

thus avoid detection. PD-1 inhibitors, a new class of drugs that block PD-1, activate the immune system to attack tumors and are used to treat certain types of cancer.

[0004] In contrast, defective PD-1 inhibitory functions have also been associated with pathophysiology of immune-mediated diseases, and expression of PD-1 or its ligands may be dysregulated or not fully engaged in certain autoimmune indications. Induction of PD-1 activation and the use of the PD-1 / PD-L1 and/or PD-L2 system thus represent an alternative approach to suppress the immune response and provide treatments for various immune and inflammatory disorders.

[0005] There is therefore a need for therapies, which induce the PD-1 pathway, enhance suppressive function and provide treatments for immune and inflammatory disorders controlled by the PD-1 / PD-L1 and/or PD-L2 system. In particular, there is a need for biological therapeutics, such as antibodies, which modulate the interaction between PD-1 and PD-L1 or PD-L2 without blocking such interaction.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0006] The present ~~invention disclosure~~ provides antibodies that specifically bind to human PD-1. In one aspect of the ~~invention disclosure~~, the antibodies of the present ~~invention disclosure~~ do not block the interaction between PD-1 and PD-L1. In one ~~aspect example~~ of the ~~invention disclosure~~, the antibodies of the present ~~invention disclosure~~ enhance the interaction between PD-1 and PD-L1. In one ~~aspect example~~ of the ~~invention disclosure~~, the antibodies of the present ~~invention disclosure~~ activate the PD-1 signaling pathway. In one ~~aspect example~~ of the ~~invention disclosure~~, the antibodies of the present ~~invention disclosure~~ are anti-PD-1 agonist antibodies. The antibodies of the ~~invention disclosure~~ are useful, for example, for the treatment and/or prevention of diseases or disorders that can be alleviated by modulating the interaction between PD-1 and PD-L1, in particular by activating the PD-1 pathway.

[0006a] In one example, the present disclosure provides 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: 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: 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: 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).

[0006b] In another example, the present disclosure provides a pharmaceutical composition comprising the anti-PD-1 antibody or antigen-binding fragment thereof according to the disclosure, and a pharmaceutically acceptable excipient.

[0006c] In another example, the present disclosure provides an anti-PD-1 antibody or antigen-binding fragment thereof according to the disclosure for use as a medicament.

[0006d] In another example, the present disclosure provides an anti-PD-1 antibody or antigen-binding fragment thereof according to the disclosure for use in treating a PD-1 pathway disorder.

[0006e] In another example, the present disclosure provides a use of the anti-PD-1 antibody or antigen-binding fragment thereof according to the disclosure in the manufacture of a medicament for treating a PD-1 pathway disorder.

[0006f] In another example, the present disclosure provides an isolated polynucleotide encoding an anti-PD-1 antibody or antigen-binding fragment thereof according to the disclosure.

[0006g] In another example, the present disclosure provides an isolated polynucleotide encoding a heavy chain variable region and/or a light chain variable region according to the disclosure.

[0006h] In another example, the present disclosure provides an isolated polynucleotide encoding a heavy chain and/or a light chain according to the disclosure.

[0006i] In another example, the present disclosure provides an expression vector comprising a polynucleotide according to the disclosure.

[0006j] In another example, the present disclosure provides a host cell comprising an expression vector according to the disclosure.

[0006k] In another example, the present disclosure provides a method of manufacturing an antibody comprising the steps of: - culturing a host cell comprising an expression vector comprising a polynucleotide encoding a heavy chain variable region according to the disclosure and an expression vector comprising a polynucleotide encoding a light chain variable region according to the disclosure under conditions that allow formation of an antibody; and - recovering said antibody.

[0006l] In another example, the present disclosure provides a multi-specific antibody comprising a first anti-PD-1 agonist antigen-binding site and a second antigen-binding site, wherein said first anti-PD-1 agonist antigen-binding site comprises a heavy chain variable region and a light chain variable region according to the disclosure.

