sequence of SEQ ID NO: 143, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 215, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions; or

(35) a CDR1 comprising the amino acid sequence of SEQ ID NO: 72, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 144, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 216, or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions.

[10a] In one aspect, the present disclosure refers to an isolated anti-PD-1 construct comprising a single-domain antibody (sdAb) moiety specifically recognizing PD-1 (~~"~~anti-PD-1 sdAb moiety~~"~~), wherein the anti-PD-1 sdAb moiety comprises any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 70, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 142, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 214~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 69, a CDR2 comprising the amino acid sequence of SEQ ID NO: 141, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 213;

(~~3~~2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 43, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 115, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 187~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(~~4~~3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 42, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 114, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(~~5~~4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 40, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 112, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 184~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(65) a CDR1 comprising the amino acid sequence of SEQ ID NO: 48, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 120, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 192~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(76) a CDR1 comprising the amino acid sequence of SEQ ID NO: 45, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 117, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(87) a CDR1 comprising the amino acid sequence of SEQ ID NO: 62, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 134, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 206~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(98) a CDR1 comprising the amino acid sequence of SEQ ID NO: 47, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 119, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 191~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(109) a CDR1 comprising the amino acid sequence of SEQ ID NO: 46, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 118, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 190~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(110) a CDR1 comprising the amino acid sequence of SEQ ID NO: 38, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 110, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 182~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(121) a CDR1 comprising the amino acid sequence of SEQ ID NO: 41, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 113, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3

comprising the amino acid sequence of SEQ ID NO: 185~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(132) a CDR1 comprising the amino acid sequence of SEQ ID NO: 37, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 109, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 181~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(143) a CDR1 comprising the amino acid sequence of SEQ ID NO: 44, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 116, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 188~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(154) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 111, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(165) a CDR1 comprising the amino acid sequence of SEQ ID NO: 49, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 121, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 193~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(176) a CDR1 comprising the amino acid sequence of SEQ ID NO: 50, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 122, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 194~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(187) a CDR1 comprising the amino acid sequence of SEQ ID NO: 51, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 123, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 195~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(198) a CDR1 comprising the amino acid sequence of SEQ ID NO: 52, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 124, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(2019) a CDR1 comprising the amino acid sequence of SEQ ID NO: 53, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 125, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 197~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(210) a CDR1 comprising the amino acid sequence of SEQ ID NO: 54, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 126, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 198~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(221) a CDR1 comprising the amino acid sequence of SEQ ID NO: 55, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 127, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 199~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(232) a CDR1 comprising the amino acid sequence of SEQ ID NO: 56, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 128, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 200~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(243) a CDR1 comprising the amino acid sequence of SEQ ID NO: 57, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 129, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(254) a CDR1 comprising the amino acid sequence of SEQ ID NO: 58, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 130, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3

comprising the amino acid sequence of SEQ ID NO: 202~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(2~~6~~5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 59, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 131, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 203~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(2~~7~~6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 60, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 132, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 204~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(2~~8~~7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 61, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 133, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 205~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(2~~9~~8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 63, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 135, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 207~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(30~~29~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 64, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 136, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 208~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(31~~0~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 65, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 137, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 209~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(321) a CDR1 comprising the amino acid sequence of SEQ ID NO: 66, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 138, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 210~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(332) a CDR1 comprising the amino acid sequence of SEQ ID NO: 67, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 139, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 211~~, or a variant thereof comprising up to about 3 amino acid substitutions~~; or

(343) a CDR1 comprising the amino acid sequence of SEQ ID NO: 68, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 140, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 212~~, or a variant thereof comprising up to about 3 amino acid substitutions~~.

