRVTVLRQADSQVTEVCAATYMMGNE--LT 96
SP|P10747|CD28_HUMAN   -------AYDNAVNLSCKYSYNLFS---REFRASLHKGLDSA-VEVCVVYGNYSQQLQVY 79
SP|Q9Y6W8|ICOS_HUMAN   -------FHNGGVQILCKYPD--IV---QQFKMQLLKGGQ----ILCDLTKTKGSGNTVS 76
SP|Q7Z6A9|BTLA_HUMAN   RQSEHSILAGDPFELECPVKYCANRPHVTWCKLN---GT------TCVKLEDRQ------ 86
SP|Q15116|PDCD1_HUMAN  -------TEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDK----LAAFPEDR------- 86
                              : *             :             .

SP|P16410|CTLA4_HUMAN  FLDDSICT----GTSSGNQVNLTI---QGLRAMDTGLYICKVELMYPPPYYLGIG----- 144
TR|G7PL88|G7PL88_MACFA FLDDSICT----GTSSGNQVNLTI---QGLRAMDTGLYICKVELMYPPPYYMGIG----- 144
SP|P10747|CD28_HUMAN   SKTGFNCD----GKLGNESVTFYL---QNLYVNQTDIYFCKIEVMYPPPYLDNEK----- 127
SP|Q9Y6W8|ICOS_HUMAN   IKSLKFCH----SQLSNNSVSFFL---YNLDHSHANYYFCNLSIFDPPPFKVTLT----- 124
SP|Q7Z6A9|BTLA_HUMAN   -----------TSWKEEKNISFFILHFEPVLPNDNGSYRCSANFQSNL---IE------- 125
SP|Q15116|PDCD1_HUMAN  SQPGQDCRFRVTQLPNGRDFHMSV---VRARRNDSGTYLCGAISLAPKAQIKESLRAELR 143
                                  ... : :         .   * *
```

Figure 7C

```
SP|P16410|CTLA4_HUMAN   -NGTQIYVIDP-----EPCPDS-----DFLLWILAAVSSGLFFYSFLLTAVSL--S-KML 190
TR|G7PL88|G7PL88_MACFA  -NGTQIYVIDP-----EPCPDS-----DFLLWILAAVSSGLFFYSFLLTAVSL--S-KML 190
SP|P10747|CD28_HUMAN    SNGTIIHVKGK-----HLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFI--IFWVR 180
SP|Q9Y6W8|ICOS_HUMAN    --GGYLHIYES-----QLCCQL-------KFWLPIGCAA---FVVVCILGCIL--ICWLT 165
SP|Q7Z6A9|BTLA_HUMAN    SHSTTLYVTDVKSASERPSKDEMASR-PWLLYRLLPLGG---LPLLITTCFCLFCCLRR 180
SP|Q15116|PDCD1_HUMAN   VTERRAEVPTA-----HPSPSPRPAG-QFQTLVVGVVGGLLGSLVLLVWVLAV--ICSRA 195
                                :       . . .                 ..      . :

SP|P16410|CTLA4_HUMAN   KKRSP----LTTGVYVKMPPTE-----PEC-EKQFQPYFIPIN---------------- 223
TR|G7PL88|G7PL88_MACFA  KKRSP----LTTGVYVKMPPTE-----PEC-EKQFQPYFIPIN---------------- 223
SP|P10747|CD28_HUMAN    SKRSR----LLHSDYMNMTPRR-----PGPTRKHYQPYAPPRD--FAAYRS--------- 220
SP|Q9Y6W8|ICOS_HUMAN    KKKYSSSVHDPNGEYMFMRAVN-----TAKKSRLTDVTL---------------------- 199
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SP|Q7Z6A9|BTLA_HUMAN    EVYSNPCLEENKP--GIVYASLNHSVIGPNSRLARNVKEAPTEYASI-----CVRS- 289
SP|Q15116|PDCD1_HUMAN   PEPPVPCVPEQTEYATIVFP----SGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL 288
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SEQUENCE LISTING