[0007] In one ~~aspect~~example, the present ~~invention~~disclosure provides an anti-PD-1 antibody, in particular a monoclonal anti-PD-1 antibody, for example a humanized monoclonal anti-PD-1 antibody, having one or more of the properties described herein below. In one ~~aspect~~example, an anti-PD-1 antibody of the present ~~invention~~disclosure binds to purified recombinant human PD-1 at high affinity, for example 20 nM or less, for example 10 nM or less, for

example 5 nM or less. In one aspectexample, an anti-PD-1 antibody of the present inventiondisclosure binds to purified recombinant cynomolgus PD-1 at an affinity of 50 nM or less. In one aspectexample, an anti-PD-1 antibody of the present inventiondisclosure selectively binds to PD-1, in particular human PD-1. In one aspectexample, an antibody of the present inventiondisclosure does not bind to mouse, rat, or rabbit PD-1. In one aspectexample, an anti-PD-1 antibody of the present inventiondisclosure does not block the binding of PD-L1 to PD-1. In one aspectexample, an anti-PD-1 antibody of the present inventiondisclosure enhances the binding of PD-L1 to PD-1. In one aspectexample, an anti-PD-1 antibody of the present inventiondisclosure attenuates T cell activity in a functional cell assay, for example by inhibition of IFN γ production, inhibition of IL-17A production or inhibition of IL-21 production. In one aspectexample, an anti-PD-1 antibody of the present inventiondisclosure inhibits human cell accumulation in a mouse model and reduces the levels of human inflammatory cytokines in the mouse model. In one aspectexample, an anti-PD-1 antibody of the present inventiondisclosure has favorable pharmacokinetic properties. In one aspectexample, an anti-PD-1 antibody of the present inventiondisclosure has favorable biophysical properties, for example yield, quality, stability or solubility. In one aspectexample, the present inventiondisclosure provides antigen-binding fragments of an antibody of the present inventiondisclosure.

[0008] In one embodimentexample, the present inventiondisclosure provides 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).

[0009] In one embodiment example, the present invention disclosure provides an anti-PD-1 antibody or antigen-binding fragment 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).

[0010] In one embodiment example, the present invention disclosure provides an anti-PD-1 antibody or antigen-binding fragment comprising:

a heavy chain variable region comprising any one of:

the amino acid sequence 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),

the amino acid sequence 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),

the amino acid sequence 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), or

the amino acid sequence 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 any one of:

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),

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), 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), 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).

[0011] In one embodimentexample, the CDRs of the anti-PD-1 antibody or antigen-binding fragment thereof are defined per the Chemical Computing Group (CCG) numbering.

[0012] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof as set forth above, wherein the antibody or antigen-binding fragment thereof is a humanized antibody or antigen-binding fragment thereof.

[0013] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof as set forth above, wherein the 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.

[0014] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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.

[0015] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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.

[0016] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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.

[0017] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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: 133 and SEQ ID NO: 127, respectively.

[0018] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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: 135 and SEQ ID NO: 127, respectively.

[0019] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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: 137 and SEQ ID NO: 129, respectively.

[0020] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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: 139 and SEQ ID NO: 129, respectively.

[0021] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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.

[0022] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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: 133 and SEQ ID NO: 127, respectively.

[0023] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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: 135 and SEQ ID NO: 127, respectively.

[0024] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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: 137 and SEQ ID NO: 129, respectively.

[0025] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof, wherein the 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: 139 and SEQ ID NO: 129, respectively.

[0026] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof as described above, wherein the antibody comprises a heavy chain constant region selected from the group consisting of IgG1,

IgG2, IgG3, IgG4, IgM, IgA and IgE constant regions, for example human IgG1, IgG2, IgG3, IgG4, IgM, IgA or IgE.

[0027] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody as described above, wherein the heavy chain constant region is a heavy chain constant region of an IgG4 with a Ser228Pro mutation.

[0028] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody as described above, wherein the heavy chain constant region is a heavy chain constant region of an IgG1.

