

CLAIMS

1. An antibody that binds specifically to both PD1 and VEGFR2 or an antigen-binding portion of the antibody, wherein the antibody or antigen-binding portion comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein
- 5 (a) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGSNKYYVDSVKG (SEQ ID NO: 42) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of RASQESGIWLS (SEQ ID NO: 39), LCDR2 of TATSLAD (SEQ ID NO: 5) and LCDR3 of
- 10 QQVSVTPFT (SEQ ID NO:11);
- (b) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGSNKYYVDSVKG (SEQ ID NO: 42) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of RASQESGIWLS (SEQ ID NO: 39), LCDR2 of AASSLQS (SEQ ID NO: 43) and LCDR3 of
- 15 QQVSVTPFT (SEQ ID NO:11);
- (c) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQESGIWLS (SEQ ID NO:8), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of
- 20 QQVSVTPFT (SEQ ID NO:11);
- (d) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQGIGPWLS (SEQ ID NO:4), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of
- 25 QQVYSIPWT (SEQ ID NO:6);
- (e) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQPLGIWLS (SEQ ID NO:7), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of
- 30 QQVYSIPWT (SEQ ID NO:6);
- (f) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQESGIWLS (SEQ ID NO:8), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of
- 35 QQVYSIPWT (SEQ ID NO:6);
- (g) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY

(SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQTIGTWLT (SEQ ID NO:9), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of QQVAELPFG (SEQ ID NO:10);

5 (h) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQTIGTWLT (SEQ ID NO:9), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of QQVSVTPFT (SEQ ID NO:11);

10 (i) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQGIGPWLS (SEQ ID NO:4), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of QQVAELPFG (SEQ ID NO:10);

15 (j) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQPLGIWLS (SEQ ID NO:7), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of QQVAELPFG (SEQ ID NO:10);

20 (k) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQESGIWLG (SEQ ID NO:12), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of QQVAELPFG (SEQ ID NO:10);

25 (l) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQGIGPWLS (SEQ ID NO:4), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of QQVSVTPFT (SEQ ID NO:11);

30 (m) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO:2) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of LASQPLGIWLS (SEQ ID NO:7), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of QQVSVTPFT (SEQ ID NO:11);

35 (n) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYPDSVKG (SEQ ID NO: 38) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of

RASQESGIWLS (SEQ ID NO: 39), LCDR2 of TATSLAD (SEQ ID NO:5) and LCDR3 of QQVSVTPFT (SEQ ID NO:11);

(o) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYVDSVKG (SEQ ID NO: 38) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of RASQESGIWLS (SEQ ID NO: 39), LCDR2 of TASSLAD (SEQ ID NO: 40) and LCDR3 of QQVSVTPFT (SEQ ID NO:11);

(p) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYVDSVKG (SEQ ID NO: 38) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of RASQESGIWLS (SEQ ID NO: 39), LCDR2 of AASSLAD (SEQ ID NO: 41) and LCDR3 of QQVSVTPFT (SEQ ID NO:11);

(q) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGANTYYVDSVKG (SEQ ID NO: 38) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of RASQESGIWLS (SEQ ID NO: 39), LCDR2 of AASSLQS (SEQ ID NO: 43) and LCDR3 of QQVSVTPFT (SEQ ID NO:11);

(r) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGSNKYYVDSVKG (SEQ ID NO: 42) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of RASQESGIWLS (SEQ ID NO: 39), LCDR2 of TASSLAD (SEQ ID NO: 40) and LCDR3 of QQVSVTPFT (SEQ ID NO:11);

(s) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGSNKYYVDSVKG (SEQ ID NO: 42) and HCDR3 of QLYYFDY (SEQ ID NO:3); and the VL region amino acid sequence comprises LCDR1 of RASQESGIWLS (SEQ ID NO: 39), LCDR2 of AASSLAD (SEQ ID NO: 41) and LCDR3 of QQVSVTPFT (SEQ ID NO:11); or

(t) the VH region amino acid sequence comprises HCDR1 of GFTFSSYMMS (SEQ ID NO:1), HCDR2 of TISGGGSNKYYVDSVKG (SEQ ID NO:42) and HCDR3 of QVYYFDY (SEQ ID NO:64); and the VL region amino acid sequence comprises LCDR1 of RASQESGIWLS (SEQ ID NO: 39), LCDR2 of AASSLQS (SEQ ID NO: 43) and LCDR3 of QQVSVTPFT (SEQ ID NO:11).

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

(a) the VH region amino acid sequence comprises SEQ ID NO:49 and the VL region amino acid sequence comprises SEQ ID NO:44;

- (b) the VH region amino acid sequence comprises SEQ ID NO:49 and the VL region amino acid sequence comprises SEQ ID NO:47;
- (c) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:24;
- 5 (d) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:14;
- (e) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:15;
- (f) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:16;
- 10 (g) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:17;
- (h) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:18;
- 15 (i) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:19;
- (j) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:20;
- (k) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:21;
- 20 (l) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:22;
- (m) the VH region amino acid sequence comprises SEQ ID NO:13 and the VL region amino acid sequence comprises SEQ ID NO:23;
- 25 (n) the VH region amino acid sequence comprises SEQ ID NO:48 and the VL region amino acid sequence comprises SEQ ID NO:44;
- (o) the VH region amino acid sequence comprises SEQ ID NO:48 and the VL region amino acid sequence comprises SEQ ID NO:45;
- (p) the VH region amino acid sequence comprises SEQ ID NO:48 and the VL region amino acid sequence comprises SEQ ID NO:46;
- 30 (q) the VH region amino acid sequence comprises SEQ ID NO:48 and the VL region amino acid sequence comprises SEQ ID NO:47;
- (r) the VH region amino acid sequence comprises SEQ ID NO:49 and the VL region amino acid sequence comprises SEQ ID NO:45;
- 35 (s) the VH region amino acid sequence comprises SEQ ID NO:49 and the VL region amino acid sequence comprises SEQ ID NO:46; or

(t) the VH region amino acid sequence comprises SEQ ID NO:73 and the VL region amino acid sequence comprises SEQ ID NO:47.

