

WHAT IS CLAIMED

- 1) An isolated antagonistic antibody specifically binding PD-1 or an antigen-binding portion thereof, comprising a heavy chain complementarity determining region 1 (HCDR1), a HCDR2 and a HCDR3 of SEQ ID NOs: 82, 83 and 84, respectively and a light chain complementarity determining region 1 (LCDR1), a LCDR2 and a LCDR3 of SEQ ID NOs: 86, 87 and 88, respectively.
- 2) The antibody or the antigen-binding portion thereof of claim 1, wherein the antibody has one, two, three, four or five of the following properties:
 - a) enhances an activation of antigen specific CD4⁺ or CD8⁺ T cells in a dose dependent manner, wherein the activation is measured using a cytomegalovirus antigen recall assay (CMV assay) as described in Example 1;
 - b) binds human PD-1 with an equilibrium dissociation constant (K_D) of less than about 100 nM, wherein the K_D is measured using ProteOn XPR36 system at +25°C;
 - c) binds human PD-1 with the K_D of less than about 1 nM, wherein the K_D is measured using ProteOn XPR36 system at +25°C;
 - d) binds cynomolgus PD-1 of SEQ ID NO: 3 with the K_D of less than about 100 nM, wherein the K_D is measured using ProteOn XPR36 system at +25°C; or
 - e) binds cynomolgus PD-1 of SEQ ID NO: 3 with the K_D of less than about 1 nM, wherein the K_D is measured using ProteOn XPR36 system at +25°C.
- 3) The antibody or the antigen-binding portion thereof of claim 1 or 2, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:
 - a) 10, 13, 16, 20, 26 and 31, respectively;
 - b) 10, 13, 16, 21, 26 and 32, respectively;
 - c) 10, 14, 16, 22, 27 and 33, respectively;
 - d) 10, 14, 16, 22, 26 and 34, respectively;
 - e) 10, 14, 16, 23, 28 and 35, respectively;
 - f) 10, 13, 17, 20, 26 and 31, respectively;
 - g) 10, 13, 17, 20, 26 and 36, respectively;
 - h) 10, 13, 17, 21, 26 and 32, respectively;
 - i) 10, 13, 17, 21, 27 and 37, respectively;
 - j) 10, 13, 17, 23, 26 and 32, respectively;
 - k) 10, 14, 17, 23, 28 and 35, respectively;

- l) 10, 14, 17, 22, 26 and 34, respectively; or
 - m) 10, 14, 17, 23, 26 and 32, respectively.
- 4) The antibody or the antigen-binding portion thereof of any of the claims 1-3, comprising
- a) a heavy chain variable region (VH) of SEQ ID NOs: 41, 42, 43 or 48;
 - b) a light chain variable region (VL) of SEQ ID NOs: 49, 50, 51, 52, 53, 54, 55 or 56; or
 - c) the VH of SEQ ID NOs: 41, 42, 43 or 48 and the VL of SEQ ID NOs: 49, 50, 51, 52, 53, 54, 55 or 56.
- 5) The antibody or the antigen-binding portion thereof of any of the claims 1-4, comprising
- a) the VH of SEQ ID NO: 41 and the VL of SEQ ID NO: 49;
 - b) the VH of SEQ ID NO: 41 and the VL of SEQ ID NO: 50;
 - c) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 51;
 - d) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 52;
 - e) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 53;
 - f) the VH of SEQ ID NO: 43 and the VL of SEQ ID NO: 49;
 - g) the VH of SEQ ID NO: 43 and the VL of SEQ ID NO: 54;
 - h) the VH of SEQ ID NO: 43 and the VL of SEQ ID NO: 50;
 - i) the VH of SEQ ID NO: 43 and the VL of SEQ ID NO: 55;
 - j) the VH of SEQ ID NO: 43 and the VL of SEQ ID NO: 56;
 - k) the VH of SEQ ID NO: 48 and the VL of SEQ ID NO: 53;
 - l) the VH of SEQ ID NO: 48 and the VL of SEQ ID NO: 52; or
 - m) the VH of SEQ ID NO: 48 and the VL of SEQ ID NO: 56.
- 6) The antibody or the antigen-binding portion thereof of any of the claims 1-5, wherein the antibody is human or humanized.
- 7) The antibody or the antigen-binding portion thereof of any of the claims 1-6, wherein the antibody is
- a) an IgG1 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in an Fc region;
 - b) an IgG2 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in the Fc region;
 - c) an IgG3 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in the Fc region;