[0029] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody as described above, wherein the heavy chain constant region is a heavy chain constant region of an IgG1 with Leu234Ala and Leu235Ala mutations.

[0030] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof as described above wherein the antibody or antigen-binding fragment thereof comprises a light chain constant region selected from the group consisting of kappa and lambda.

[0031] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the 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.

[0032] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the antibody comprises a heavy chain and a light chain comprising the amino acid sequences of SEQ ID NO: 147 and SEQ ID NO: 145, respectively.

[0033] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the antibody comprises a heavy chain and a light chain comprising the amino acid sequences of SEQ ID NO: 149 and SEQ ID NO: 145, respectively.

[0034] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the antibody comprises a heavy chain and a light chain comprising the amino acid sequences of SEQ ID NO: 153 and SEQ ID NO: 151, respectively.

[0035] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the antibody comprises a heavy chain and a light chain comprising the amino acid sequences of SEQ ID NO: 155 and SEQ ID NO: 151, respectively.

[0036] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the antibody comprises a heavy chain and a light chain, wherein the amino acid sequence of said heavy chain consists of the amino acids of SEQ ID NO: 143 and the amino acid sequence of said light chain consists of the amino acids of SEQ ID NO:141.

[0037] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the antibody comprises a heavy chain and a light chain, wherein the amino acid sequence of said heavy chain consists of the amino acids of SEQ ID NO: 147 and the amino acid sequence of said light chain consists of the amino acids of SEQ ID NO:145.

[0038] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the antibody comprises a heavy chain and a light chain, wherein the amino acid sequence of said heavy chain consists of the amino acids of SEQ ID NO: 149 and the amino acid sequence of said light chain consists of the amino acids of SEQ ID NO:145.

[0039] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the antibody comprises a heavy chain and a light chain, wherein the amino acid sequence of said heavy chain consists of the amino acids of SEQ ID NO: 153 and the amino acid sequence of said light chain consists of the amino acids of SEQ ID NO:151.

[0040] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody, wherein the antibody comprises a heavy chain and a light chain, wherein the amino acid sequence of said heavy chain consists of the amino acids of SEQ ID NO: 155 and the amino acid sequence of said light chain consists of the amino acids of SEQ ID NO:151.

[0041] In one embodimentexample, an anti-PD1 antibody or antigen-binding fragment thereof as described above is a monoclonal antibody or antigen-binding fragment thereof.

[0042] In one embodimentexample, an anti-PD1 antibody or antigen-binding fragment thereof as described above is a humanized antibody or antigen-binding fragment thereof.

[0043] In one embodimentexample, an anti-PD1 antibody or antigen-binding fragment thereof as described above is an agonist anti-PD1 antibody or antigen-binding fragment thereof.

[0044] In one embodimentexample, an anti-PD1 antibody or antigen-binding fragment thereof as described above binds to human PD-1 at high affinity, for example 20 nM or less, for example 10 nM or less, for example 5 nM or less.

[0045] In one embodimentexample, the present inventiondisclosure provides an anti-PD1 antibody or antigen-binding fragment thereof that competes for binding to PD-1 with an anti-PD-1 antibody or antigen-binding fragment thereof as described above. In one embodimentexample, the present inventiondisclosure provides an anti-PD-1 antibody or antigen-binding fragment thereof that competes for binding to PD-1 with Antibody A, Antibody B, Antibody C, Antibody D or Antibody E.

[0046] In one embodimentexample, the present inventiondisclosure provides a pharmaceutical composition comprising an anti-PD-1 antibody or antigen-binding fragment thereof as described above, and a pharmaceutically acceptable excipient.

[0047] In one embodimentexample, the present inventiondisclosure provides an anti-PD-1 antibody or antigen-binding fragment thereof as described above for use as a medicament.