[11] In some examples according to any one of the isolated anti-PD-1 constructs described above, the sdAb moiety specifically recognizing PD-1 comprises any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 37; a CDR2 comprising the amino acid sequence of SEQ ID NO: 109; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 181; or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions in the CDR regions;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 38; a CDR2 comprising the amino acid sequence of SEQ ID NO: 110; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 182; or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions in the CDR regions;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR2 comprising the amino acid sequence of SEQ ID NO: 111; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183; or a variant thereof comprising up to about 3 (such as about any of 1, 2, or 3) amino acid substitutions in the CDR regions;

acid sequence of SEQ ID NO: 385, and a V_L comprising LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 386. In some examples, the anti-PD-1 full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 385, and a light chain comprising the amino acid sequence of SEQ ID NO: 386. In some examples, the full-length antibody (or antigen binding portion comprising a V_H and a V_L) specifically recognizing PD-1 is derived from pembrolizumab (*e.g.*, Keytruda®) or nivolumab (*e.g.*, Opdivo®).

[18] In some examples according to any one of the isolated anti-PD-1 constructs described above, the isolated anti-PD-1 construct further comprises a biologically active protein or fragments thereof.

[19] Further provided is an isolated anti-PD-1 construct comprising an sdAb moiety specifically recognizing PD-1, wherein the sdAb moiety comprises CDR1, CDR2, and CDR3 of any one of SEQ ID NOs: 289-324.

[20] Further provided is an isolated anti-PD-1 construct (e.g., anti-PD-1 sdAb, anti-PD-1 HCAb (e.g., anti-PD-1 sdAb-Fc fusion), PD-1×TIGIT BABP, PD-1×LAG-3 BABP, PD-1×TIM-3 BABP, PD-1×CTLA-4 BABP, or PD-1×PD-1 BABP) that specifically binds to PD-1 competitively with the any of the isolated anti-PD-1 constructs described above.

[20a] In another ~~aspect~~example, the present disclosure refers to an isolated anti-PD-1 construct that specifically binds to PD-1 competitively with the isolated anti-PD-1 construct as disclosed herein.

[21] Further provided is a pharmaceutical composition comprising any one of the isolated anti-PD-1 constructs described above, and optionally a pharmaceutical acceptable carrier.

[21a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the isolated anti-PD-1 construct as disclosed herein, and optionally a pharmaceutical acceptable carrier.

[22] Another example of the present application provides a method of treating an individual having a PD-1-related disease (such as cancer, or immune-related disease), comprising administering to the individual an effective amount of any one of the pharmaceutical compositions described above. In some examples, the PD-1-related disease is cancer. In some examples, the cancer is a solid tumor, such as a colon cancer. In some examples, the PD-1-related disease is an immune-related disease. In some examples, immune-related disease is associated with a T cell dysfunctional disorder. In some examples, the T cell dysfunctional disorder is characterized by T cell anergy or decreased ability to secrete cytokines, proliferate or execute cytolytic activity. In some examples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some examples, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some examples, the PD-1 related disease is a pathogenic infection. In some examples, the method further comprises administering to the individual an additional therapy (e.g., cancer therapy), such as surgery, radiation, chemotherapy, immunotherapy, hormone therapy, or a combination thereof. In some examples, the additional therapy is immunotherapy. In some examples, the immunotherapy

comprises administering to the individual an effective amount of a second pharmaceutical composition comprising an immunomodulator, such as an immune checkpoint inhibitor (e.g., antibody specifically recognizing TIGIT, LAG-3, TIM-3, CTLA-4, PD-1, or PD-L1). In some examples, the pharmaceutical composition is administered systemically, such as intravenously (i.v.) or intraperitoneally (i.p.). In some examples, the pharmaceutical composition is administered locally, such as intratumorally. In some examples, the individual is a human.

[22a] In another aspect, the present disclosure refers to use of an effective amount of the isolated anti-PD-1 construct as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a cancer, a pathogenic infection, or an immune-related disease, wherein the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity, ~~or a pathogenic infection,~~ preferably wherein the cancer is a solid tumor, more preferably wherein the cancer is a colon cancer.

[23] Further provided is an isolated nucleic acid encoding any one of the isolated anti-PD-1 constructs described above. In some examples, the isolated nucleic acid comprises the nucleic acid sequence of any one of SEQ ID NOs: 253-288.