<110> AGENUS INC.
LUDWIG INSTITUTE FOR CANCER RESEARCH LTD
MEMORIAL SLOAN KETTERING CANCER CENTER

<120> ANTIBODIES AND METHODS OF USE THEREOF

<130> 596311:AGBW-094PC

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<150> 62/586,605
<151> 2017-11-15

<150> 62/582,814
<151> 2017-11-07

<150> 62/570,451
<151> 2017-10-10

<150> 62/431,279
<151> 2016-12-07

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

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

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

Met Val Thr Val Ser Ser
115

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

<220>
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<400> 9
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

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

Met Val Thr Val Ser Ser
        115


<210> 10
<211> 118
<212> PRT
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      polypeptide"

<400> 10
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
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Ala Arg Val Gly Leu Met Gly Pro Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110


Met Val Thr Val Ser Ser
        115


<210> 11
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 11
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


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


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


Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


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


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


Met Val Thr Val Ser Ser
        115


<210> 12
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 12
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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1               5                   10                  15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Ala Arg Val Gly Leu Met Gly Pro Phe Asn Ile Trp Gly Gln Gly Thr
            100                 105                 110

Met Val Thr Val Ser Ser
        115


<210> 13
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 13
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
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Ala Arg Val Gly Leu Met Gly Pro Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110


Met Val Thr Val Ser Ser
        115


<210> 14
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 14
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