[0048] In one embodimentexample, the present inventiondisclosure provides 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 as described above. In one embodimentexample, the present inventiondisclosure provides an anti-PD-1 antibody or antigen-binding fragment thereof as described above for use in treating a PD-1 pathway disorder. In one embodimentexample, the present inventiondisclosure provides the use of the anti-PD-1 antibody or antigen-binding fragment thereof as described above in manufacture of a medicament for treating a PD-1 pathway disorder.

[0049] In one embodimentexample, the present inventiondisclosure provides a method of modulating the interaction between PD-1 and PD-L1 in a human patient comprising administering to the human patient a composition comprising an anti-PD-1 antibody or the antigen-binding fragment as described above in an amount sufficient to activate the PD-1 pathway in the human patient. In one embodimentexample, the present inventiondisclosure provides

an anti-PD-1 antibody or the antigen-binding fragment as described above for use in modulating the interaction between PD-1 and PD-L1 in a human patient. In one embodimentexample, the present inventiondisclosure provides the use of an anti-PD-1 antibody or the antigen-binding fragment as described above in the manufacture of a medicament for modulating the interaction between PD-1 and PD-L1 in a human patient.

[0050] In one embodimentexample, the present inventiondisclosure provides a method of attenuating PD-1 expressing T cell activity in a human patient comprising administering to the human patient a composition comprising an anti-PD-1 antibody or the antigen-binding fragment as described above in an amount sufficient to down-modulate an immune response in the human patient. In one embodimentexample, the present inventiondisclosure provides an anti-PD-1 antibody or the antigen-binding fragment as described above for use in attenuating PD-1 expressing T cell activity in a human patient. In one embodimentexample, the present inventiondisclosure provides the use of an anti-PD-1 antibody or the antigen-binding fragment as described above in the manufacture of a medicament for attenuating PD-1 expressing T cell activity in a human patient.

[0051] In one embodimentexample, in a method above, in an anti-PD-1 antibody or antigen-binding fragment thereof for use above, or in the use of an anti-PD-1 antibody or antigen-binding fragment thereof above, 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.

[0052] In one embodimentexample, in the method above, in the anti-PD-1 antibody or antigen-binding fragment thereof for use above, or in the use of the anti-PD-1 antibody or antigen-binding fragment thereof above, the antibody or antigen-binding fragment thereof is administered by a parenteral route, intravenous route or subcutaneous route of administration.

[0053] In one embodimentexample, the present inventiondisclosure provides an isolated polynucleotide encoding a heavy chain variable region amino and/or a light chain variable region as described above.

[0054] In one embodimentexample, the present inventiondisclosure provides an isolated polynucleotide encoding a heavy chain and/or a light chain as described above.

[0055] In one embodimentexample, the present inventiondisclosure provides an expression vector comprising a polynucleotide as described above.

[0056] In one embodimentexample, the present inventiondisclosure provides a host cell comprising an expression vector as described above. In one embodimentexample, the host cell is a mammalian cell.

[0057] In one embodimentexample, the present inventiondisclosure provides 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 as described above and an expression vector comprising polynucleotide encoding light chain variable region as described above under conditions that allow formation of an antibody, and
- recovering said antibody.

[0058] In one embodimentexample, the present inventiondisclosure provides 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 as described above and an expression vector comprising polynucleotide encoding light chain as described above under conditions that allow formation of an antibody; and
- recovering said antibody.

[0059] In one embodimentexample, a method above further comprises the step of purifying the antibody. In one embodimentexample, a method above further comprises the step of formulating the antibody into a pharmaceutical composition.

[0060] In one embodimentexample, the present inventiondisclosure provides a multi-specific antibody comprising a first anti-PD-1 agonist antigen-binding site and a second antigen-binding site.

[0061] In one [embodimentexample](#), the 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.

[0062] In one [embodimentexample](#), the first anti-PD-1 agonist antigen-binding site comprises a heavy chain variable region and a light chain variable region as described above.

[0063] In one [embodimentexample](#), the multi-specific antibody is a bi-specific antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

[0064] Figure 1: Selectivity of anti-PD-1 antibody to human PD-1 protein in a cell-based assay evaluated by flow cytometry. MFI stands for “mean fluorescence intensity”.

