

WHAT IS CLAIMED IS:

1. An antigen-binding protein construct, comprising a first antigen-binding site that specifically binds to PD-1, and a second antigen-binding site that specifically binds to CD40.

2. The antigen-binding protein construct of claim 1, characterized by one or more of the following:

(1) wherein the first antigen-binding site binds to a cell expressing PD-1, optionally, the cell expressing PD-1 is a T cell, a B cell, a NK cell, or a myeloid cell (e.g., a macrophage, a Myeloid-derived suppressor cell (MDSC));

(2)3. The antigen-binding protein construct of claim 1 or 2, wherein the second antigen-binding site binds to a cell expressing CD40, optionally, the cell expressing CD40 is an antigen-presenting cell;-

(3)4. The antigen-binding protein construct of any one of claims 1-3, wherein the antigen-binding protein construct is capable of activating CD40 pathway, wherein the activation of CD40 pathway depends on the binding of the antigen-binding protein construct to a cell expressing PD-1, optionally, the cell expressing PD-1 is a T cell, a B cell, a NK cell, or a myeloid cell (e.g., a macrophage, a Myeloid-derived suppressor cell (MDSC));

(4)5. The antigen-binding protein construct of any one of claims 1-4, wherein the antigen-binding protein construct induces CD40 pathway activities in the presence of one or more cells expressing PD-1, optionally, the cell expressing PD-1 is a T cell, a B cell, a NK cell, or a myeloid cell (e.g., a macrophage, a Myeloid-derived suppressor cell (MDSC));-

(5)6. The antigen-binding protein construct of any one of claims 1-5, wherein the antigen-binding protein construct induces CD40 pathway activities in a tumor microenvironment or a tumor-draining lymph node;-

(6)7. The antigen-binding protein construct of any one of claims 1-6, wherein the antigen-binding protein construct does not induce CD40 pathway activities in the absence of one or more

cells expressing PD-1, optionally, the cell expressing PD-1 is a T cell, a B cell, a NK cell, or a myeloid cell (e.g., a macrophage, a Myeloid-derived suppressor cell (MDSC));-

~~8. The antigen-binding protein construct of any one of claims 1-7, wherein the cell expressing PD-1 is a T cell, a B cell, a NK cell, or a myeloid cell (e.g., a macrophage, a Myeloid-derived suppressor cell (MDSC)).~~

~~9. The antigen-binding protein construct of any one of claims 1-8, wherein the cell expressing CD40 is an antigen-presenting cell.~~

~~(7)10. The antigen-binding protein construct of any one of claims 1-9, wherein the antigen-binding protein construct comprises an Fc region, wherein the second antigen-binding site is linked to the Fc region;~~

~~(8)11. The antigen-binding protein construct of any one of claims 1-10, wherein the antigen-binding protein construct comprises an Fc region, wherein the second antigen-binding site is linked to the C-terminal of the Fc region;~~

~~(9)12. The antigen-binding protein construct of any one of claims 1-11, wherein the antigen-binding protein construct comprises an Fc region, wherein the antigen-binding protein construct is incapable of activating CD40 pathway through Fc receptor-mediated activity;~~

~~(10)13. The antigen-binding protein construct of any one of claims 1-12, wherein the antigen-binding protein construct is a bispecific antibody;~~

~~(11)14. The antigen-binding protein construct of any one of claims 1-13, wherein the first antigen-binding site that specifically binds to PD-1 comprises a ScFv₂ or a VHH domain.~~

~~15. The antigen-binding protein construct of any one of claims 1-13, wherein the antigen binding site that specifically binds to PD-1 comprises, or a PD-1 ligand (e.g., PD-L1) or a soluble portion thereof;~~

~~(12)~~16. The antigen-binding protein construct of any one of claims 1-15, wherein the second antigen-binding site that specifically binds to CD40 comprises a ScFv₂ or a VHH domain;

~~17. The antigen-binding protein construct of any one of claims 1-15, wherein the second antigen binding site that specifically binds to CD40 comprises, or~~ a CD40 ligand (e.g., CD40L) or a soluble portion thereof.