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


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


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


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


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


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


<210> 15
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 15
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15
```

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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Thr Tyr
            20                  25                  30

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

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

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

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

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


<210> 16
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 16
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

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

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

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

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

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

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


<210> 17
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<211> 107
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 17
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Phe Ser Pro Gly
1 5 10 15

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

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

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

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

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

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

<210> 18
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
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<400> 18
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

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

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

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

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


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


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


<210> 19
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 19
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


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


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


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


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


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


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


<210> 20
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
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<400> 20
Ser Tyr Ser Met Asn
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1 5

<210> 21
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 21
Ser Tyr Ala Met Ser
1 5

<210> 22
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 22
Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 23

<400> 23
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<210> 24
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 24
Val Gly Leu Met Gly Pro Phe Asp Ile
1 5

<210> 25

<400> 25
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<210> 26
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 26
Val Gly Leu Met Gly Pro Phe Asn Ile
1 5

<210> 27
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 27
Arg Ala Ser Gln Ser Val Ser Arg Tyr Leu Gly
1 5 10

<210> 28
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 28
Arg Ala Ser Gln Ser Val Gly Thr Tyr Leu Ala
1 5 10

<210> 29
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 29
Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 30
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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peptide"

<400> 30
Gly Ala Ser Thr Arg Ala Thr
1 5

<210> 31
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 31
Gly Ala Ser Arg Arg Ala Thr
1 5

<210> 32
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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peptide"

<400> 32
Ala Thr Ser Ser Arg Ala Thr
1 5

<210> 33
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 33
Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 34
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 34
Ala Ala Ser Thr Arg Ala Thr
1 5

<210> 35
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 35
Gly Ala Ser Asn Arg Ala Thr
1 5

<210> 36
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 36
Gln Gln Tyr Gly Ser Ser Pro Trp Thr
1 5

<210> 37
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 37
Gln Gln Tyr Gly Thr Ser Pro Trp Thr
1 5

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

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 38
Gln Gln Tyr Gly Ser Ser Pro Phe Thr

1 5

<210> 39
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
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<222> (3)..(3)
<223> /replace="Ala"

<220>
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<222> (5)..(5)
<223> /replace="Ser"

<220>
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<222> (1)..(5)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 39
Ser Tyr Ser Met Asn
1 5

<210> 40

<400> 40
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<210> 41

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<210> 42

<400> 42
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<210> 43
<211> 11
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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<222> (7)..(7)
<223> /replace="Gly"

<220>
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<223> /replace="Ser" or "Thr"

<220>
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<222> (11)..(11)
<223> /replace="Ala"

<220>
<221> MISC_FEATURE
<222> (1)..(11)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 43
Arg Ala Ser Gln Ser Val Ser Arg Tyr Leu Gly
1 5 10

<210> 44
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> VARIANT
<222> (1)..(1)
<223> /replace="Ala"

<220>
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<222> (2)..(2)
<223> /replace="Thr"

<220>
<221> VARIANT
<222> (4)..(4)
<223> /replace="Ser" or "Arg" or "Asn"

<220>
<221> MISC_FEATURE
<222> (1)..(7)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 44
Gly Ala Ser Thr Arg Ala Thr
1 5

<210> 45
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Thr"

<220>
<221> VARIANT
<222> (8)..(8)
<223> /replace="Phe"

<220>
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<222> (1)..(9)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 45
Gln Gln Tyr Gly Ser Ser Pro Trp Thr
1 5

<210> 46

<400> 46
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<210> 47
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
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<222> (9)..(9)
<223> /replace="Ala"

<220>
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<222> (13)..(13)
<223> /replace="Val" or "Phe"

<220>
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<222> (30)..(30)
<223> /replace="Gly"

<220>
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<222> (31)..(31)
<223> /replace="Thr" or "Ser"

<220>
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<222> (34)..(34)
<223> /replace="Ala"

<220>
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<222> (38)..(38)
<223> /replace="His"

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<222> (40)..(40)
<223> /replace="Val"

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<222> (45)..(45)
<223> /replace="Ser"

<220>
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<222> (50)..(50)
<223> /replace="Ala"

<220>
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<222> (51)..(51)
<223> /replace="Thr"

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<223> /replace="Arg" or "Ser" or "Asn"

<220>
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<222> (60)..(60)
<223> /replace="Ala"

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<223> /replace="Val" or "Ala"

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<223> /replace="Phe"

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<222> (76)..(76)
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<223> /replace="Ser"

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<222> (93)..(93)
<223> /replace="Thr"

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<222> (96)..(96)
<223> /replace="Phe"

<220>
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<222> (100)..(100)
<223> /replace="Pro"

<220>
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<222> (105)..(105)
<223> /replace="Asp"

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<222> (1)..(107)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 47
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

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

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

<210> 48
<211> 98
<212> PRT
<213> Homo sapiens

<400> 48
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg

<210> 49
<211> 96
<212> PRT
<213> Homo sapiens

<400> 49
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

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

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

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

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

<210> 50
<211> 96
<212> PRT
<213> Homo sapiens

<400> 50
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

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

<210> 51
<211> 447
<212> PRT
<213> Artificial Sequence

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<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 51
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

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

```
Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

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

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

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

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

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

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

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

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

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

```
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

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

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

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

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


<210> 52
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 52
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

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

Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125
```

```
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

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

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

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

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

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

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

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

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

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

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380
```

```
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

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

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

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445
```

<210> 53
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 53

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

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

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

Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
```

```
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

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

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

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

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

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

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

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

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

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

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

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

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

405 410 415

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

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

<210> 54
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 54
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

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

Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

```
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

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

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

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

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

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

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

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

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

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

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

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

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

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430
```

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

<210> 55

<400> 55
000

<210> 56

<400> 56
000

<210> 57

<400> 57
000

<210> 58

<400> 58
000

<210> 59
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 59
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

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

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

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

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

```
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 60
<211> 329
<212> PRT
<213> Homo sapiens

<400> 60

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

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

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

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

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

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

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
```

```
            100                 105                 110

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

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

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

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

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

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

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

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

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

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

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

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

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

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> 61
<211> 329
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 61
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> 62
<211> 329
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 62

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

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

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

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

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

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

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