[0065] Figure 2: Competition binding assay of human PD-1-Fc binding to human PD-L1-Fc. Sensorgram depicting the binding curve of 25 nM PD-1-Fc to PD-L1-Fc amine coupled on the GLM chip surface (Figure 2A). Sensorgrams of Antibody C, MK-3475, and PD1AB-6-4P (500nM) pre-mixed with 25 nM PD-1-Fc binding to PD-L1-Fc amine coupled to the GLM chip surface (Figure 2B).

[0066] Figure 3: Enhanced binding of PD-L1 to PD-1 in the presence of anti-PD-1 agonist antibody. PD-1 Biotin: PD-L1 interaction assay (Figure 3A). CHO PD-1 – PD-L1 Delphia-Eu TRF assay (Figures 3B and 3D). CHO PD-1: Biotin PD-L1 binding assay (Figure 3C). In Figure 3D, the individual data points are only depicted for Antibody C; the individual data points for the other antibodies are not depicted in Figure 3D because of their close proximity to each other. POC stands for “percentage of control”.

[0067] Figure 4: T cell functional activity in the presence of anti-PD-1 agonist antibody or F(ab')₂ fragments derived from parental 723C2 agonist antibody (Figure 4A) or parental agonist antibody 820C3 (Figure 4B). POC stands for “percentage of control”.

[0068] Figure 5: Induction of PD-1 activation by a MAb against CD48 to upon crosslinking.

[0069] Figure 6: Labeling of human pan-T cell with CellTrace-Violet, activation with CD3 MAbs, and analysis of cell proliferation by dilution of the CellTrace.

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: 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: 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).

32. 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.

43. The anti-PD1 antibody or antigen-binding fragment thereof of ~~any one of claims 1 to 3~~claim 1 or claim 2, 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.~~

~~64.~~ The anti-PD-1 antibody or antigen-binding fragment thereof of any one of claims 1 to 3, wherein said antibody or antigen-binding fragment thereof comprises a heavy chain variable region having at least 90% identity to comprising the amino acid sequence of any one of ~~SEQ NO: 131, SEQ NO: 133,~~ SEQ NO: 135, SEQ NO: 131, SEQ NO: 133, SEQ NO: 137 or SEQ NO: 139, and a light chain variable region having at least 90% identity to comprising the amino acid sequence of any one of ~~SEQ NO: 125,~~ SEQ NO: 127, SEQ NO: 125 or SEQ NO: 129.

~~75.~~ The anti-PD-1 antibody or antigen-binding fragment thereof of any one of claims 1 to 4, wherein said antibody or antigen-binding fragment thereof comprises:
a heavy chain variable region and a light chain variable region having at least 90% identity to 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;

a heavy chain variable region and a light chain variable region having at least 90% identity to the amino acid sequences of SEQ ID NO: 131 and SEQ ID NO: 125, respectively;

a heavy chain variable region and a light chain variable region having at least 90% identity to the amino acid sequences of SEQ ID NO: 133 and SEQ ID NO: 127, respectively;

a heavy chain variable region and a light chain variable region having at least 90% identity to the amino acid sequences of SEQ ID NO: 137 and SEQ ID NO: 129, respectively; or a heavy chain variable region and a light chain variable region having at least 90% identity to the amino acid sequences of SEQ ID NO: 139 and SEQ ID NO: 129, respectively.

6. The anti-PD-1 antibody or antigen-binding fragment thereof of any one of claims 1 to 5, 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: 135 and SEQ ID NO: 127, respectively;

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;

a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 133 and SEQ ID NO: 127, respectively;

a heavy chain variable region and a light chain variable region comprising the amino acid sequences of SEQ ID NO: 137 and SEQ ID NO: 129, respectively; or

a heavy chain variable region and a light chain variable region comprising the amino acid sequences of 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.~~

97. The anti-PD1 antibody of any one of claims 1 to 86, wherein said antibody comprises a heavy chain constant region selected from the group consisting of: IgG4, IgG1, IgG2, IgG3, ~~IgG4~~, IgM, IgA and IgE constant regions.