[23a] In another aspect, the present disclosure refers to an isolated nucleic acid encoding the isolated anti-PD-1 construct as disclosed herein.

[24] Further provided is a vector comprising any one of the isolated nucleic acids described above.

[24a] In another aspect, the present disclosure refers to a vector comprising the isolated nucleic acid as disclosed herein.

[25] Further provided is an isolated host cell comprising any one of the isolated nucleic acid or vector described above.

[25a] In another aspect, the present disclosure refers to an isolated host cell comprising the isolated nucleic acid as disclosed herein, or the vector as disclosed herein.

[26] Further provided is a kit comprising any one of the isolated anti-PD-1 construct, isolated nucleic acid, vector, or isolated host cell described above.

[27] Another example of the present application provides a method of producing any one of isolated anti-PD-1 constructs described above, comprising culturing a host cell comprising any one of the isolated nucleic acid or vector described above, or culturing any one of the isolated host cell described above, under conditions effective to express the encoded anti-PD-1 construct; and obtaining the expressed anti-PD-1 construct from said host cell. In some examples, the method further comprises producing a host cell comprising any one of the isolated nucleic acid or vector described above.

BRIEF DESCRIPTION OF THE DRAWINGS

[28] FIGs. 1A-1B depict immune response evaluation of the first camel after PD-1 immunization. FIG. 1A depicts immune response evaluation of pre-immune serum and immune serum of the first camel after the 6th immunization. FIG. 1B depicts immune response evaluation of heavy chain antibodies (IgG2 and IgG3) after the 6th immunization (terminal bleed). Heavy chain antibodies fractionated from pre-immune serum were used as negative controls.

[29] FIGs. 2A-2B depict immune response evaluation of the second camel after PD-1 immunization. FIG. 2A depicts immune response evaluation of pre-immune serum and immune serum of the 2nd camel after the 6th immunization. FIG. 2B depicts immune response evaluation of heavy chain antibodies (IgG2 and IgG3) after the 6th immunization (terminal bleed). Heavy chain antibodies fractionated from pre-immune serum were used as negative controls.

CLAIMS

What is claimed is:

1. An isolated anti-PD-1 construct comprising a single-domain antibody (sdAb) moiety specifically recognizing PD-1 (~~"~~anti-PD-1 sdAb moiety~~"~~), wherein the anti-PD-1 sdAb moiety comprises any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 70, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 142, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 214~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 69, a CDR2 comprising the amino acid sequence of SEQ ID NO: 141, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 213;

(3~~2~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 43, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 115, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 187~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(4~~3~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 42, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 114, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(5~~4~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 40, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 112, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 184~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(6~~5~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 48, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 120, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 192~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(76) a CDR1 comprising the amino acid sequence of SEQ ID NO: 45, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 117, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(87) a CDR1 comprising the amino acid sequence of SEQ ID NO: 62, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 134, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 206~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(98) a CDR1 comprising the amino acid sequence of SEQ ID NO: 47, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 119, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 191~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(109) a CDR1 comprising the amino acid sequence of SEQ ID NO: 46, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 118, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 190~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(110) a CDR1 comprising the amino acid sequence of SEQ ID NO: 38, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 110, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 182~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(121) a CDR1 comprising the amino acid sequence of SEQ ID NO: 41, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 113, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 185~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(132) a CDR1 comprising the amino acid sequence of SEQ ID NO: 37, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 109, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3

comprising the amino acid sequence of SEQ ID NO: 181~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(1~~4~~3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 44, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 116, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 188~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(1~~5~~4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 111, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(1~~6~~5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 49, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 121, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 193~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(1~~7~~6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 50, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 122, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 194~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(1~~8~~7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 51, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 123, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 195~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(1~~9~~8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 52, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 124, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(20~~19~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 53, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of