```
Pro Ala Pro Glu Leu Leu Gly Gly Pro Asp Val Phe Leu Phe Pro Pro
        115                 120                 125

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

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

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

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

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

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

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

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

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

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

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

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

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> 63
<211> 329
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 63

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> 64
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 64

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
```

<210> 65

<211> 223
<212> PRT
<213> Homo sapiens

<400> 65
Met Ala Cys Leu Gly Phe Gln Arg His Lys Ala Gln Leu Asn Leu Ala
1 5 10 15

Thr Arg Thr Trp Pro Cys Thr Leu Leu Phe Phe Leu Leu Phe Ile Pro
20 25 30

Val Phe Cys Lys Ala Met His Val Ala Gln Pro Ala Val Val Leu Ala
35 40 45

Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly
50 55 60

Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln
65 70 75 80

Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr
85 90 95

Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val
100 105 110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile
115 120 125

Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly
130 135 140

Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145 150 155 160

Asp Phe Leu Leu Trp Ile Leu Ala Ala Val Ser Ser Gly Leu Phe Phe
165 170 175

Tyr Ser Phe Leu Leu Thr Ala Val Ser Leu Ser Lys Met Leu Lys Lys
180 185 190

Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu
195 200 205

Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
210 215 220

<210> 66
<211> 113
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 66
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

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

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

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

Ala Ser Asn Gly Asp His Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 67
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 67
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val

50 55 60

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

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

Ala Ser Asn Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 68
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 68
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

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

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

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

Ala Thr Asn Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 69
<211> 113

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 69
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

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

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

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

Ala Ser Asn Gly Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 70
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 70
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

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

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

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

Ala Ser Asn Gly Asp His Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 71
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 71
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Met Val Gln Pro Gly Arg
1 5 10 15

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

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

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

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

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

Ala Ser Asn Gly Asp His Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 72

<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 72
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

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

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

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

Ala Ser Asn Gly Asp His Trp Gly His Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 73
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 73
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

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

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

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

Ala Ser Asn Gly Asp His Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110

Ser
```

<210> 74
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 74

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

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

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

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

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

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

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

<210> 75
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 75
Ser Tyr Gly Met His
1 5

<210> 76
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 76
Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 77
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 77
Val Ile Trp Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 78
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 78
Val Ile Trp Phe Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 79
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 79
Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Met
1 5 10 15

Gly

<210> 80
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 80
Asn Val Asp Tyr
1

<210> 81
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 81
Asn Gly Asp His
1

<210> 82
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 82

Asn Gly Asp Tyr
1

<210> 83
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 83
Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
1 5 10

<210> 84
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 84
Gly Ala Ser Thr Arg Ala Thr
1 5

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

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 85
Gln Gln Tyr Asn Asn Trp Pro Arg Thr
1 5

<210> 86
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> VARIANT
<222> (4)..(4)
<223> /replace="Phe"

<220>
<221> VARIANT
<222> (9)..(9)
<223> /replace="Glu"

<220>
<221> VARIANT
<222> (16)..(16)
<223> /replace="Met"

<220>
<221> MISC_FEATURE
<222> (1)..(17)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 86
Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 87
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> VARIANT
<222> (2)..(2)
<223> /replace="Val"

<220>
<221> VARIANT
<222> (4)..(4)
<223> /replace="Tyr"

<220>
<221> MISC_FEATURE
<222> (1)..(4)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 87
Asn Gly Asp His
1

<210> 88
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> VARIANT
<222> (11)..(11)
<223> /replace="Met"

<220>
<221> VARIANT
<222> (53)..(53)
<223> /replace="Phe"

<220>
<221> VARIANT
<222> (58)..(58)
<223> /replace="Glu"

<220>
<221> VARIANT
<222> (65)..(65)
<223> /replace="Met"

<220>
<221> VARIANT
<222> (98)..(98)
<223> /replace="Thr"

<220>
<221> VARIANT
<222> (100)..(100)
<223> /replace="Val"

