

CLAIMS

What is claimed is:

1. An anti-PD-1 antibody or antigen-binding fragment thereof comprising:

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 43 (H-CDR1); the amino acid sequence of SEQ ID NO: 44 (H-CDR2); and the amino acid sequence of SEQ ID NO: 45 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 1 (L-CDR1); the amino acid sequence of SEQ ID NO: 2 (L-CDR2); and the amino acid sequence of SEQ ID NO: 3 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 43 (H-CDR1); the amino acid sequence of SEQ ID NO: 46 (H-CDR2); and the amino acid sequence of SEQ ID NO: 45 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 1 (L-CDR1); the amino acid sequence of SEQ ID NO: 2 (L-CDR2); and the amino acid sequence of SEQ ID NO: 3 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 47 (H-CDR1); the amino acid sequence of SEQ ID NO: 48 (H-CDR2); and the amino acid sequence of SEQ ID NO: 49 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 4 (L-CDR1); the amino acid sequence of SEQ ID NO: 5 (L-CDR2); and the amino acid sequence of SEQ ID NO: 6 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 50 (H-CDR1); the amino acid sequence of SEQ ID NO: 51 (H-CDR2); and the amino acid sequence of SEQ ID NO: 52 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7 (L-CDR1); the amino acid sequence of SEQ ID NO: 8 (L-CDR2); and the amino acid sequence of SEQ ID NO: 9 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 53 (H-CDR1); the amino acid sequence of SEQ ID NO: 54 (H-CDR2); and the amino acid sequence of SEQ ID NO: 55 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 10 (L-CDR1); the amino acid sequence of SEQ ID NO: 11 (L-CDR2); and the amino acid sequence of SEQ ID NO: 12 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56 (H-CDR1); the amino acid sequence of SEQ ID NO: 57 (H-CDR2); and the amino acid sequence of SEQ ID NO: 58 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 13 (L-CDR1); the amino acid sequence of SEQ ID NO: 14 (L-CDR2); and the amino acid sequence of SEQ ID NO: 15 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59 (H-CDR1); the amino acid sequence of SEQ ID NO: 60 (H-CDR2); and the amino acid sequence of SEQ ID NO: 61 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 16 (L-CDR1); the amino acid sequence of SEQ ID NO: 17 (L-CDR2); and the amino acid sequence of SEQ ID NO: 18 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 62 (H-CDR1); the amino acid sequence of SEQ ID NO: 63 (H-CDR2); and the amino acid sequence of SEQ ID NO: 64 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 19 (L-CDR1); the amino acid sequence of SEQ ID NO: 20 (L-CDR2); and the amino acid sequence of SEQ ID NO: 21 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 65 (H-CDR1); the amino acid sequence of SEQ ID NO: 66 (H-CDR2); and the amino acid sequence of SEQ ID NO: 67 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 22 (L-CDR1); the amino acid sequence of SEQ ID NO: 23 (L-CDR2); and the amino acid sequence of SEQ ID NO: 24 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 68 (H-CDR1); the amino acid sequence of SEQ ID NO: 69 (H-CDR2); and the amino acid sequence of SEQ ID NO: 70 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 25 (L-CDR1); the amino acid sequence of SEQ ID NO: 26 (L-CDR2); and the amino acid sequence of SEQ ID NO: 27 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 71 (H-CDR1); the amino acid sequence of SEQ ID NO: 72 (H-CDR2); and the amino acid sequence of SEQ ID NO: 58 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 28 (L-CDR1); the amino acid sequence of SEQ ID NO: 14 (L-CDR2); and the amino acid sequence of SEQ ID NO: 29 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 74 (H-CDR2); and the amino acid sequence of SEQ ID NO: 75 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 76 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 78 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 79 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 76 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 164 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 79 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 165 (L-CDR1); the amino acid sequence of SEQ ID NO: 166 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 78 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 165 (L-CDR1); the amino acid sequence of SEQ ID NO: 166 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 79 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 165 (L-CDR1); the amino acid sequence of SEQ ID NO: 167 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 80 (H-CDR1); the amino acid sequence of SEQ ID NO: 81 (H-CDR2); and the amino acid sequence of SEQ ID NO: 82 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 33 (L-CDR1); the amino acid sequence of SEQ ID NO: 14 (L-CDR2); and the amino acid sequence of SEQ ID NO: 34 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83 (H-CDR1); the amino acid sequence of SEQ ID NO: 84 (H-CDR2); and the amino acid sequence of SEQ ID NO: 85 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 16 (L-CDR1); the amino acid sequence of SEQ ID NO: 35 (L-CDR2); and the amino acid sequence of SEQ ID NO: 36 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 86 (H-CDR1); the amino acid sequence of SEQ ID NO: 87 (H-CDR2); and the amino acid sequence of SEQ ID NO: 88 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 37 (L-CDR1); the amino acid sequence of SEQ ID NO: 38 (L-CDR2); and the amino acid sequence of SEQ ID NO: 39 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 89 (H-CDR1); the amino acid sequence of SEQ ID NO: 90 (H-CDR2); and the amino acid sequence of SEQ ID NO: 91 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 40 (L-CDR1); the amino acid sequence of SEQ ID NO: 41 (L-CDR2); and the amino acid sequence of SEQ ID NO: 42 (L-CDR3).

