[0034] Despite such advances in identifying the molecules involved in mammalian immune responses, a need remains for improved therapies for treating cancers and infectious diseases. The present invention is directed to this and other goals.

SUMMARY

[0035] The present disclosure is directed to a combination therapy for the treatment of cancer and pathogen-associated diseases, that comprises the administration of: (1) a molecule (*e.g.*, a diabody, an scFv, an antibody, a TandAb, *etc*.) capable of binding PD-1 or a natural ligand of PD-1, and (2) a molecule (*e.g.,* a diabody, a BiTe, a bispecific antibody, a CAR, *etc.*) capable of mediating the redirected killing of a target cell (*e.g.*, a cancer cell or a pathogen-infected cell, *etc*.) expressing a Disease Antigen. The disclosure particularly concerns the example in which the molecule capable of mediating the redirected killing of the target cell is a bispecific binding molecule that comprises a first epitope-binding site capable of immunospecifically binding an epitope of a cell surface molecule of an effector cell and a second epitope-binding site that is capable of immunospecifically binding an epitope of such target cells (*i.e.,* a Disease Antigen such as a Cancer Antigen or a Pathogen-Associated Antigen). The present disclosure is also directed to pharmaceutical compositions that comprise such molecule(s).

[0036] In detail, the disclosure provides a method for the treatment of cancer or a pathogen-associated disease, comprising administering to a subject in need thereof a therapeutically effective amount of:

(1) a molecule capable of binding PD-1 or a natural ligand of PD-1, and

(2) a molecule capable of mediating the redirected killing of a target cell, wherein the target cell is:

  (a) a cancer cell that expresses a Cancer Antigen; or

  (b) a pathogen-infected cell that expresses a Pathogen-Associated Antigen.

[0036a] In an aspect, there is provided a composition comprising a first binding molecule and a second binding molecule for use in the treatment of a cancer, wherein:

(A) the first binding molecule comprises an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) the second binding molecule a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

[0036b] In another aspect, there is provided use of a first binding molecule and a second binding molecule in the manufacture of a medicament for treating cancer, wherein:

(A) the first binding molecule comprises an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) the second binding molecule is a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

[0036c] In another aspect, there is provided use of a first binding molecule in the manufacture of a medicament for treating a cancer, wherein the medicament is to be administered with a second binding molecule, and wherein:

(A) the first binding molecule comprises an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) the second binding molecule is a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

[0036d] In another aspect, there is provided use of a second binding molecule in the manufacture of a medicament for treating a cancer, wherein the medicament is to be administered with a first binding molecule, and wherein:

(A) the first binding molecule comprises an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) the second binding molecule is a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

[0037] The disclosure particularly concerns the example of such method wherein the molecule capable of binding PD-1 or a natural ligand of PD-1 is capable of inhibiting binding between PD-1 and a natural ligand of PD-1.

[0038] The disclosure further concerns the example of such method, wherein the method comprises administration of two binding molecules that cumulatively comprise three epitope-binding domains, the two binding molecules being:

Human Immunodeficiency Virus gp41, *etc*.), Human Papillomavirus E6, Human Papillomavirus E7, human T-cell leukemia virus gp64, human T-cell leukemia virus gp46, and human T-cell leukemia virus gp21.

[0055] The disclosure further provides a pharmaceutical composition that comprises:

(A) therapeutically effective amounts of:

(1) a molecule capable of binding PD-1 or a natural ligand of PD-1, and

(2) a molecule capable of mediating the redirected killing of a target cell expressing a Cancer Antigen or a Pathogen Antigen; and

(B) a pharmaceutically acceptable carrier.

[0055a] In another aspect, there is provided a pharmaceutical composition, comprising:

(I) therapeutically effective amounts of:

(A) a first binding molecule comprising an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) a second binding molecule is a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193;

and

(II) a pharmaceutically acceptable carrier.