- d) an IgG4 isotype, optionally comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in the Fc region;
 - e) an IgG1 isotype comprising L234A, L235A, G237A, P238S, H268A, A330S and P331S substitutions;
 - f) an IgG2 isotype comprising V234A, G237A, P238S, H268A, V309L, A330S and P331S substitutions;
 - g) an IgG4 isotype comprising F234A, L235A, G237A, P238S and Q268A substitutions;
 - h) an IgG1 isotype comprising L234A, L235A or L234A and L235A substitutions;
 - i) an IgG4 isotype comprising F234A, L235A or F234A and L235A substitutions;
 - j) an IgG2 isotype comprising a V234A substitution;
 - k) an IgG4 isotype comprising a S228P substitution; or
 - l) an IgG4 isotype comprising S228P, F234A and L235A substitutions, wherein residue numbering is according to the EU Index.
- 8) The antibody or the antigen-binding portion thereof of any of the claims 1-7, comprising
- a) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 10, 14, 17, 23, 26 and 32, respectively;
 - b) the VH of SEQ ID NO: 48 and the VL of SEQ ID NO: 56; and/or
 - c) a heavy chain (HC) of SEQ ID NO: 72 and a light chain (LC) of SEQ ID NO: 73.
- 9) The antibody or the antigen-binding portion thereof of any of the claims 1-8, wherein the antibody is a bispecific antibody, optionally binding PD-L1 (SEQ ID NO: 5), PD-L2 (SEQ ID NO: 8), LAG-3 (SEQ ID NO: 293), TIM-3 (SEQ ID NO: 138), CEACAM-1 (SEQ ID NO: 296), CEACAM-5 (SEQ ID NO: 307), OX-40 (SEQ ID NO: 279), GITR (SEQ ID NO: 271), CD27 (SEQ ID NO: 280), VISTA (SEQ ID NO: 286), CD137 (SEQ ID NO: 281), TIGIT (SEQ ID NO: 301) or CTLA-4 (SEQ ID NO: 292).
- 10) A pharmaceutical composition comprising the antibody or the antigen-binding portion thereof of any of the claims 1-9 and a pharmaceutically accepted carrier.
- 11) A polynucleotide
- a) encoding the VH of SEQ ID NOs: 41, 42, 43 or 48;
 - b) encoding the VL of SEQ ID NOs: 49, 50, 51, 52, 53, 54, 55 or 56;
 - c) encoding the VH of SEQ ID NOs: 41, 42, 43 or 48 and the VL of SEQ ID NOs: 49, 50, 51, 52, 53, 54, 55 or 56; or
 - d) comprising the polynucleotide sequence of SEQ ID NOs: 196 or 197.

- 12) A vector comprising the polynucleotide of claim 11.
- 13) A host cell comprising the vector of claim 12.
- 14) A method of producing an antagonistic antibody specifically binding PD-1 or an antigen-binding portion thereof, comprising culturing the host cell of claim 13 in conditions that the antibody of the antigen-binding portion thereof is expressed, and recovering the antibody or the antigen-binding portion thereof produced by the host cell.
- 15) An isolated antagonistic antibody specifically binding PD-1 or an antigen-binding portion thereof, comprising
 - a) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 66, 67, 68, 69, 70 and 71, respectively;
 - b) the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65; and/or
 - c) the HC of SEQ ID NO: 74 and the LC of SEQ ID NO: 75.
- 16) A pharmaceutical composition comprising the antibody or the antigen-binding portion thereof of claim 15 and a pharmaceutically accepted carrier.
- 17) A polynucleotide
 - a) encoding the VH of SEQ ID NO: 64;
 - b) encoding the VL of SEQ ID NO: 65;
 - c) encoding the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65; or
 - d) comprising the polynucleotide sequence of SEQ ID NOs: 198 or 199.
- 18) A vector comprising the polynucleotide of claim 17.
- 19) A host cell comprising the vector of claim 18.
- 20) A method of producing an antagonistic antibody specifically binding PD-1 or an antigen-binding portion thereof, comprising culturing the host cell of claim 19 in conditions that the antibody or the antigen-binding portion thereof is expressed, and recovering the antibody or the antigen-binding portion thereof produced by the host cell.
- 21) A method of treating a cancer in a subject, comprising administering a therapeutically effective amount of the isolated antibody or the antigen-binding portion thereof of any of the claims 1-9 or the pharmaceutical composition of claim 10 to the subject in need thereof for a time sufficient to treat the cancer.
- 22) A method of treating a cancer in a subject, comprising administering a therapeutically effective amount of the isolated antibody or the antigen-binding portion thereof of claim 15 or the pharmaceutical composition of claim 16 to the subject in need thereof for a time sufficient to treat the cancer.

