

CLAIMS

1. An anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region,
5 wherein
 - (a) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39) and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of
10 QQSYSTPWT (SEQ ID NO: 43);
 - (b) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39) and HCDR3 of QVYYFDY (SEQ ID NO: 44); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of
15 QQSYSTPWT (SEQ ID NO: 43);
 - (c) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39) and HCDR3 of QLYFFDY (SEQ ID NO: 45); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of
20 QQSYSTPWT (SEQ ID NO: 43);
 - (d) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39) and HCDR3 of QLYAFDY (SEQ ID NO: 46); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of
25 QQSYSTPWT (SEQ ID NO: 43);
 - (e) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSETYYVDSVKG (SEQ ID NO: 48) and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42) and LCDR3 of
30 QQSYSIPWT (SEQ ID NO: 47);
 - (f) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGAEKYYVDSVKG (SEQ ID NO: 49) and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQD (SEQ ID NO: 50) and LCDR3 of
35 QQSYSTPWT (SEQ ID NO: 43);
 - (g) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSETYYVDSVKG (SEQ ID NO: 48), and HCDR3 of

QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42), and LCDR3 of QQSYSIPWT (SEQ ID NO: 47);

5 (h) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGAEKYYVDSVKG (SEQ ID NO: 49), and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQD (SEQ ID NO: 50), and LCDR3 of QQSYSTPWT (SEQ ID NO: 43);

10 (i) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSNTYYVDSVKG (SEQ ID NO: 51), and HCDR3 of QLYGFDY (SEQ ID NO: 40); and the VL region amino acid sequence comprises LCDR1 of RASQSISTWLN (SEQ ID NO: 52), LCDR2 of AASSLAS (SEQ ID NO: 53), and LCDR3 of QQSYSTPWT (SEQ ID NO: 43);

15 (j) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39), and HCDR3 of QVYYFDY (SEQ ID NO: 44); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLHS (SEQ ID NO: 54), and LCDR3 of QQSYSTPWT (SEQ ID NO: 43); or

20 (k) the VH region amino acid sequence comprises HCDR1 of GFTFSSYLMS (SEQ ID NO: 38), HCDR2 of VATISGGGSEKYYVDSVKG (SEQ ID NO: 39), and HCDR3 of QVYYFDY (SEQ ID NO: 44); and the VL region amino acid sequence comprises LCDR1 of RASQSISSWLN (SEQ ID NO: 41), LCDR2 of AASSLQS (SEQ ID NO: 42), and LCDR3 of QQSYSTPWT (SEQ ID NO: 43).

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

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

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

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

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

35 (e) the VH region amino acid sequence comprises SEQ ID NO:9 and the VL region amino acid sequence comprises SEQ ID NO:10; or

(f) the VH region amino acid sequence comprises SEQ ID NO:11 and the VL region amino acid sequence comprises SEQ ID NO:12.

3. An anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable (VL) region comprising LCDR1, LCDR2, and LCDR3, wherein
- 5 (a) the HCDR1 comprises the amino acid sequence G-F-T-F-S-S-Y-X₁-M-S, wherein X₁ is L or any other amino acid (SEQ ID NO: 26);
- (b) the HCDR2 comprises the amino acid sequence X₁-A-X₂-I-S-G-G-X₃-X₄-X₅-Y-Y-X₆-D-S-V-K-G, wherein X₁ is V or a conservative substitution of V, X₂ is T or N, X₃ is A or S, X₄ is E or N, X₅ is T or K, and X₆ is P or V (SEQ ID NO: 27);
- 10 (c) the HCDR3 comprises the amino acid sequence X₁-X₂-X₃-X₄-X₅-D-Y, wherein X₁ is Q or any other amino acid (for example, T, L, M, or N), X₂ is L or any other amino acid (for example, G, K, M, Q, S, or V), X₃ is Y or a conservative substitution of Y (for example, H), X₄ is Y or any other amino acid (for example, A, D, F, G, M, E, I, K, S, or W) and X₅ is F or any other amino acid (for example, A, D, E, I, K, M, S, or W) (SEQ ID NO: 28);
- 15 (d) the LCDR1 comprises the amino acid sequence R-A-S-Q-S-I-X₁-X₂-X₃-X₄-X₅, wherein X₁ is S or a conservative substitution of S, X₂ is S or a conservative substitution of S, X₃ is Y or a conservative substitution of Y, X₄ is L or a conservative substitution of L, and X₅ is N or T or a conservative substitution of N or T (SEQ ID NO: 32);
- (e) the LCDR2 comprises the amino acid sequence X₁-A-X₂-S-L-X₃-X₄, wherein X₁
- 20 is A or T or a conservative substitution of A or T, X₂ is S or a conservative substitution of S, X₃ is Q or any other amino acid, and X₄ is S or any other amino acid (SEQ ID NO: 33); and
- (f) the LCDR3 comprises the amino acid sequence Q-Q-X₁-Y-S-X₂-P-X₃-T, wherein X₁ is S or any other amino acid, X₂ is T or any other amino acid, and X₃ is W or any other amino acid (SEQ ID NO: 34).
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4. An anti-PD1 antibody or an antigen-binding portion thereof, wherein the antibody or antigen-binding portion cross-competes for binding to PD1 with the antibody or antigen-binding portion of any one of claims 1-3; and
- (a) comprises fully germline human framework amino acid sequences;
- 30 (b) binds specifically to human PD1 and cynomolgus PD1;
- (c) antagonizes binding of human PD1 to human PD-L1 with an EC₅₀ lower than 260 ng/ml;
- (d) binds to monomeric cynomolgus PD1 with a K_D lower than 32 nM;
- (e) binds to cynomolgus PD1-expressing cells with an EC₅₀ lower than 6.5 nM;
- 35 (f) binds to a functionally identical epitope on cynomolgus PD1 and human PD1;
- (g) comprises a human germline peptide sequence with high MHC class II binding affinity in LCDR2;