~~18~~3. The antigen-binding protein construct of claim 1 or 2~~any one of claims 1-17~~, wherein the first antigen binding site comprises a heavy chain variable region and a light chain variable region₂

~~19. The antigen-binding protein construct of claim 18~~, wherein the heavy chain variable region (VH1) of the first antigen binding site comprises complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR1 amino acid sequence, the VH1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR2 amino acid sequence, and the VH1 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR3 amino acid sequence; and

the light chain variable region (VL1) of the first antigen binding site ~~comprising~~ comprises CDRs 1, 2, and 3, wherein the VL1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR1 amino acid sequence, the VL1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR2 amino acid sequence, and the VL1 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR3 amino acid sequence, wherein the selected VH1 CDRs 1, 2, and 3 amino acid sequences, the selected VL1 CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1, 2, and 3, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4, 5, and 6, respectively, according to the Kabat numbering scheme;

(2) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19, 20, and 21, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 22, 23, and 24, respectively, according to the Chothia numbering scheme;

(3) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 7, 8, and 9, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 10, 11, and 12, respectively, according to the Kabat numbering scheme;

(4) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 25, 26, and 27, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 28, 29, and 30, respectively, according to the Chothia numbering scheme;

(5) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13, 14, and 15, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 16, 17, and 18, respectively, according to the Kabat numbering scheme; and

(6) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 31, 32, and 33, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 34, 35, and 36, respectively, according to the Chothia numbering scheme.

~~204.~~ The antigen-binding protein construct of any one of claims 1-~~193~~, wherein the second antigen binding site comprises a heavy chain variable region and a light chain variable region-

~~21. The antigen-binding protein construct of claim 20,~~ wherein the heavy chain variable region (VH2) of the second antigen binding site comprises CDRs 1, 2, and 3, wherein the VH2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR1 amino acid sequence, the VH2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR2 amino acid sequence, and the VH2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR3 amino acid sequence; and the light chain variable region (VL2) of the second antigen binding site comprises CDRs 1, 2, and 3, wherein the VL2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR1 amino acid sequence, the VL2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR2 amino acid sequence,

and the VL2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR3 amino acid sequence,

wherein the selected VH2 CDRs 1, 2, and 3 amino acid sequences, and the selected VL2 CDRs 1, 2, and 3 amino acid sequences are one of the following:

~~(1) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 59, 60, and 61, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 62, 63, and 64, respectively, according to the Kabat numbering scheme;~~

~~(2) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 77, 78, and 79, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 80, 81, and 82, respectively, according to the Chothia numbering scheme;~~

~~(3)~~ the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 65, 66, and 67, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 68, 69, and 70, respectively, according to the Kabat numbering scheme;

~~(4)~~ the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 83, 84, and 85, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 86, 87, and 88, respectively, according to the Chothia numbering scheme;

(3) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 59, 60, and 61, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 62, 63, and 64, respectively, according to the Kabat numbering scheme;

(4) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 77, 78, and 79, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 80, 81, and 82, respectively, according to the Chothia numbering scheme;

(5) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 71, 72, and 73, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 74, 75, and 76, respectively, according to the Kabat numbering scheme; and

(6) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 89, 90, and 91, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 92, 93, and 94, respectively, according to the Chothia numbering scheme.

~~225~~. An antigen-binding protein construct, comprising

a first heavy chain variable region and a first light chain variable region, wherein the first heavy chain variable region and the first light chain variable region associate with each other, forming a first antigen binding site that specifically binds to PD-1; and

a second heavy chain variable region and a second light chain variable region, wherein the second heavy chain variable region and the second light chain variable region associate with each other, forming a second antigen binding site that specifically binds to CD40.

~~236.~~ The antigen-binding protein construct of claim ~~225~~, wherein the antigen-binding protein construct comprises

a first polypeptide comprising the first heavy chain variable region, a first heavy chain constant region 2 (CH2), and a first heavy chain constant region 3 (CH3); and

a second polypeptide comprising the second heavy chain variable region, a second heavy chain constant region 2 (CH2), and a second heavy chain constant region 3 (CH3).