[0056] The disclosure further concerns the example of such pharmaceutical composition wherein the pharmaceutical composition comprises two binding molecules that cumulatively comprise three epitope-binding domains, the two binding molecules being:

(A) a binding molecule that comprises an epitope-binding domain of an antibody that is capable of binding PD-1, or an epitope-binding domain of an antibody that is capable of binding a natural ligand of PD-1; and

(B) a binding molecule that comprises:

catenin, blood group ALe^b/Le^y, Burkitt's lymphoma antigen-38.13, C14, CA125, Carboxypeptidase M, CD5, CD19, CD20, CD22, CD23, CD25, CD27, CD28, CD33, CD36, CD40/CD154, CD45, CD56, CD46, CD52, CD56, CD79a/CD79b, CD103, CD123, CD317, CDK4, CEA, CEACAM5/CEACAM6, CO17-1A, CO-43, CO-514, CTA-1, CTLA-4, Cytokeratin 8, D1.1, $D_1$56-22, DR5, E_1 series, EGFR, an Ephrin receptor, Erb, GAGE, a GD2/GD3/GM2 ganglioside, GICA 19-9, gp100, Gp37, gp75, gpA33, HER2/neu, HMFG, human papillomavirus-E6/human papillomavirus-E7, HMW-MAA, I antigen, IL13Rα2, Integrin β6, JAM-3, KID3, KID31, KS 1/4 pan-carcinoma antigen, L6,L20, LEA, LUCA-2, M1:22:25:8, M18, M39, MAGE, MART, mesothelin, MUC-1, MUM-1, Myl, N-acetylglucosaminyltransferase, neoglycoprotein, NS-10, OFA-1, OFA-2, Oncostatin M, p15, p97, PEM, PEMA, PIPA, PSA, PSMA, prostatic acid phosphate, R_{24}, ROR1, a sphingolipid, SSEA-1, SSEA-3, SSEA-4, sTn, the T cell receptor derived peptide, T_5A_7, TAG-72, TL5, TNF-receptor, TNF-γ receptor, TRA-1-85, a Transferrin Receptor, 5T4, TSTA, VEGF, a VEGF Receptor, VEP8, VEP9, VIM-D5, and Y hapten, Le^y.

[0072] The disclosure further concerns the example of such pharmaceutical compositions wherein the Pathogen-Associated Antigen is selected from the group consisting of the Pathogen Antigens: Herpes Simplex Virus infected cell protein (ICP)47, Herpes Simplex Virus gD, Epstein-Barr Virus LMP-1, Epstein-Barr Virus LMP-2A, Epstein-Barr Virus LMP-2B, Human Immunodeficiency Virus gp160, Human Immunodeficiency Virus gp120, Human Immunodeficiency Virus gp41, *etc*.), Human Papillomavirus E6, Human Papillomavirus E7, human T-cell leukemia virus gp64, human T-cell leukemia virus gp46, and human T-cell leukemia virus gp21.

[0073] In another example, there is provided a kit comprising any of the above-described pharmaceutical compositions, wherein the binding molecules thereof are compartmentalized in one or more containers.

BRIEF DESCRIPTION OF THE DRAWINGS:

[0074] **Figure 1** provides a schematic of a representative covalently bonded diabody having two epitope-binding domains composed of two polypeptide chains, each having an E-coil or K-coil Heterodimer-Promoting Domain (alternative Heterodimer-Promoting Domains are provided below). A cysteine residue may be present in a linker and/or in the Heterodimer-Promoting Domain as shown in **Figure 3B**. VL and VH Domains that recognize the same epitope are shown using the same shading or fill pattern.

WHAT IS CLAIMED IS:

Claim 1. A composition comprising a first binding molecule and a second binding molecule for use in the treatment of a cancer, wherein:

(A) the first binding molecule comprises an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) the second binding molecule is a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

Claim 2. Use of a first binding molecule and a second binding molecule in the manufacture of a medicament for treating a cancer, wherein:

(A) the first binding molecule comprises an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) the second binding molecule is a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

Claim 3. Use of a first binding molecule in the manufacture of a medicament for treating a cancer, wherein the medicament is to be administered with a second binding molecule, and wherein:

(A) the first binding molecule comprises an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) the second binding molecule is a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

Claim 4. Use of a second binding molecule in the manufacture of a medicament for treating a cancer, wherein the medicament is to be administered with a first binding molecule, and wherein:

(A) the first binding molecule comprises an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) the second binding molecule is a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

Claim 5. The composition of claim 1 or use of any one of claims 2-4, wherein:
the second binding molecule comprises a bispecific diabody, a BiTe, or bispecific antibody; and
the diabody optionally consists of two polypeptide chains, three polypeptide chains, four polypeptide chains or five polypeptide chains.