<220>
<221> VARIANT
<222> (102)..(102)
<223> /replace="Tyr"

<220>
<221> VARIANT
<222> (105)..(105)
<223> /replace="His"

<220>
<221> MISC_FEATURE
<222> (1)..(113)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 88
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

```
        35                  40                  45

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

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

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

Ala Ser Asn Gly Asp His Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110

Ser
```

<210> 89
<211> 98
<212> PRT
<213> Homo sapiens

<400> 89

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

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

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

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

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

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

Ala Arg
```

<210> 90
<211> 95
<212> PRT
<213> Homo sapiens

<400> 90

```
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
```

```
1               5                   10                  15

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

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

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

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

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


<210> 91
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 91
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

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

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

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

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

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

Ala Ser Asn Gly Asp His Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
        115                 120                 125
```

```
Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                165                 170                 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
            180                 185                 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
        195                 200                 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
    210                 215                 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225                 230                 235                 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
                245                 250                 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
            260                 265                 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
        275                 280                 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
    290                 295                 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305                 310                 315                 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
                325                 330                 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
            340                 345                 350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
        355                 360                 365

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
    370                 375                 380
```

```
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385                 390                 395                 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
                405                 410                 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
            420                 425                 430

Ser Leu Ser Leu Ser Leu Gly
        435
```

<210> 92
<211> 442
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 92

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

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

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

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

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

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

Ala Ser Asn Gly Asp His Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110

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

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140
```

```
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                165                 170                 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
            180                 185                 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
        195                 200                 205

Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
    210                 215                 220

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
225                 230                 235                 240

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

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
            260                 265                 270

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
        275                 280                 285

Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
    290                 295                 300

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
305                 310                 315                 320

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
                325                 330                 335

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
            340                 345                 350

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        355                 360                 365

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    370                 375                 380

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
385                 390                 395                 400
```

```
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
                405                 410                 415


Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
            420                 425                 430


Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210> 93
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 93
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15


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


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


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


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


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


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160
```

```
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> 94
<211> 329
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 94
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

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

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

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

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

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

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

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

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

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
```

```
145                 150                 155                 160

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

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

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

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

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

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

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

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

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

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

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> 95
<211> 326
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 95

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Leu Ser Leu Ser Leu Gly
                325
```

<210> 96
<211> 288
<212> PRT
<213> Homo sapiens

<400> 96

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

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

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

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

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

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

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

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

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

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

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

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


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


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


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


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


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


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


<210> 97
<211> 4
<212> PRT
<213> Homo sapiens

<400> 97
Tyr Leu Gly Ile
1


<210> 98
<211> 9
<212> PRT
<213> Homo sapiens

<400> 98
Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile
1               5


<210> 99
<211> 10
<212> PRT
<213> Homo sapiens

<400> 99
Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
1               5                   10


<210> 100
<211> 15
<212> PRT
<213> Homo sapiens

<400> 100
```

Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
1 5 10 15

<210> 101
<211> 7
<212> PRT
<213> Homo sapiens

<400> 101
Met Tyr Pro Pro Pro Tyr Tyr
1 5

<210> 102
<211> 3
<212> PRT
<213> Homo sapiens

<400> 102
Gln Val Thr
1

<210> 103
<211> 16
<212> PRT
<213> Homo sapiens

<400> 103
Ser Leu Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu
1 5 10 15

<210> 104
<211> 18
<212> PRT
<213> Homo sapiens

<400> 104
Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr Phe Ser Pro Ala
1 5 10 15

Leu Leu

<210> 105
<211> 10
<212> PRT
<213> Homo sapiens

<400> 105
Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro
1 5 10

<210> 106
<211> 9
<212> PRT
<213> Homo sapiens

<400> 106

Glu Val Pro Thr Ala His Pro Ser Pro
1 5

<210> 107
<211> 8
<212> PRT
<213> Homo sapiens

<400> 107
Ile Ser Leu Ala Pro Lys Ala Gln
1 5

<210> 108
<211> 223
<212> PRT
<213> Macaca fascicularis

<400> 108
Met Ala Cys Leu Gly Phe Gln Arg His Lys Ala Arg Leu Asn Leu Ala
1 5 10 15

Thr Arg Thr Arg Pro Tyr Thr Leu Leu Phe Ser Leu Leu Phe Ile Pro
20 25 30

Val Phe Ser Lys Ala Met His Val Ala Gln Pro Ala Val Val Leu Ala
35 40 45

Asn Ser Arg Gly Ile Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly
50 55 60

Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln
65 70 75 80

Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr
85 90 95

Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val
100 105 110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile
115 120 125

Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Tyr Met Gly Ile Gly
130 135 140

Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145 150 155 160

Asp Phe Leu Leu Trp Ile Leu Ala Ala Val Ser Ser Gly Leu Phe Phe
165 170 175