~~247.~~ The antigen-binding protein construct of claim ~~236~~, characterized by one of the following:

~~(1) wherein the antigen-binding protein construct comprises~~

a third polypeptide comprising the first light chain variable region; and

a fourth polypeptide comprising the second light chain variable region;

~~(2) 25. The antigen-binding protein construct of claim 23, wherein the second polypeptide further comprises the second light chain variable region;~~

~~(3) the second polypeptide further comprises the second light chain variable region~~~~26. The antigen-binding protein construct of claim 25, and wherein the antigen-binding protein construct comprises a third polypeptide comprising the first light chain variable region;~~

~~(4) 27. The antigen-binding protein construct of claim 23 or 25, wherein the second polypeptide further comprises the second light chain variable region, and/or the first polypeptide further comprises the first light chain variable region.~~

28. The antigen-binding protein construct of claim ~~22~~5, wherein the antigen-binding protein construct comprises

a first polypeptide comprising the first heavy chain variable region, the second heavy chain variable region, and the second light chain variable region; and

a second polypeptide comprising the first light chain variable region;

~~29. The antigen-binding protein construct of claim 28, wherein~~optionally, the first polypeptide further comprises a heavy chain constant region 1 (CH1), a heavy chain constant region 2 (CH2), and a heavy chain constant region 3 (CH3).

~~30~~9. The antigen-binding protein construct of any one of claims ~~5-8~~5-8~~22-29~~, wherein the first heavy chain variable region (VH1) comprises ~~regions~~complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR1 amino acid sequence, the VH1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR2 amino acid sequence, and the VH1 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR3 amino acid sequence; and

the first light chain variable region (VL1) ~~comprising~~comprises CDRs 1, 2, and 3, wherein the VL1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR1 amino acid sequence, the VL1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR2 amino acid sequence, and the VL1 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR3 amino acid sequence,

wherein the selected VH1 CDRs 1, 2, and 3 amino acid sequences, and the selected VL1 CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1, 2, and 3, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4, 5, and 6, respectively, according to the Kabat numbering scheme;

(2) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19, 20, and 21, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 22, 23, and 24, respectively, according to the Chothia numbering scheme;

(3) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 7, 8, and 9, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 10, 11, and 12, respectively, according to the Kabat numbering scheme;

(4) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 25, 26, and 27, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 28, 29, and 30, respectively, according to the Chothia numbering scheme;

(5) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 13, 14, and 15, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 16, 17, and 18, respectively, according to the Kabat numbering scheme; and

(6) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 31, 32, and 33, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 34, 35, and 36, respectively, according to the Chothia numbering scheme.

~~3110~~. The antigen-binding protein construct of any one of claims ~~5-9-22-30~~, wherein the second heavy chain variable region (VH2) ~~comprising~~ comprises CDRs 1, 2, and 3, wherein the VH2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR1 amino acid sequence, the VH2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR2 amino acid sequence, and the VH2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR3 amino acid sequence; and

the second light chain variable region (VL2) ~~comprising~~ comprises CDRs 1, 2, and 3, wherein the VL2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR1 amino acid sequence, the VL2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR2 amino acid sequence, and the VL2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR3 amino acid sequence,

wherein the selected VH2 CDRs 1, 2, and 3 amino acid sequences, and the selected VL2 CDRs 1, 2, and 3 amino acid sequences are one of the following:

~~(1) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 59, 60, and 61, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 62, 63, and 64, respectively, according to the Kabat numbering scheme;~~

~~(2) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 77, 78, and 79, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 80, 81, and 82, respectively, according to the Chothia numbering scheme;~~

(31) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 65, 66, and 67, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 68, 69, and 70, respectively, according to the Kabat numbering scheme;

(42) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 83, 84, and 85, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 86, 87, and 88, respectively, according to the Chothia numbering scheme;

(3) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 59, 60, and 61, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 62, 63, and 64, respectively, according to the Kabat numbering scheme;

(4) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 77, 78, and 79, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 80, 81, and 82, respectively, according to the Chothia numbering scheme;

(5) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 71, 72, and 73, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 74, 75, and 76, respectively, according to the Kabat numbering scheme; and

(6) the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 89, 90, and 91, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 92, 93, and 94, respectively, according to the Chothia numbering scheme.