2. The anti-PD-1 antibody or antigen-binding fragment thereof of claim 1 comprising:

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 74 (H-CDR2); and the amino acid sequence of SEQ ID NO: 75 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 76 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 78 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 79 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 76 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 164 (L-CDR1); the amino acid sequence of SEQ ID NO: 31 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 79 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 165 (L-CDR1); the amino acid sequence of SEQ ID NO: 166 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 78 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 165 (L-CDR1); the amino acid sequence of SEQ ID NO: 166 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3),

or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73 (H-CDR1); the amino acid sequence of SEQ ID NO: 79 (H-CDR2); and the amino acid sequence of SEQ ID NO: 77 (H-CDR3), and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 165 (L-CDR1); the amino acid sequence of SEQ ID NO: 167 (L-CDR2); and the amino acid sequence of SEQ ID NO: 32 (L-CDR3).

3. The anti-PD1 antibody or antigen-binding fragment thereof of claim 1 or 2, wherein said antibody or antigen-binding fragment thereof is a humanized antibody or antigen-binding fragment thereof.
4. The anti-PD1 antibody or antigen-binding fragment thereof of any one of claims 1 to 3, wherein said antibody or antigen-binding fragment thereof is selected from the group consisting of a monoclonal antibody, a Fab, a F(ab')₂, a Fv and an scFv.
5. The anti-PD-1 or antigen-binding fragment thereof antibody of claim 1, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 108 and SEQ ID NO: 92, respectively; SEQ ID NO: 109 and SEQ ID NO: 93, respectively; SEQ ID NO: 110 and SEQ ID NO: 94, respectively; SEQ ID NO: 111 and SEQ ID NO: 95, respectively; SEQ ID NO: 112 and SEQ ID NO: 96, respectively; SEQ ID NO: 113 and SEQ ID NO: 97, respectively; SEQ ID NO: 114 and SEQ ID NO: 98, respectively; SEQ ID NO: 115 and SEQ ID NO: 99, respectively; SEQ ID NO: 116 and SEQ ID NO: 100, respectively; SEQ ID NO: 117 and SEQ ID NO: 101, respectively; SEQ ID NO: 118 and SEQ ID NO: 102, respectively; SEQ ID NO: 119 and SEQ ID NO: 103, respectively; SEQ ID NO: 120 and SEQ ID NO: 104, respectively; SEQ ID NO: 121 and SEQ ID NO: 105, respectively; SEQ ID NO: 122 and SEQ ID NO: 106, respectively; SEQ ID NO: 123 and SEQ ID NO: 107, respectively.
6. The anti-PD-1 antibody or antigen-binding fragment thereof of claim 1, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of any one of SEQ NO: 131, SEQ NO: 133, SEQ NO: 135, SEQ NO: 137 or SEQ NO: 139 and a light chain variable region comprising the amino acid sequence of any one of SEQ NO: 125, SEQ NO: 127 or SEQ NO: 129.
7. The anti-PD-1 antibody or antigen-binding fragment thereof of claim 1, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO:

131 and SEQ ID NO: 125, respectively; SEQ ID NO: 133 and SEQ ID NO: 127, respectively; SEQ ID NO: 135 and SEQ ID NO: 127, respectively; SEQ ID NO: 137 and SEQ ID NO: 129, respectively; or SEQ ID NO: 139 and SEQ ID NO: 129, respectively.

8. The anti-PD-1 antibody or antigen-binding fragment thereof of claim 1, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region having at least 90%, at least 95%, at least 98%, or at least 99% identity to the amino acid sequences of SEQ ID NO: 131 and SEQ ID NO: 125, respectively; SEQ ID NO: 133 and SEQ ID NO: 127, respectively; SEQ ID NO: 135 and SEQ ID NO: 127, respectively; SEQ ID NO: 137 and SEQ ID NO: 129, respectively; SEQ ID NO: 139 and SEQ ID NO: 129, respectively.

9. The anti-PD1 antibody of any one of claims 1 to 8, wherein said antibody comprises a heavy chain constant region selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgM, IgA and IgE constant regions.