```
Tyr Ser Phe Leu Leu Thr Ala Val Ser Leu Ser Lys Met Leu Lys Lys
            180                 185                 190

Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu
        195                 200                 205

Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
    210                 215                 220

<210> 109
<211> 223
<212> PRT
<213> Mus musculus

<400> 109
Met Ala Cys Leu Gly Leu Arg Arg Tyr Lys Ala Gln Leu Gln Leu Pro
1               5                   10                  15

Ser Arg Thr Trp Pro Phe Val Ala Leu Leu Thr Leu Leu Phe Ile Pro
            20                  25                  30

Val Phe Ser Glu Ala Ile Gln Val Thr Gln Pro Ser Val Val Leu Ala
        35                  40                  45

Ser Ser His Gly Val Ala Ser Phe Pro Cys Glu Tyr Ser Pro Ser His
    50                  55                  60

Asn Thr Asp Glu Val Arg Val Thr Val Leu Arg Gln Thr Asn Asp Gln
65                  70                  75                  80

Met Thr Glu Val Cys Ala Thr Thr Phe Thr Glu Lys Asn Thr Val Gly
                85                  90                  95

Phe Leu Asp Tyr Pro Phe Cys Ser Gly Thr Phe Asn Glu Ser Arg Val
            100                 105                 110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Val Asp Thr Gly Leu Tyr Leu
        115                 120                 125

Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Phe Val Gly Met Gly
    130                 135                 140

Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145                 150                 155                 160

Asp Phe Leu Leu Trp Ile Leu Val Ala Val Ser Leu Gly Leu Phe Phe
                165                 170                 175

Tyr Ser Phe Leu Val Ser Ala Val Ser Leu Ser Lys Met Leu Lys Lys
            180                 185                 190
```

```
Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu
        195                 200                 205

Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
    210                 215                 220

<210> 110
<211> 223
<212> PRT
<213> Rattus norvegicus

<400> 110
Met Ala Cys Leu Gly Leu Gln Arg Tyr Lys Thr His Leu Gln Leu Pro
1               5                   10                  15

Ser Arg Thr Trp Pro Phe Gly Val Leu Leu Ser Leu Leu Phe Ile Pro
            20                  25                  30

Ile Phe Ser Glu Ala Ile Gln Val Thr Gln Pro Ser Val Val Leu Ala
        35                  40                  45

Ser Ser His Gly Val Ala Ser Phe Pro Cys Glu Tyr Ala Ser Ser His
    50                  55                  60

Asn Thr Asp Glu Val Arg Val Thr Val Leu Arg Gln Thr Asn Asp Gln
65                  70                  75                  80

Val Thr Glu Val Cys Ala Thr Thr Phe Thr Val Lys Asn Thr Leu Gly
                85                  90                  95

Phe Leu Asp Asp Pro Phe Cys Ser Gly Thr Phe Asn Glu Ser Arg Val
            100                 105                 110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Ala Asp Thr Gly Leu Tyr Phe
        115                 120                 125

Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Phe Val Gly Met Gly
    130                 135                 140

Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145                 150                 155                 160

Asp Phe Leu Leu Trp Ile Leu Ala Ala Val Ser Ser Gly Leu Phe Phe
                165                 170                 175

Tyr Ser Phe Leu Val Thr Ala Val Ser Leu Asn Arg Thr Leu Lys Lys
            180                 185                 190
```

```
Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu
        195                 200                 205

Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
    210                 215                 220

<210> 111
<211> 220
<212> PRT
<213> Homo sapiens

<400> 111
Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1               5                   10                  15

Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
            20                  25                  30

Asp Asn Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser
        35                  40                  45

Arg Glu Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu
    50                  55                  60

Val Cys Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser
65                  70                  75                  80

Lys Thr Gly Phe Asn Cys Asp Gly Lys Leu Gly Asn Glu Ser Val Thr
                85                  90                  95

Phe Tyr Leu Gln Asn Leu Tyr Val Asn Gln Thr Asp Ile Tyr Phe Cys
            100                 105                 110

Lys Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser
        115                 120                 125

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
    130                 135                 140

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
145                 150                 155                 160

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
                165                 170                 175

Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
            180                 185                 190

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
        195                 200                 205
```

```
Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
    210                 215                 220


<210> 112
<211> 199
<212> PRT
<213> Homo sapiens

<400> 112
Met Lys Ser Gly Leu Trp Tyr Phe Phe Leu Phe Cys Leu Arg Ile Lys
1               5                  10                  15


Val Leu Thr Gly Glu Ile Asn Gly Ser Ala Asn Tyr Glu Met Phe Ile
            20                  25                  30


Phe His Asn Gly Gly Val Gln Ile Leu Cys Lys Tyr Pro Asp Ile Val
        35                  40                  45


Gln Gln Phe Lys Met Gln Leu Leu Lys Gly Gly Gln Ile Leu Cys Asp
    50                  55                  60


Leu Thr Lys Thr Lys Gly Ser Gly Asn Thr Val Ser Ile Lys Ser Leu
65                  70                  75                  80


Lys Phe Cys His Ser Gln Leu Ser Asn Asn Ser Val Ser Phe Phe Leu
                85                  90                  95


Tyr Asn Leu Asp His Ser His Ala Asn Tyr Tyr Phe Cys Asn Leu Ser
            100                 105                 110


Ile Phe Asp Pro Pro Pro Phe Lys Val Thr Leu Thr Gly Gly Tyr Leu
        115                 120                 125


His Ile Tyr Glu Ser Gln Leu Cys Cys Gln Leu Lys Phe Trp Leu Pro
    130                 135                 140


Ile Gly Cys Ala Ala Phe Val Val Val Cys Ile Leu Gly Cys Ile Leu
145                 150                 155                 160


Ile Cys Trp Leu Thr Lys Lys Lys Tyr Ser Ser Ser Val His Asp Pro
                165                 170                 175


Asn Gly Glu Tyr Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser
            180                 185                 190