~~3211.~~ The antigen-binding protein construct of claim ~~30-9~~ or ~~3110~~, wherein

(1) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1, 2, and 3, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4, 5, and 6, respectively, the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 65, 66, and 67, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 68, 69, and 70, respectively, according to the Kabat numbering scheme; or

(2) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19, 20, and 21, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in

SEQ ID NOs: 22, 23, and 24, respectively, the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 83, 84, and 85, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 86, 87, and 88, respectively, according to the Chothia numbering scheme.

~~33~~12. The antigen-binding protein construct of any one of claims ~~22-32~~5-10, wherein the first heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 40, 41, 42, or 53, and the first light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 43, 44, 45, or 54-

~~34. The antigen-binding protein construct of any one of claims 22-31, or~~ wherein the first heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 46, 47, 48, 49, or 55, and the first light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 50, 51, 52, or 56-

~~35. The antigen-binding protein construct of any one of claims 22-31, or~~ wherein the first heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 57, and the first light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 58-

~~36. The antigen-binding protein construct of any one of claims 22-31, or~~ wherein the second heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 98, 99, 100, or 120, and the second light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 101, 102, 103, 104, or 121-

~~37. The antigen-binding protein construct of any one of claims 22-32, or~~ wherein the second heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 105, 106, 107, 108, 122, 126, or 128, and the second light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 109, 110, 111, 123, 127, or 129-

~~38. The antigen-binding protein construct of any one of claims 22-31, or wherein the second heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 112, 113, 114, 115, or 124, and the second light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 116, 117, 118, 119, or 125.~~

~~39. The antigen-binding protein construct of any one of claims 22-32, 33, and 37, or wherein the first heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 41, the first light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 45, the second heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 108 or 126, and the second light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 110 or 127.~~

~~40~~13. The antigen-binding protein construct of claim 26, wherein the second polypeptide further comprises the second light chain variable region, and the antigen-binding protein construct comprises a third polypeptide comprising the first light chain variable region, wherein the first polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 130, and the third polypeptide comprise a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 131.

~~41. The antigen-binding protein construct of claim 26 or 40, and/or wherein the second polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 132 or 133.~~

~~42. The antigen-binding protein construct of claim 26, wherein the first polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 130; the second polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 132 or 133; and the third polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 131.~~

~~43~~14. The antigen-binding protein construct of claim ~~28 or 29~~8, wherein the first polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 134 or 135, and the second polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 136.

~~44. The antigen-binding protein construct of claim 28 or 29, or~~ wherein the first polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 137 or 138, and the second polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 139.

~~45~~15. The antigen-binding protein construct of any one of claims 1-~~44~~14, wherein the antigen-binding protein construct is a bispecific antibody.

~~46. The antigen-binding protein construct of any one of claims 1-44, or~~ wherein the antigen-binding protein construct is a Fab-scFv-Fc.

~~47. The antigen-binding protein construct of any one of claims 1-44, or~~ wherein the antigen-binding protein construct is a TrioMab, a bispecific antibody with a common light chain, a CrossMab, a 2:1 CrossMab, a 2:2 CrossMab, a Duobody, a Dual-variable-domain antibody (DVD-Ig), a scFv-IgG, a IgG-IgG format antibody, a Fab-scFv-Fc format antibody, a TF, an ADAPTIR, a Bispecific T cell Engager (BiTE), a BiTE-Fc, a Dual affinity retargeting (DART), a DART-Fc, a tetravalent DART, a Tandem diabody (TandAb), a scFv-scFv-scFv, an ImmTAC, a Tri-specific nanobody, or a Trispecific Killer Engager (TriKE);

~~optionally~~48. The antigen-binding protein construct of any one of claims 1-47, wherein the antigen binding protein construct comprises one or more heavy chain constant domains from IgG1 or IgG4;

~~optionally~~49. The antigen-binding protein construct of any one of claims 1-48, wherein the antigen binding protein construct comprises one or more heavy chain constant domains and the

one or more heavy chain constant domain comprises LALA mutations and/or knob-into-hole (KIH) mutations.