SEQ ID NO: 125, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 197~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(2~~1~~0) a CDR1 comprising the amino acid sequence of SEQ ID NO: 54, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 126, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 198~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(22~~1~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 55, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 127, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 199~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(23~~2~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 56, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 128, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 200~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(24~~3~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 57, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 129, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(25~~4~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 58, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 130, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 202~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(26~~5~~) a CDR1 comprising the amino acid sequence of SEQ ID NO: 59, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 131, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 203~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(276) a CDR1 comprising the amino acid sequence of SEQ ID NO: 60, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 132, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 204~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(287) a CDR1 comprising the amino acid sequence of SEQ ID NO: 61, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 133, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 205~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(298) a CDR1 comprising the amino acid sequence of SEQ ID NO: 63, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 135, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 207~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(3029) a CDR1 comprising the amino acid sequence of SEQ ID NO: 64, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 136, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 208~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(310) a CDR1 comprising the amino acid sequence of SEQ ID NO: 65, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 137, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 209~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(321) a CDR1 comprising the amino acid sequence of SEQ ID NO: 66~~, or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 138, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 210~~, or a variant thereof comprising up to about 3 amino acid substitutions~~;

(332) a CDR1 comprising the amino acid sequence of SEQ ID NO: 67, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 139, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3

comprising the amino acid sequence of SEQ ID NO: 211~~, or a variant thereof comprising up to about 3 amino acid substitutions~~; or

(3~~4~~3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 68, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ a CDR2 comprising the amino acid sequence of SEQ ID NO: 140, ~~or a variant thereof comprising up to about 3 amino acid substitutions;~~ and a CDR3 comprising the amino acid sequence of SEQ ID NO: 212~~, or a variant thereof comprising up to about 3 amino acid substitutions~~.

2. The isolated anti-PD-1 construct of claim 1, wherein the anti-PD-1 sdAb moiety comprises a heavy chain variable domain (V_HH) domain comprising the amino acid sequence of any one of the following:

a-1) the amino acid residue at position 37 is selected from the group consisting of F, Y, L, I, and V;

a-2) the amino acid residue at position 44 is selected from the group consisting of A, G, E, D, G, Q, R, S, and L;

a-3) the amino acid residue at position 45 is selected from the group consisting of L, R, and C;

a-4) the amino acid residue at position 103 is selected from the group consisting of W, R, G, and S; and

a-5) the amino acid residue at position 108 is Q; or

b-1) the amino acid residue at position 37 is selected from the group consisting of F, Y, L, I, and V;

b-2) the amino acid residue at position 44 is selected from the group consisting of E, Q, and G;

b-3) the amino acid residue at position 45 is R;

b-4) the amino acid residue at position 103 is selected from the group consisting of W, R, and S; and

b-5) the amino acid residue at position 108 is selected from the group consisting of Q and L;

wherein the amino acid position is according to Kabat numbering, and wherein position 108 can be optionally humanized to L when position 108 is Q.

3. The isolated anti-PD-1 construct of claim 1 or 2, wherein the anti-PD-1 sdAb moiety comprises a V_HH domain comprising the amino acid sequence of any one of SEQ ID NOs: 289-324, or a variant thereof having at least about 80% sequence identity ~~identify~~ to any one of SEQ ID NOs: 289-324.

4. The isolated anti-PD-1 construct of any one of claims 1-3, wherein the anti-PD-1 sdAb moiety is camelid, chimeric, human, partially humanized, or fully humanized.

5. The isolated anti-PD-1 construct of any one of claims 1-4, wherein the isolated anti-PD-1 construct is a heavy chain-only antibody (HCAb) comprising the anti-PD-1 sdAb moiety fused to an Fc fragment via an optional linker; optionally wherein the HCAb is monomeric or dimeric; optionally wherein the Fc fragment is a human IgG1 (hIgG1) Fc, effectorless (inert) hIgG1 Fc, hIgG4 Fc, or hIgG4 Fc

(S228P); and optionally wherein the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 367-376.