Arg Leu Thr Asp Val Thr Leu
        195
```

<210> 113
<211> 289
<212> PRT
<213> Homo sapiens

<400> 113
Met Lys Thr Leu Pro Ala Met Leu Gly Thr Gly Lys Leu Phe Trp Val
1 5 10 15

Phe Phe Leu Ile Pro Tyr Leu Asp Ile Trp Asn Ile His Gly Lys Glu
20 25 30

Ser Cys Asp Val Gln Leu Tyr Ile Lys Arg Gln Ser Glu His Ser Ile
35 40 45

Leu Ala Gly Asp Pro Phe Glu Leu Glu Cys Pro Val Lys Tyr Cys Ala
50 55 60

Asn Arg Pro His Val Thr Trp Cys Lys Leu Asn Gly Thr Thr Cys Val
65 70 75 80

Lys Leu Glu Asp Arg Gln Thr Ser Trp Lys Glu Glu Lys Asn Ile Ser
85 90 95

Phe Phe Ile Leu His Phe Glu Pro Val Leu Pro Asn Asp Asn Gly Ser
100 105 110

Tyr Arg Cys Ser Ala Asn Phe Gln Ser Asn Leu Ile Glu Ser His Ser
115 120 125

Thr Thr Leu Tyr Val Thr Asp Val Lys Ser Ala Ser Glu Arg Pro Ser
130 135 140

Lys Asp Glu Met Ala Ser Arg Pro Trp Leu Leu Tyr Arg Leu Leu Pro
145 150 155 160

Leu Gly Gly Leu Pro Leu Leu Ile Thr Thr Cys Phe Cys Leu Phe Cys
165 170 175

Cys Leu Arg Arg His Gln Gly Lys Gln Asn Glu Leu Ser Asp Thr Ala
180 185 190

Gly Arg Glu Ile Asn Leu Val Asp Ala His Leu Lys Ser Glu Gln Thr
195 200 205

Glu Ala Ser Thr Arg Gln Asn Ser Gln Val Leu Leu Ser Glu Thr Gly
210 215 220

Ile Tyr Asp Asn Asp Pro Asp Leu Cys Phe Arg Met Gln Glu Gly Ser
225 230 235 240

Glu Val Tyr Ser Asn Pro Cys Leu Glu Glu Asn Lys Pro Gly Ile Val
245 250 255

Tyr Ala Ser Leu Asn His Ser Val Ile Gly Pro Asn Ser Arg Leu Ala
260 265 270

Arg Asn Val Lys Glu Ala Pro Thr Glu Tyr Ala Ser Ile Cys Val Arg
275 280 285

Ser

<210> 114

<400> 114
000

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

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> VARIANT
<222> (8)..(8)
<223> /replace="Asn"

<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 115
Val Gly Leu Met Gly Pro Phe Asp Ile
1 5

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

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>

<221> VARIANT
<222> (5)..(5)
<223> /replace="Leu"

<220>
<221> VARIANT
<222> (13)..(13)
<223> /replace="Gln"

<220>
<221> VARIANT
<222> (19)..(19)
<223> /replace="Thr"

<220>
<221> VARIANT
<222> (33)..(33)
<223> /replace="Ala"

<220>
<221> VARIANT
<222> (35)..(35)
<223> /replace="Ser"

<220>
<221> VARIANT
<222> (46)..(46)
<223> /replace="Val"

<220>
<221> VARIANT
<222> (78)..(78)
<223> /replace="Thr"

<220>
<221> VARIANT
<222> (106)..(106)
<223> /replace="Asn"

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 116
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

65 70 75 80

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

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

Met Val Thr Val Ser Ser
115

<210> 117
<211> 443
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 117
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

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

Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

```
Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys
    210                 215                 220

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
225                 230                 235                 240

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
            260                 265                 270

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

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
    290                 295                 300

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305                 310                 315                 320

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
                325                 330                 335

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

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
        355                 360                 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
    370                 375                 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
385                 390                 395                 400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
                405                 410                 415
```

```
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
            420                 425                 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440

<210> 118
<211> 325
<212> PRT
<213> Homo sapiens

<400> 118
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Leu Ser Pro Gly
                325
```

<210> 119

<400> 119
000

<210> 120
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 120

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

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

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

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

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

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

Ala Ser Asn Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
        115                 120                 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                165                 170                 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
            180                 185                 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
        195                 200                 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
    210                 215                 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225                 230                 235                 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
                245                 250                 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
            260                 265                 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
        275                 280                 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
    290                 295                 300
```

```
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305                 310                 315                 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
                325                 330                 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
            340                 345                 350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
        355                 360                 365

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
    370                 375                 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385                 390                 395                 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
                405                 410                 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
            420                 425                 430

Ser Leu Ser Leu Ser Leu Gly
        435
```