~~50. A bispecific antibody or antigen-binding fragment thereof, comprising
a first heavy chain polypeptide comprising a first heavy chain variable region;
a first light chain polypeptide comprising a first light chain variable region;
a second heavy chain polypeptide comprising a second heavy chain variable region; and
a second light chain polypeptide, comprising a second light chain variable region;
wherein the first heavy chain variable region and the first light chain variable region associate
with each other, forming a first antigen-binding site that specifically binds to PD-1, and the
second heavy chain variable region and the second light chain variable region associate with
each other, forming a second antigen-binding site that specifically binds to CD40.~~

~~51. The bispecific antibody or antigen-binding fragment thereof of claim 50, comprising
the first heavy chain variable region (VH1) comprising complementarity determining regions
(CDRs) 1, 2, and 3, wherein the VH1 CDR1 region comprises an amino acid sequence that is at
least 80% identical to a selected VH1 CDR1 amino acid sequence, the VH1 CDR2 region
comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR2 amino
acid sequence, and the VH1 CDR3 region comprises an amino acid sequence that is at least 80%
identical to a selected VH1 CDR3 amino acid sequence;
the first light chain variable region (VL1) comprising CDRs 1, 2, and 3, wherein the VL1 CDR1
region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR1
amino acid sequence, the VL1 CDR2 region comprises an amino acid sequence that is at least
80% identical to a selected VL1 CDR2 amino acid sequence, and the VL1 CDR3 region
comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR3 amino
acid sequence;
the second heavy chain variable region (VH2) comprising complementarity determining regions
(CDRs) 1, 2, and 3, wherein the VH2 CDR1 region comprises an amino acid sequence that is at
least 80% identical to a selected VH2 CDR1 amino acid sequence, the VH2 CDR2 region
comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR2 amino~~

acid sequence, and the VH2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR3 amino acid sequence; and

the second light chain variable region (VL2) comprising CDRs 1, 2, and 3, wherein the VL2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR1 amino acid sequence, the VL2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR2 amino acid sequence, and the VL2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR3 amino acid sequence;

wherein the selected VH1 CDRs 1, 2, and 3 amino acid sequences, the selected VL1 CDRs 1, 2, and 3 amino acid sequences, the selected VH2 CDRs 1, 2, and 3 amino acid sequences, and the selected VL2 CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1, 2, and 3, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4, 5, and 6, respectively, the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 65, 66, and 67, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 68, 69, and 70, respectively, according to the Kabat numbering scheme; and

(2) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19, 20 and 21, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 22, 23, and 24, respectively, the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 83, 84, and 85, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 86, 87, and 88, respectively, according to the Chothia numbering scheme.

52. The bispecific antibody or antigen-binding fragment thereof of claim 50 or 51, wherein the first heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 41, the first light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 45, the second heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 108 or 126, and the second light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 110 or 127.

~~53. The bispecific antibody or antigen-binding fragment thereof of any one of claims 50-52, wherein the first heavy chain polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 130, and the first light chain polypeptide comprise a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 131.~~

5416. A bispecific antibody or antigen-binding fragment thereof, comprising
a heavy chain polypeptide comprising a first heavy chain variable region;
a light chain polypeptide comprising a first light chain variable region; and
a single-chain variable fragment polypeptide comprising a second heavy chain variable region,
and a second light chain variable region,
wherein the first heavy chain variable region and the first light chain variable region associate with each other, forming a first antigen binding site that specifically binds to PD-1, and the second heavy chain variable region and the second light chain variable region associate with each other, forming a second antigen binding site that specifically binds to CD40.