3. The antibody or antigen-binding portion of claim 1 or 2, wherein the antibody or antigen-binding portion is capable of antagonizing both the PD1-PDL1 and the VEGFR2-VEGF signaling pathways.

4. An antibody that binds specifically to both PD1 and VEGFR2 or an antigen-binding portion of the antibody, wherein the antibody or antigen-binding portion cross-competes for binding to both PD1 and VEGFR2 with the antibody or antigen-binding portion of any one of claims 1-3; and

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

(b) binds specifically to human PD1, cynomolgus PD1, human VEGFR2 and rhesus VEGFR2; and

(c) antagonizes binding of human PD1 to human PD-L1 and antagonizes the signalling of human VEGFR2 in response to human VEGF.

5. The antibody or antigen-binding portion of any one of claims 1-4, wherein the antibody is ~~human~~, humanized or chimeric.

6. The antibody or antigen-binding portion of any one of claims 1-5, wherein the VH region, the VL region, or both the VH and the VL region comprise one or more human framework region amino acid sequences.

7. The antibody or antigen-binding portion of any one of claims 1-6, wherein the VH region, the VL region, or both the VH and the VL region comprise a human variable region framework scaffold amino acid sequence into which the CDRs have been inserted.

8. The antibody or antigen-binding portion of claim 1 or 3, wherein the VH region comprises an IGHV3-7 human germline scaffold amino acid sequence into which the HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted.

9. The antibody or antigen-binding portion of any one of claims 1, 3 and 8, wherein the VL region comprises an IGKV1-39 human germline scaffold amino acid sequence into which the LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted.

10. The antibody or antigen-binding portion of any one of claims 1-9, wherein the antibody or antigen-binding portion comprises an immunoglobulin constant region.

11. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.

12. The antibody or antigen-binding portion of claim 11, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.

13. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is immunologically inert.

14. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A or a wild-type human IgG2 constant region.

15. The antibody or antigen-binding portion of claim 13, wherein the immunoglobulin constant region comprises any one of SEQ ID NOs:25-31.

16. The antibody or antigen-binding portion of any one of claims 1-15, wherein the antibody or antigen-binding portion is an Fab, an Fab', an F(ab')₂, an Fd, an Fv, an scFv, a maxibody, a minibody, an intrabody, a diabody, a triabody, a tetrabody, or a bis-scFv.

17. The antibody or antigen-binding portion of any one of claims 1-16, wherein the antibody or antigen-binding portion is monoclonal.

18. The antibody or antigen-binding portion of any one of claims 1-17, wherein the antibody or antigen-binding portion is ~~a tetrameric antibody, a tetravalent antibody or a multispecific antibody.~~

19. The antibody or antigen-binding portion of any one of claims 1-18, wherein the antibody or antigen-binding portion binds specifically to (a) human PD1 or (b) human PD1 and cynomolgus PD1 or (c) human PD1 and rhesus PD1 or (d) human PD1, cynomolgus PD1 and rhesus PD1.

20. The antibody or antigen-binding portion of any one of claims 1-19, wherein the antibody or antigen-binding portion binds specifically to (a) human VEGFR2 or (b) human VEGFR2 and cynomolgus VEGFR2 or (c) human VEGFR2 and rhesus VEGFR2 or (d) human VEGFR2, cynomolgus VEGFR2 and rhesus VEGFR2 .
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21. An immunoconjugate comprising the antibody or antigen-binding portion of any one of claims 1-20 linked to a therapeutic agent.
22. The immunoconjugate of claim 21, wherein the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, an anti-angiogenic agent, an antiproliferative agent, a pro-apoptotic agent, a cytostatic enzyme, a cytolytic enzymes, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.
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23. A pharmaceutical composition comprising the antibody or antigen-binding portion of any one of claims 1-20 or the immunoconjugate of claim 21 or 22, and a pharmaceutically acceptable carrier, diluent or excipient.
- 15
24. A nucleic acid molecule encoding
- 20 (a) the VH region amino acid sequence;
(b) the VL region amino acid sequence; or
(c) both the VH and the VL region amino acid sequences
of the antibody or antigen-binding portion of any one of claims 1-20.
- 25
25. An expression vector comprising the nucleic acid molecule of claim 24.
26. A recombinant host cell comprising the nucleic acid molecule of claim 24 or the expression vector of claim 25.
- 30
27. A method of producing an anti-PD1 antibody or an antigen-binding portion thereof, the method comprising:
- culturing ~~a-the~~ recombinant host cell ~~comprising the expression vector~~ of claim ~~25~~
~~26~~ under conditions whereby the nucleic acid molecule is expressed, thereby producing the antibody or antigen-binding portion; and
- 35 isolating the antibody or antigen-binding portion from the host cell or culture.

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

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

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

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

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

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

34. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 33, wherein the cancer is pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical

cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

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

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

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