- 23) The method of claim 21 or 22, wherein the cancer is a solid tumor or a hematological malignancy.
- 24) The method of any of the claims 21-23, wherein the solid tumor is a melanoma, a lung cancer, a squamous non-small cell lung cancer (NSCLC), a non-squamous NSCLC, a colorectal cancer, a prostate cancer, a castration-resistant prostate cancer, a stomach cancer, an ovarian cancer, a gastric cancer, a liver cancer, a pancreatic cancer, a thyroid cancer, a squamous cell carcinoma of the head and neck, carcinomas of the esophagus or gastrointestinal tract, a breast cancer, a fallopian tube cancer, a brain cancer, an urethral cancer, a genitourinary cancer, an endometriosis, a cervical cancer or a metastatic lesion of the cancer.
- 25) The method of any of the claims 21-23, wherein the hematological malignancy is a lymphoma, a myeloma or a leukemia.
- 26) A method of enhancing an immune response in a subject, comprising administering a therapeutically effective amount of the antibody or the antigen-binding portion thereof of any of the claims 1-9 or 15 or a pharmaceutical composition of claim 10 or 16 to the subject in need thereof for a time sufficient to enhance the immune response.
- 27) The method of claim 26, wherein the subject has a cancer or a viral infection.
- 28) The method of any of the claims 21-27, wherein the antibody or the antigen-binding portion thereof is administered in combination with a second therapeutic agent.
- 29) The method of any of the claims 21-28, wherein the second therapeutic agent is
- a) a standard of care drug for treatment of the solid tumor or the hematological malignancy;
 - b) an agonist of a T cell activating molecule;
 - c) an agonist of CD86 (SEQ ID NO: 264), CD80 (SEQ ID NO: 265), CD28 (SEQ ID NO: 266), ICOS (SEQ ID NO: 267), ICOS ligand (SEQ ID NO: 268), TMIGD2 (SEQ ID NO: 269), CD40 (SEQ ID NO: 270), GITR (SEQ ID NO: 271), 4-1BB ligand (SEQ ID NO: 271), OX40 ligand (SEQ ID NO: 272), CD70 (SEQ ID NO: 274), CD40L (SEQ ID NO: 275), TNFRSF25 (SEQ ID NO: 264), LIGHT (SEQ ID NO: 277), GITR ligand (SEQ ID NO: 278), OX-40 (SEQ ID NO: 279), CD27 (SEQ ID NO: 280), CD137 (SEQ ID NO: 281), NKG2D (SEQ ID NO: 282), CD48 (SEQ ID NO: 283), CD226 (SEQ ID NO: 284), or MICA (SEQ ID NO: 285);
 - d) an inhibitor of a T cell inhibitory molecule;
 - e) an inhibitor of PD-1 (SEQ ID NO: 1), PD-L1 (SEQ ID NO: 5), PD-L2 (SEQ ID NO: 8), VISTA (SEQ ID NO: 286), BTNL2 (SEQ ID NO: 287), B7-H3 (SEQ ID

NO: 288), B7-H4 (SEQ ID NO: 289), HVEM (SEQ ID NO: 290), HHLA2 (SEQ ID NO: 291), CTLA-4 (SEQ ID NO: 292), LAG-3 (SEQ ID NO: 293), TIM-3 (SEQ ID NO: 138), BTLA (SEQ ID NO: 294), CD160 (SEQ ID NO: 295), CEACAM-1 (SEQ ID NO: 296), LAIR1 (SEQ ID NO: 297), TGFβ (SEQ ID NO: 298), IL-10 (SEQ ID NO: 299), CD96 (SEQ ID NO: 300), TIGIT (SEQ ID NO: 301), NKG2A (SEQ ID NO: 302), CD112 (SEQ ID NO: 303), CD47 (SEQ ID NO: 304), SIRPA (SEQ ID NO: 305) or CD244 (SEQ ID NO: 306);

- f) an antagonistic antibody specifically binding TIM-3;
 - g) an antagonistic antibody specifically binding TIM-3 comprising the VH and the VL of
 - i) SEQ ID NOs: 145 and 155, respectively;
 - ii) SEQ ID NOs: 146 and 156, respectively;
 - iii) SEQ ID NOs: 148 and 157, respectively;
 - iv) SEQ ID NOs: 147 and 155, respectively;
 - v) SEQ ID NOs: 149 and 158, respectively;
 - vi) SEQ ID NOs: 150 and 159, respectively;
 - vii) SEQ ID NOs: 151 and 160, respectively;
 - viii) SEQ ID NOs: 152 and 161, respectively;
 - ix) SEQ ID NOs: 153 and 162, respectively;
 - x) SEQ ID NOs: 154 and 163, respectively; or
 - xi) SEQ ID NOs: 172 and 173, respectively;
 - h) a fibroblast growth factor receptor (FGFR) inhibitor;
 - i) a vaccine;
 - j) an agonistic antibody specifically binding GITR;
 - k) an agonistic antibody specifically binding OX40;
 - l) an agonistic antibody specifically binding OX40, comprising the VH and the VL of SEQ ID NOs: 309 and 310, respectively;
 - m) an agonistic antibody specifically binding OX40, comprising the VH and the VL of SEQ ID NOs: 311 and 312, respectively;
 - n) an agonistic antibody specifically binding CD137;
 - o) radiation therapy; or
 - p) surgery.
- 30) The method of any of the claims 21-29, wherein the antibody or the antigen-binding portion thereof and the second therapeutic agent are administered simultaneously, sequentially or separately.

- 31) An anti-idiotypic antibody binding to the antibody or the antigen-binding portion thereof of any of the claims 1-9 or 15.
- 32) A kit comprising the antibody of any of the claims 1-9 or 15.