~~55. The bispecific antibody or antigen-binding fragment thereof of claim 54, wherein the single-chain variable fragment polypeptide comprises from N-terminus to C-terminus: the second heavy chain variable region; a linker peptide sequence; the second light chain variable region; a heavy chain constant region 2 (CH2); and a heavy chain constant region 3 (CH3).~~

~~56. The bispecific antibody or antigen-binding fragment thereof of claim 55, wherein the linker peptide sequence comprises a sequence that is at least 80% identical to
ASTGGGSGGGSGGGSGGGGS (SEQ ID NO: 152).~~

~~57. The bispecific antibody or antigen-binding fragment thereof of claim any one of claims 54-56, comprising
the first heavy chain variable region (VH1) comprising complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR1 amino acid sequence, the VH1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR2 amino~~

acid sequence, and the VH1 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR3 amino acid sequence;

the first light chain variable region (VL1) comprising CDRs 1, 2, and 3, wherein the VL1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR1 amino acid sequence, the VL1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR2 amino acid sequence, and the VL1 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR3 amino acid sequence;

the second heavy chain variable region (VH2) comprising complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR1 amino acid sequence, the VH2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR2 amino acid sequence, and the VH2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR3 amino acid sequence; and

the second light chain variable region (VL2) comprising CDRs 1, 2, and 3, wherein the VL2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR1 amino acid sequence, the VL2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR2 amino acid sequence, and the VL2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR3 amino acid sequence;

wherein the selected VH1 CDRs 1, 2, and 3 amino acid sequences, the selected VL1 CDRs 1, 2, and 3 amino acid sequences, the selected VH2 CDRs 1, 2, and 3 amino acid sequences, and the selected VL2 CDRs 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1, 2, and 3, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4, 5, and 6, respectively, the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 65, 66, and 67, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 68, 69, and 70, respectively, according to the Kabat numbering scheme; and

(2) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19, 20, and 21, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in

~~SEQ ID NOs: 22, 23, and 24, respectively, the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 83, 84, and 85, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 86, 87, and 88, respectively, according to the Chothia numbering scheme.~~

~~58. The bispecific antibody or antigen binding fragment thereof of any one of claims 54-57, wherein the first heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 41, the first light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 45, the second heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 108 or 126, and the second light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 110 or 127.~~

~~59. The bispecific antibody or antigen binding fragment thereof of any one of claims 54-58, wherein~~

~~(1) the heavy chain polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 130, and the light chain polypeptide comprise a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 131; and~~

~~(2) the single-chain variable fragment polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 132 or 133.~~

~~60~~17. A bispecific antibody or antigen-binding fragment thereof, comprising a heavy chain polypeptide comprising a first heavy chain variable region, and a light chain polypeptide comprising a first light chain variable region; wherein a single-chain variable fragment polypeptide is linked to the C-terminus of the heavy chain polypeptide; wherein the single-chain variable fragment polypeptide comprises a second heavy chain variable region and a second light chain variable region; wherein the first heavy chain variable region and the first light chain variable region associate with each other, forming a first antigen binding site that specifically binds to PD-1, and the second heavy chain variable region and the second light chain variable region associate with each other, forming a second antigen binding site that specifically binds to CD40.

~~61. The bispecific antibody or antigen-binding fragment thereof of claim 60, wherein the single-chain variable fragment polypeptide is linked to the first heavy chain polypeptide through a first linker peptide sequence.~~

~~62. The bispecific antibody or antigen-binding fragment thereof of claim 61, wherein the first linker peptide sequence comprises a sequence that is at least 80% identical to GGGSGGGSGGGGS (SEQ ID NO: 153).~~

~~63. The bispecific antibody or antigen-binding fragment thereof of any one of claims 60-62, wherein the single-chain variable fragment polypeptide comprises from N-terminus to C-terminus: the second light chain variable region; a second linker peptide sequence; and the second heavy chain variable region.~~