~~108~~. The anti-PD1 antibody of claim 97, 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.~~

~~129~~. The anti-PD1 antibody of claim 97, wherein the heavy chain constant region is a heavy chain constant region of an IgG1 with Leu234Ala and Leu235Ala mutations.

~~1310~~. The anti-PD1 antibody or antigen-binding fragment thereof of any one of claims 1 to 129, wherein the antibody or antigen-binding fragment thereof comprises a light chain constant region selected from the group consisting of kappa and lambda.

1411. The anti-PD-1 antibody of any one of claims 1 to 8 and 10, wherein said antibody comprises a heavy chain and a light chain comprising the amino acid sequences of SEQ ID NO: 149 and SEQ ID NO: 145, respectively;

a heavy chain and a light chain comprising the amino acid sequences of SEQ ID NO: 143 and SEQ ID NO: 141, respectively;

a heavy chain and a light chain comprising the amino acid sequences of SEQ ID NO: 147 and SEQ ID NO: 145, respectively; ~~SEQ ID NO: 149 and SEQ ID NO: 145, respectively;~~

~~a heavy chain and a light chain comprising the amino acid sequences of~~ SEQ ID NO: 153 and SEQ ID NO: 151, respectively; or

a heavy chain and a light chain comprising the amino acid sequences of SEQ ID NO: 155 and SEQ ID NO: 151, respectively.

12. The anti-PD-1 antibody of any one of claims 1 to 8 and 10 to 11, wherein the antibody consists of a heavy chain and a light chain consisting of the amino acid sequences of SEQ ID NO: 149 and SEQ ID NO: 145, respectively.

13. The anti-PD-1 antibody of any one of claims 1 to 8 and 10 to 11, wherein the antibody consists of a heavy chain and a light chain consisting of the amino acid sequences of SEQ ID NO: 143 and SEQ ID NO: 141, respectively.

14. The anti-PD-1 antibody of any one of claims 1 to 8 and 10 to 11, wherein the antibody consists of a heavy chain and a light chain consisting of the amino acid sequences of SEQ ID NO: 147 and SEQ ID NO: 145, respectively.

15. The anti-PD-1 antibody of any one of claims 1 to 8 and 10 to 11, wherein the antibody consists of a heavy chain and a light chain consisting of the amino acid sequences of SEQ ID NO: 153 and SEQ ID NO: 151, respectively.

16. The anti-PD-1 antibody of any one of claims 1 to 8 and 10 to 11, wherein the antibody consists of a heavy chain and a light chain consisting of the amino acid sequences of SEQ ID NO: 155 and SEQ ID NO: 151, respectively.

~~15~~17. The anti-PD-1 antibody or antigen-binding fragment thereof of any one of claims ~~5 to 14~~1 to 16, wherein said antibody or antigen-binding fragment thereof is a monoclonal antibody.

~~16~~18. A pharmaceutical composition comprising the anti-PD-1 antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~15~~17, and a pharmaceutically acceptable excipient.

~~17~~19. An anti-PD-1 antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~16~~17 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~~20. An anti-PD-1 antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~16-17~~ for use in treating a PD-1 pathway disorder.

~~20~~21. Use of the anti-PD-1 antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~16-17~~ in the manufacture of a medicament for treating a PD-1 pathway disorder.

22. The anti-PD-1 antibody or antigen-binding fragment thereof for use according to claim 20, or the use of the anti-PD-1 antibody or antigen-binding fragment thereof of claim 21, wherein the PD-1 pathway disorder is a chronic inflammatory disease or an acute inflammatory disease.