- (h) comprises a reduced number of immunogenic peptides compared to an anti-PD1 antibody comprising the variable domain sequences of antibody Mab005;
- (i) exhibits reduced immunogenicity compared to an anti-PD1 antibody comprising the variable domain sequences of antibody Mab005;
- 5 (j) comprises a deimmunized VL region;
- (k) exhibits no binding to one or more of KDR, FZD5, ULBP2 and EPHB6;
- (l) does not agonise or minimally agonises one or more of KDR, FZD5, ULBP2 and EPHB6.
- 10 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
- 15 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
- 20 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.
- 25 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
- 30 antibody 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.
- 35 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:13-19.
16. The antigen-binding portion of any one of claims 1-15, wherein the antibody or antigen-binding portion is an Fab, an Fab', an F(ab')₂, an Fd, an Fv, an scFv, a single domain antibody (dAb), a maxibody, a minibody, an intrabody, a diabody, a triabody, a tetrabody, a v-NAR or a bis-scFv.
17. The antibody or antigen-binding portion of any one of claims 1-16, wherein the antibody is monoclonal.
18. The antibody or antigen-binding portion of any one of claims 1-17, wherein the antibody is a tetrameric antibody, a tetravalent antibody or a multispecific antibody.
19. The antibody or antigen-binding portion of any one of claims 1-18, wherein the antibody is a bispecific antibody that binds specifically to a first antigen and a second antigen, wherein the first antigen is PD1 and the second antigen is not PD1.
20. The antibody or antigen-binding portion of any one of claims 1-19, wherein the antibody or antigen-binding portion binds specifically to (a) human PD1 or (b) human PD1 and cynomolgus PD1.
21. The antibody or antigen-binding portion of any one of claims 1-20, wherein the antibody or antigen-binding portion is in an IgG1 format and wherein the antigen-binding portion has a melting temperature (T_m) from about 90°C to about 93°C.
22. The antibody or antigen-binding portion of any one of claims 1-21, wherein the antibody or antigen-binding portion undergoes reduced oxidation of exposed amino acid

residues compared to an anti-PD1 antibody comprising the variable domain sequences of humanized antibody Mab005.

23. An immunoconjugate comprising the antibody or antigen-binding portion of any one
5 of claims 1-22 linked to a therapeutic agent.

24. The immunoconjugate of claim 23, 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
10 enzymes, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent,
or a pro-apoptotic agent.

25. A pharmaceutical composition comprising the antibody or antigen-binding portion of
any one of claims 1-22 or the immunoconjugate of claim 23 or 24, and a pharmaceutically
15 acceptable carrier, diluent or excipient.

26. A nucleic acid molecule encoding
(a) the VH region amino acid sequence;
(b) the VL region amino acid sequence; or
20 (c) both the VH and the VL region amino acid sequences
of the antibody or antigen-binding portion of any one of claims 1-22.

27. An expression vector comprising the nucleic acid molecule of claim 26.

28. A recombinant host cell comprising the nucleic acid molecule of claim 26 or the
expression vector of claim 27.

29. A method of producing an anti-PD1 antibody or an antigen-binding portion thereof,
the method comprising:
30 culturing a recombinant host cell comprising the expression vector of claim 27
under conditions whereby the nucleic acid molecule is expressed, thereby producing the
antibody or antigen-binding portion; and
isolating the antibody or antigen-binding portion from the host cell or culture.

30. A method for enhancing an immune response in a subject, comprising
35 administering to the subject a therapeutically effective amount of the antibody or antigen-

binding portion of any one of claims 1-22, the immunoconjugate of claim 23 or 24 or the pharmaceutical composition of claim 25.

31. A method of treating or preventing cancer, an infectious disease, or an immune
5 disease in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-22, the immunoconjugate of claim 23 or 24 or the pharmaceutical composition of claim 25.

32. The method of claim 31, wherein the cancer is pancreatic cancer, melanoma,
10 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
15 cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

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

34. The method of claim 31, wherein the infectious disease is human immunodeficiency virus (HIV) infection.

35. The method of any one of claims 30-34, wherein administration of the antibody
25 molecule, the antigen-binding portion, the immunoconjugate, or the pharmaceutical composition does not induce or induces minimal hemangioma in the subject.

36. The antibody or antigen-binding portion of any one of claims 1-22, the
30 immunoconjugate of claim 23 or 24 or the pharmaceutical composition of claim 25 for use in the treatment of cancer, an infectious disease, or an immune disease.

37. The antibody or antigen-binding portion, the immunoconjugate or the
pharmaceutical composition for use according to claim 36, wherein the cancer is pancreatic
35 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.

- 5 38. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 36, wherein the infectious disease is viral, bacterial, fungal, or parasitic.
39. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 36, wherein the infectious disease is human immunodeficiency virus (HIV) infection.
- 10 40. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 36, wherein the use of the antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition in the treatment of cancer, an infectious disease, or an immune disease does not induce or induces minimal hemangioma.
- 15 41. The antibody or antigen-binding portion of any one of claims 1-22, the immunoconjugate of claim 23 or 24 or the pharmaceutical composition of claim 25, for use as a medicament.
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