~~64. The bispecific antibody or antigen-binding fragment thereof of claim 63, wherein the second linker peptide sequence comprises a sequence that is at least 80% identical to GGGSGGGSGGGSGGGGS (SEQ ID NO: 154).~~

~~65. The bispecific antibody or antigen-binding fragment thereof of any one of claims 60-64, comprising~~
~~the first heavy chain variable region (VH1) comprising complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR1 amino acid sequence, the VH1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR2 amino acid sequence, and the VH1 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH1 CDR3 amino acid sequence;~~
~~the first light chain variable region (VL1) comprising CDRs 1, 2, and 3, wherein the VL1 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR1 amino acid sequence, the VL1 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR2 amino acid sequence, and the VL1 CDR3 region~~

comprises an amino acid sequence that is at least 80% identical to a selected VL1 CDR3 amino acid sequence;

~~the second heavy chain variable region (VH2) comprising complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR1 amino acid sequence, the VH2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR2 amino acid sequence, and the VH2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VH2 CDR3 amino acid sequence; and~~

~~the second light chain variable region (VL2) comprising CDRs 1, 2, and 3, wherein the VL2 CDR1 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR1 amino acid sequence, the VL2 CDR2 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR2 amino acid sequence, and the VL2 CDR3 region comprises an amino acid sequence that is at least 80% identical to a selected VL2 CDR3 amino acid sequence;~~

~~wherein the selected VH1 CDRs 1, 2, and 3 amino acid sequences, the selected VL1 CDRs 1, 2, and 3 amino acid sequences, the selected VH2 CDRs 1, 2, and 3 amino acid sequences, and the selected VL2 CDRs 1, 2, and 3 amino acid sequences are one of the following:~~

~~(1) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 1, 2, and 3, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4, 5, and 6, respectively, the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 65, 66, and 67, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 68, 69, and 70, respectively, according to the Kabat numbering scheme; and~~

~~(2) the selected VH1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 19, 20, and 21, respectively, and the selected VL1 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 22, 23, and 24, respectively, the selected VH2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 83, 84, and 85, respectively, and the selected VL2 CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 86, 87, and 88, respectively, according to the Chothia numbering scheme.~~

~~66. The bispecific antibody or antigen-binding fragment thereof of any one of claims 60-65, wherein the first heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 41, the first light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 45, the second heavy chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 108 or 126, and the second light chain variable region comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 110 or 127.~~

~~67. The bispecific antibody or antigen-binding fragment thereof of any one of claims 60-66, wherein~~

~~(1) the heavy chain polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 134 or 135; and~~

~~(2) the light chain polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 136.~~

~~68. The bispecific antibody or antigen-binding fragment thereof of any one of claims 60-66, wherein~~

~~(1) the heavy chain polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 137 or 138; and~~

~~(2) the light chain polypeptide comprises a sequence that is at least 80%, 85%, 90%, or 95% identical to SEQ ID NO: 139.~~

~~69. A bispecific antibody or antigen-binding fragment thereof, comprising:~~

~~an antibody comprising an Fc region, wherein the antibody specifically binds to a target, and an antigen-binding site that specifically binds to CD40,~~

~~wherein the antigen-binding site is linked to the Fc region of the antibody.~~

~~70. The bispecific antibody of claim 69, wherein the bispecific antibody induces CD40 pathway activities in an immune cell in the presence of one or more cells expressing the target.~~

~~71. The bispecific antibody of claim 69, wherein the bispecific antibody is capable of activating CD40 pathway, wherein the activation of CD40 pathway depends on the binding of the antigen-binding protein construct to a cell expressing the target.~~

~~72. The bispecific antibody of claim 69, wherein the bispecific antibody induces CD40 pathway activities in a tumor microenvironment or a tumor draining lymph node.~~

~~73. The bispecific antibody of claim 69, wherein the bispecific antibody does not induce CD40 pathway activities in the absence of one or more cells expressing the target.~~