23. The anti-PD-1 antibody or antigen-binding fragment thereof for use according to claim 20 or 22, or the use of the anti-PD-1 antibody or antigen-binding fragment thereof of claim 21 or 22, wherein the PD-1 pathway disorder is selected from the group consisting of: arthritis, rheumatoid arthritis, asthma, COPD, pelvic inflammatory disease, Alzheimer's Disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Peyronie's Disease, coeliac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, psoriatic arthritis, vasculitis, surgical adhesions, stroke, Type I Diabetes, Lyme disease, meningoencephalitis, autoimmune uveitis, multiple sclerosis, lupus, systemic lupus erythematosus, Guillain-Barré syndrome, Atopic dermatitis, autoimmune hepatitis, fibrosing alveolitis, Grave's disease, IgA nephropathy, idiopathic thrombocytopenic purpura, Meniere's disease, pemphigus, primary biliary cirrhosis, sarcoidosis, scleroderma, Wegener's granulomatosis, other autoimmune disorders, pancreatitis, trauma, surgery, graft-versus-host disease, transplant rejection, heart disease including ischaemic diseases such as myocardial infarction as well as atherosclerosis, intravascular coagulation, bone resorption, osteoporosis, osteoarthritis,

periodontitis and hypochlorhydria, infertility related to lack of fetal-maternal tolerance, Sjogren's Syndrome, vitiligo, myasthenia gravis and systemic sclerosis.

~~2124.~~ The ~~method of claim 18, the~~ anti-PD-1 antibody or antigen-binding fragment thereof for use according to any one of claims 1920, 22, and 23, or the use of the anti-PD-1 antibody or antigen-binding fragment thereof of any one of claims 2021 to 23, wherein the PD-1 pathway disorder~~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.

~~2225.~~ The ~~method, the~~ anti-PD-1 antibody or antigen-binding fragment thereof for use according to any one of claims 20 and 22 to 24, or the use according to any one of claims ~~17 to 21~~21 to 24, wherein said antibody or antigen-binding fragment thereof is administered by a parenteral route, intravenous route or subcutaneous route of administration.

26. An isolated polynucleotide encoding an anti-PD-1 antibody or antigen-binding fragment thereof according to any one of claims 1 to 17.

~~2327.~~ 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~~1, 2 or 4 to 6.

~~2428.~~ An isolated polynucleotide encoding a heavy chain and/or a light chain according to ~~claim 14~~any one of claims 7 to 16.

~~2529.~~ An expression vector comprising a polynucleotide according to any one of claims 26 to 28~~23 or 24~~.

~~2630.~~ A host cell comprising an expression vector according to claim ~~25~~29.

2731. The host cell of claim 2630, wherein the cell is a mammalian cell.

2832. A method of manufacturing an antibody comprising the steps of:

- culturing a host cell comprising an expression vector comprising ~~an isolated~~a polynucleotide encoding a heavy chain variable region according to any one of claims ~~5 to 7~~1, 2 or 4 to 6 and an expression vector comprising a polynucleotide encoding a light chain variable region according to any one of claims 1, 2 or 4 to 6 ~~5 to 7~~ under conditions that allow formation of an antibody; and
- recovering said antibody.

2933. ~~A~~The method of ~~manufacturing an antibody comprising the steps of~~claim 32 wherein:

- ~~culturing a~~the host cell ~~comprising~~comprises an expression vector comprising ~~an isolated~~a polynucleotide encoding a heavy chain according to any one of claims ~~7 to 16~~14 and an expression vector comprising a polynucleotide encoding light chain according to any one of claims ~~14-7 to 16~~under conditions that allow formation of an antibody; and
- ~~recovering said antibody.~~

3034. The method of claim 28-32 or 2933, further comprising the step of purifying said antibody.

3135. The method of any one of claims ~~28 or 2932~~to 34, further comprising the step of formulating said antibody into a pharmaceutical composition.

3236. A multi-specific antibody comprising a first anti-PD-1 agonist antigen-binding site and a second antigen-binding site, 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, 2 or 4 to 6.

~~33~~37. The multi-specific antibody of claim ~~32~~36, 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~~38. The multi-specific antibody of ~~any one of claims 32 to 34~~claim 36 or claim 37, wherein said antibody is a bi-specific antibody.