6. The isolated anti-PD-1 construct of claim 5, wherein the HCAb comprises the amino acid sequence of any one of SEQ ID NOs: 325-360.
7. The isolated anti-PD-1 construct of any one of claims 1-4, wherein the isolated anti-PD-1 construct further comprises a second antibody moiety specifically recognizing a second epitope, optionally wherein the second antibody moiety is a full-length antibody, a Fab, a Fab', a $(Fab')_2$, an Fv, a single chain Fv (scFv), an scFv-scFv, a minibody, a diabody, or an sdAb.
8. The isolated anti-PD-1 construct of claim 7, wherein the anti-PD-1 sdAb moiety and the second antibody moiety are connected by an optional peptide linker, optionally wherein the peptide linker comprises the amino acid sequence of any one of SEQ ID NOs: 367-376.
9. The isolated anti-PD-1 construct of claim 7 or 8, wherein the second antibody moiety is a full-length antibody consisting of two heavy chains and two light chains, optionally wherein the Fc fragment of the heavy chain is human IgG1 (hIgG1) Fc, effectorless (inert) hIgG1 Fc, hIgG4 Fc, or hIgG4 Fc (S228P).
10. The isolated anti-PD-1 construct of claim 9, wherein the isolated anti-PD-1 construct comprises a configuration selected from the group consisting of:

    (a) the N-terminus of the anti-PD-1 sdAb moiety is fused to the C-terminus of at least one of the heavy chains of the full-length antibody;

    (b) the C-terminus of the anti-PD-1 sdAb moiety is fused to the N-terminus of at least one of the heavy chains of the full-length antibody;

    (c) the N-terminus of the anti-PD-1 sdAb moiety is fused to the C-terminus of at least one of the light chains of the full-length antibody;

    (d) the C-terminus of the anti-PD-1 sdAb moiety is fused to the N-terminus of at least one of the light chains of the full-length antibody;

    (e) the isolated anti-PD-1 construct comprises four anti-PD-1 sdAb moieties, wherein the C-terminus of each anti-PD-1 sdAb moiety is fused to the N-terminus of each chain of the full-length antibody; and

    (f) the isolated anti-PD-1 construct comprises four anti-PD-1 sdAb moieties, wherein two of the four anti-PD-1 sdAb moieties are fused together, which is further fused to the N-terminus of each heavy chain of the full-length antibody.
11. The isolated anti-PD-1 construct of claim 9 or 10, wherein the full-length antibody specifically recognizes TIGIT, optionally wherein

    (a) the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain

comprising the amino acid sequence of SEQ ID NO: 377, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 378; or

(b) the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 377, and a light chain comprising the amino acid sequence of SEQ ID NO: 378.

12. The isolated anti-PD-1 construct of claim 9 or 10, wherein the full-length antibody specifically recognizes LAG-3, optionally wherein

(a) the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain comprising the amino acid sequence of SEQ ID NO: 379, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 380; or

(b) the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 379, and a light chain comprising the amino acid sequence of SEQ ID NO: 380.

13. The isolated anti-PD-1 construct of claim 9 or 10, wherein the full-length antibody specifically recognizes TIM-3, optionally wherein

(a) the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain comprising the amino acid sequence of SEQ ID NO: 381, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 382; or

(b) the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 381, and a light chain comprising the amino acid sequence of SEQ ID NO: 382.

14. The isolated anti-PD-1 construct of claim 9 or 10, wherein the full-length antibody specifically recognizes CTLA-4, optionally wherein

(a) the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain comprising the amino acid sequence of SEQ ID NO: 383, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 384; or

(b) the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 383, and a light chain comprising the amino acid sequence of SEQ ID NO: 384.

15. The isolated anti-PD-1 construct of claim 9 or 10, wherein the full-length antibody specifically recognizes PD-1, optionally wherein

(a) the full-length antibody comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a heavy chain comprising the amino acid sequence of SEQ ID NO: 385, and LC-CDR1, LC-CDR2, and LC-CDR3 of a light chain comprising the amino acid sequence of SEQ ID NO: 386; or

(b) the full-length antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 385, and a light chain comprising the amino acid sequence of SEQ ID NO: 386.