~~74. The bispecific antibody of any one of claims 69-73, wherein the bispecific antibody is incapable of activating CD40 pathway through FC-mediated activity.~~

~~75. The bispecific antibody of any one of claims 69-74, wherein the target is an immune checkpoint molecule.~~

~~76. The bispecific antibody of any one of claims 69-74, wherein the target is a cancer specific antigen or a cancer-associated antigen.~~

~~77. The bispecific antibody of any one of claims 69-74, wherein the target is PD-1.~~

~~78. The bispecific antibody of any one of claims 69-77, wherein the antigen binding site that specifically binds to CD40 comprises a ScFv or a VHH domain.~~

~~79. The bispecific antibody of any one of claims 69-77, wherein the antigen binding site that specifically binds to CD40 comprises a CD40 ligand (e.g., CD40L) or a soluble portion thereof.~~

~~80. The bispecific antibody of any one of claims 69-79, wherein the antigen binding site that specifically binds to CD40 is linked to the C-terminal of the Fc region.~~

~~81. The bispecific antibody of any one of claims 69-79, wherein the antigen binding site that specifically binds to CD40 is inserted in the Fc region.~~

~~82. An antibody drug conjugate comprising the antigen binding protein construct of any one of claims 1-49, or the bispecific antibody or antigen binding fragment thereof of any one of claims 50-81, covalently bound to a therapeutic agent.~~

~~83. The antibody drug conjugate of claim 82, wherein the therapeutic agent is a cytotoxic or cytostatic agent.~~

~~8418. Use of A method of treating a subject having cancer, the method comprising administering a therapeutically effective amount of a composition comprising the antigen-binding protein construct of any one of claims 1-4915, or the bispecific antibody or antigen-binding fragment thereof of any one of claims 50-81 16 or 17, or the antibody drug conjugate of claim 82 or 83 in manufacture of a medicament, wherein the medicament is used for;~~to the subject.

(i) treating a subject having a cancer;

(ii) decreasing the rate of tumor growth in a subject in need thereof; and/or

(iii) killing a tumor cell in a subject in need thereof.

~~8519. The method-use of claim 8418, characterized by one or more of the following:~~

(1) wherein the subject has a solid tumor;₁

(2)~~86. The method of claim 84, wherein the cancer is non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), head and neck cancer, renal cell carcinoma (RCC), melanoma, bladder cancer, gastric cancer, urothelial cancer, Merkel-cell carcinoma, triple-negative breast cancer (TNBC), or colorectal carcinoma;~~₁

(3)~~87. The method of claim 84, wherein the cancer is melanoma, pancreatic carcinoma, mesothelioma, or a hematological malignancy;~~₁

~~(4)88. The method of any one of claims 84-87, wherein the composition is administered in combination with method further comprises administering an anti-CTLA4 antibody, an anti-Her2 antibody, or an antibody targeting a tumor-associated antigen (TAA), to the subject.;~~

~~(5)89. The method of any one of claims 84-88, wherein the composition is administered in combination with method further comprises administering a chemotherapy to the subject.~~

~~90. A method of decreasing the rate of tumor growth, the method comprising administering to a subject in need thereof an effective amount of a composition comprising the antigen-binding protein construct of any one of claims 1-49, the bispecific antibody or antigen-binding fragment of any one of claims 50-81, or the antibody drug conjugate of claim 82 or 83, to the subject.~~

~~91. A method of killing a tumor cell, the method comprising contacting the tumor cell with an effective amount of a composition comprising the antigen-binding protein construct of any one of claims 1-49, the bispecific antibody or antigen-binding fragment of any one of claims 50-81, or the antibody drug conjugate of claim 82 or 83.~~

~~92)20. A pharmaceutical composition comprising the antigen-binding protein construct of any one of claims 1-4915, or the bispecific antibody or antigen-binding fragment thereof of any one of claims 50-8116 or 17, or the antibody drug conjugate of claim 82 or 83, and a pharmaceutically acceptable carrier.~~