10. The anti-PD1 antibody of claim 9, wherein the heavy chain constant region is a heavy chain constant region of an IgG4 with a Ser228Pro mutation.

11. The anti-PD1 antibody of claim 9, wherein the heavy chain constant region is a heavy chain constant region of an IgG1.

12. The anti-PD1 antibody of claim 9, wherein the heavy chain constant region is a heavy chain constant region of an IgG1 with Leu234Ala and Leu235Ala mutations.

13. The anti-PD1 antibody or antigen-binding fragment thereof of any one of claim 1 to 12, wherein the antibody or antigen-binding fragment thereof comprises a light chain constant region selected from the group consisting of kappa and lambda.

14. The anti-PD-1 antibody of claim 1, wherein said antibody comprises a heavy chain and a light chain comprising the amino acid sequences of SEQ ID NO: 143 and SEQ ID NO: 141, respectively; SEQ ID NO: 147 and SEQ ID NO: 145, respectively; SEQ ID NO: 149 and SEQ ID NO: 145, respectively; SEQ ID NO: 153 and SEQ ID NO: 151, respectively; or SEQ ID NO: 155 and SEQ ID NO: 151, respectively.
15. The PD-1 antibody or antigen-binding fragment thereof of any one of claims 5 to 14, wherein said antibody or antigen-binding fragment thereof is a monoclonal antibody.
16. A pharmaceutical composition comprising the anti-PD-1 antibody or antigen-binding fragment thereof according to any of claims 1 to 15, and a pharmaceutically acceptable excipient.
17. An anti-PD-1 antibody or antigen-binding fragment thereof according to any of claims 1 to 16 for use as a medicament.
18. A method of treating a PD-1 pathway disorder comprising administering to a patient in need thereof a pharmaceutically effective amount of the anti-PD-1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 16.
19. An anti-PD-1 antibody or antigen-binding fragment thereof according to any of claims 1 to 16 for use in treating a PD-1 pathway disorder.
20. Use of the anti-PD-1 antibody or antigen-binding fragment thereof according to any of claims 1 to 16 in manufacture of a medicament for treating a PD-1 pathway disorder.
21. The method of claim 18, the anti-PD-1 antibody or antigen-binding fragment thereof for use according to claim 19, or the use of the anti-PD-1 antibody or antigen-binding fragment thereof of claim 20, wherein the disease is selected from the group consisting of systemic sclerosis (SSc), systemic lupus erythematosus, polymyositis, giant cell arteritis, psoriasis, psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease.

22. The method, the anti-PD-1 antibody or antigen-binding fragment thereof for use, or the use according to any one of claims 17 to 21, wherein said antibody or antigen-binding fragment thereof is administered by a parenteral route, intravenous route or subcutaneous route of administration.

23. An isolated polynucleotide encoding a heavy chain variable region and/or a light chain variable region according to any one of claims 5 to 7.

24. An isolated polynucleotide encoding a heavy chain and/or a light chain according to claim 14.

25. An expression vector comprising a polynucleotide according to claim 23 or 24.

26. A host cell comprising an expression vector according to claim 25.

27. The host cell of claim 26, wherein the cell is a mammalian cell.

28. A method of manufacturing an antibody comprising the steps of:

- culturing a host cell comprising an expression vector comprising an isolated polynucleotide encoding a heavy chain variable region according to any one of claims 5 to 7 and an expression vector comprising polynucleotide encoding light chain variable region according to any one of claims 5 to 7 under conditions that allow formation of an antibody; and
- recovering said antibody.

29. A method of manufacturing an antibody comprising the steps of:

- culturing a host cell comprising an expression vector comprising an isolated polynucleotide encoding a heavy chain according to claim 14 and an expression vector comprising polynucleotide encoding light chain according to claim 14 under conditions that allow formation of an antibody; and
- recovering said antibody.

30. The method of claim 28 or 29, further comprising the step of purifying said antibody.
31. The method of claim 28 or 29, further comprising the step of formulating said antibody into a pharmaceutical composition.
32. A multi-specific antibody comprising a first anti-PD-1 agonist antigen-binding site and a second antigen-binding site.
33. The multi-specific antibody of claim 32, wherein said second antigen-binding site is an anti-CD48 binding site, an anti-CD-2 binding site, an anti-CD11a binding site or an anti-CD3 binding site.
34. The multi-specific antibody of claim 32, wherein said first anti-PD-1 agonist antigen-binding site comprises a heavy chain variable region and a light chain variable region according to any one of claims 1 to 8.
35. The multi-specific antibody of any one of claims 32 to 34, wherein said antibody is a bi-specific antibody.