16. The isolated anti-PD-1 construct of claim 7 or 8, comprising a configuration selected from the group consisting of:

(a) the isolated anti-PD-1 construct comprises four polypeptides from N-terminus to C-terminus: (i) V_L-C_L, (ii) V_H-C_H1-optional peptide linker-first anti-PD-1 sdAb moiety-C_H2-C_H3, (iii) V_H-C_H1-optional peptide linker-second anti-PD-1 sdAb moiety-C_H2-C_H3, and (iv) V_L-C_L; wherein V_L-C_L of polypeptide (i) and V_H-C_H1 of polypeptide (ii) form a second antibody moiety specifically recognizing a second epitope, and V_L-C_L of polypeptide (iv) and V_H-C_H1 of polypeptide (iii) form a third antibody moiety specifically recognizing a third epitope;

(b) the isolated anti-PD-1 construct comprises two polypeptides from N-terminus to C-terminus: (i) first scFv specifically recognizing a second epitope-optional peptide linker-first anti-PD-1 sdAb moiety-C_H2-C_H3, and (ii) second scFv specifically recognizing a third epitope-optional peptide linker-second anti-PD-1 sdAb moiety-C_H2-C_H3;

(c) the isolated anti-PD-1 construct comprises four polypeptides from N-terminus to C-terminus: (i) V_L-C_L-optional peptide linker-first anti-PD-1 sdAb moiety-C_L, (ii) V_H-C_H1-optional peptide linker-second anti-PD-1 sdAb moiety-C_H1-C_H2-C_H3, (iii) V_H-C_H1-optional peptide linker-third anti-PD-1 sdAb moiety-C_H1-C_H2-C_H3, and (iv) V_L-C_L-optional peptide linker-fourth anti-PD-1 sdAb moiety-C_L; wherein V_L-C_L of polypeptide (i) and V_H-C_H1 of polypeptide (ii) form a second antibody moiety specifically recognizing a second epitope, and V_L-C_L of polypeptide (iv) and V_H-C_H1 of polypeptide (iii) form a third antibody moiety specifically recognizing a third epitope; and

(d) the isolated anti-PD-1 construct comprises four polypeptides from N-terminus to C-terminus: (i) first anti-PD-1 sdAb moiety-C_L, (ii) first scFv specifically recognizing a second epitope-optional peptide linker-second anti-PD-1 sdAb moiety-C_H1-C_H2-C_H3, (iii) second scFv specifically recognizing a third epitope-optional peptide linker-third anti-PD-1 sdAb moiety-C_H1-C_H2-C_H3, and (iv) fourth anti-PD-1 sdAb moiety-C_L.

~~17. An isolated anti-PD-1 construct that specifically binds to PD-1 competitively with the isolated anti-PD-1 construct of any one of claims 1-16.~~

~~18.~~17. A pharmaceutical composition comprising the isolated anti-PD-1 construct of any one of claims 1-16~~7~~, and optionally a pharmaceutical acceptable carrier.

~~19.~~18. Use of an effective amount of the isolated anti-PD-1 construct of any one of claims 1-16~~7~~ or the pharmaceutical composition of claim 1~~78~~ in the manufacture of a medicament for treating a cancer, a pathogenic infection, or an immune-related disease, wherein the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity, ~~or a pathogenic infection,~~ preferably wherein the cancer is a solid tumor, more preferably wherein the cancer is a colon cancer.

~~20.~~19. An isolated nucleic acid encoding the isolated anti-PD-1 construct of any one of claims 1-16~~7~~.

~~21.~~20. A vector comprising the isolated nucleic acid of claim 19~~20~~.

~~22.~~21. An isolated host cell comprising the isolated nucleic acid of claim 19~~20~~, or the vector of claim 20~~21~~.