

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, wherein
 - 5 (a) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID NO:33), HCDR2 of VANIWQDGSTKYVDSVKG (SEQ ID NO:34), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);
 - 10 (b) the VH region amino acid sequence comprises HCDR1 of GFSLSSYGMS (SEQ ID NO:39), HCDR2 of VAVIWQDGSTNYVDSVKG (SEQ ID NO:40), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);
 - 15 (c) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMS (SEQ ID NO:33), HCDR2 of VANIWQDGSEKYVDSVKG (SEQ ID NO:41), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVTNDVA (SEQ ID NO:36), LCDR2 of YAYHRFT (SEQ ID NO:37), and LCDR3 of HQAYSSPYT (SEQ ID NO:38);
 - 20 (d) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
 - 25 (e) the VH region amino acid sequence comprises HCDR1 of GFSFTSYGMS (SEQ ID NO:47), HCDR2 of LANIWQDGSTNYVDSVKG (SEQ ID NO:48), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
 - 30 (f) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGVH (SEQ ID NO:49), HCDR2 of VGVIWQDGSENYVDSVKG (SEQ ID NO:50), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52);
 - 35 (g) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of VANIWQDGSTNYVDSVKG (SEQ ID NO:43), and HCDR3 of AYGNYWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1

- of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
- (h) the VH region amino acid sequence comprises HCDR1 of GFSFSSYGMH (SEQ ID NO:42), HCDR2 of LANIWQDGSENVDSVKG (SEQ ID NO:53), and HCDR3 of AYGNWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52);
- (i) the VH region amino acid sequence comprises HCDR1 of GFTLSSYGMH (SEQ ID NO:54), HCDR2 of LAVIWADGSTNYVDSVKG (SEQ ID NO:55), and HCDR3 of AYGNWYIDV (SEQ ID NO:56); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46);
- (j) the VH region amino acid sequence comprises HCDR1 of GFTFSSYGMH (SEQ ID NO:57), HCDR2 of VGVIKQDGSENVDSVKG (SEQ ID NO:58), and HCDR3 of AYGNWYIDR (SEQ ID NO:35); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDVA (SEQ ID NO:44), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of HQAYSTPYT (SEQ ID NO:46); or
- (k) the VH region amino acid sequence comprises HCDR1 of GFSFTSYGMH (SEQ ID NO:59), HCDR2 of VGVIWQDGSTNYVDSVKG (SEQ ID NO:60), and HCDR3 of GYGNWYIDV (SEQ ID NO:61); and the VL region amino acid sequence comprises LCDR1 of KSSQSVSNDLA (SEQ ID NO:51), LCDR2 of YASHRFT (SEQ ID NO:45), and LCDR3 of QQAYSTPYT (SEQ ID NO:52).
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;
- (c) the VH region amino acid sequence comprises SEQ ID NO:5 and the VL region amino acid sequence comprises SEQ ID NO:6; or
- (d) the VH region amino acid sequence comprises SEQ ID NO:7 and the VL region amino acid sequence comprises SEQ ID NO:8.
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

- (a) the HCDR1 comprises the amino acid sequence G-F-X₁-X₂-X₃-S-Y-X₄-X₅-X₆, wherein X₁ is T or a conservative substitution of T, X₂ is F or a conservative substitution of F, X₃ is S or a conservative substitution of S, X₄ is G or any other amino acid, X₅ is M or a conservative substitution of M, and X₆ is S or any other amino acid (SEQ ID NO:20);
- 5 (b) the HCDR2 comprises the amino acid sequence X₁-X₂-X₃-I-X₄-X₅-X₆-G-S-X₇-X₈-Y-X₉-D-S-V-K-G, wherein X₁ is V or a conservative substitution of V, X₂ is A or a conservative substitution of A, X₃ is V or N, X₄ is W or K, X₅ is Q or A, X₆ is D or G, X₇ is T or E, X₈ is N, K, or S, and X₉ is N or V (SEQ ID NO:21);
- 10 (c) the HCDR3 comprises the amino acid sequence X₁-X₂-G-X₃-X₄-X₅-Y-X₆-X₇-X₈, wherein X₁ is A or any other amino acid, X₂ is Y or a conservative substitution of Y, X₃ is N or any other amino acid, X₄ is Y or a conservative substitution of Y, X₅ is W or any other amino acid, X₆ is I or any other amino acid, X₇ is D or a conservative substitution of D, and X₈ is V or any other amino acid (SEQ ID NO:22);
- 15 (d) the LCDR1 comprises the amino acid sequence K-S-S-X₁-S-V-X₂-N-D-X₃-A, wherein X₁ is Q or E, X₂ is S or a conservative substitution of S, and X₃ is L or a conservative substitution of L (SEQ ID NO:26);
- (e) the LCDR2 comprises the amino acid sequence Y-A-X₁-X₂-R-F-X₃, wherein X₁ is F or any other amino acid, X₂ is H or any other amino acid, and X₃ is S or a conservative substitution of S (SEQ ID NO:27); and
- 20 (f) the LCDR3 comprises the amino acid sequence X₁-Q-X₂-Y-S-X₃-P-X₄-T, wherein X₁ is Q or any other amino acid, X₂ is A or any other amino acid, X₃ is T or any other amino acid, and X₄ is Y or any other amino acid (SEQ ID NO:28).
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
- 25 (a) comprises fully germline human framework amino acid sequences; and/or
- (b) binds specifically to human PD1 and cynomolgus PD1; and/or
- (c) does not comprise an oxidation site in the LCDR2; and/or
- 30 (d) comprises a human germline peptide sequence with high MHC class II binding affinity in the HCDR2/framework 3 region of the VH domain; and/or
- (e) does not comprise a human T cell epitope sequence in the HCDR1/framework 2 region of the VH domain; and/or
- (f) does not comprise a human T cell epitope sequence in the HCDR3/framework 4
- 35 region of the VH domain; and/or
- (g) exhibits reduced charge species heterogeneity compared to antibody Hu317, when in IgG1 effector null antibody format.

5. The antibody or antigen-binding portion of any one of claims 1-4, wherein the antibody is human, humanized or chimeric.
- 5 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.
- 10 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
15 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 IGKV4-1 human germline scaffold amino acid sequence into which the LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted.
20
10. The antibody or antigen-binding portion of any one of claims 1-9, wherein the antibody comprises an immunoglobulin constant region.
11. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin
25 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.
- 30 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
35 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:9-15.
- 5 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.
- 10 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.
- 15 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 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.
- 25 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.
- 30 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.
- 35 24. An nucleic acid molecule encoding

(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.

5

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.

10

27. A method of producing an anti-PD1 antibody or an antigen-binding portion thereof, the method comprising:

culturing a recombinant host cell comprising the expression vector of claim 25 under conditions whereby the nucleic acid molecule is expressed, thereby producing the antibody or antigen-binding portion; and

15

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 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.

20

29. A method of treating or preventing cancer, an infectious disease, or an immune 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 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23.

25

30. The method 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.

30

35

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

32. The method of claim 29, the infectious disease is human immunodeficiency virus (HIV) infection.
- 5 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.
- 10 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, 15 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.
- 20 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.
- 25 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.
- 30 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.