Claim 6. The composition or use of claim 5, wherein:
the first binding molecule, and/or the second binding molecule, comprises a CH2-CH3 Domain and optionally comprises one or more of a Hinge Domain, CL Domain or CH1 Domain;
the CH2-CH3 Domain, Hinge Domain, CL Domain or CH1 Domain optionally are from an IgG1, IgG2, IgG3 or IgG4 antibody;
the CH2-CH3 Domain optionally comprises one or more amino acid substitutions selected from: L234A, L235A, D265A, N297Q, and N297G;
the CH2-CH3 Domain optionally comprises two or more amino acid substitutions selected from: T250Q, M252Y, S254T, T256E, K288D, T307Q, V308P, A378V, M428L, N434A, H435K, and Y436I;
the CH2-CH3 Domain optionally comprises a T366W amino acid substitution or T366S, L368A and Y407V amino acid substitutions; and/or
the Hinge Domain optionally comprises a S228P amino acid substitution.

Claim 7. The composition of any one of claims 1, 5 and 6 or the use of any one of claims 2-6, wherein the second binding molecule is a bispecific diabody.

Claim 8. The composition of any one of claims 1 and 5-7 or use of any one of claims 2-7, wherein the first binding molecule is an antibody comprising a Heavy Chain of SEQ ID NO:186 and a Light Chain of SEQ ID NO:187.

Claim 9. The composition of any one of claims 1 and 5-8 or use of any one of claims 2-8, wherein the second binding molecule comprises:
(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

Claim 10. The composition or use of claim 9, wherein the second binding molecule comprises a first polypeptide chain comprising the polypeptide of SEQ ID NO:271, a second polypeptide chain comprising the polypeptide of SEQ ID NO:272, and a third polypeptide chain comprising the polypeptide of SEQ ID NO:273.

Claim 11. The composition of any one of claims 1 and 5-8 or use of any one of claims 2-8, wherein the second binding molecule comprises:

(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

Claim 12. The composition or use of claim 11, wherein the second binding molecule is flotetuzumab.

Claim 13. The composition of any one of claims 1 and 5-12 or use of any one of claims 2-12, wherein the cancer is acute myeloid leukemia.

Claim 14. A pharmaceutical composition, comprising:

(I) therapeutically effective amounts of:

(A) a first binding molecule comprising an epitope-binding domain of an antibody capable of immunospecifically binding to a PD-1 that comprises:

the six CDRs of SEQ ID NO: 106 and 109; or

the VH Domain of SEQ ID NO:106 and the VL Domain of SEQ ID NO:109; and

(B) a second binding molecule is a bispecific binding molecule comprising:

(1)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193; or

(2)(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193;

and

(II) a pharmaceutically acceptable carrier.

Claim 15. The pharmaceutical composition of claim 14, wherein:

the second binding molecule comprises a bispecific diabody, a BiTe, or bispecific antibody; and

the diabody optionally consists of two polypeptide chains, three polypeptide chains, four polypeptide chains or five polypeptide chains.

Claim 16. The pharmaceutical composition of claim 15, wherein:

the first binding molecule, and/or the second binding molecule, comprises a CH2-CH3 Domain and optionally comprises one or more of a Hinge Domain, CL Domain or CH1 Domain;

the CH2-CH3 Domain, Hinge Domain, CL Domain or CH1 Domain optionally are from an IgG1, IgG2, IgG3 or IgG4 antibody;

the CH2-CH3 Domain optionally comprises one or more amino acid substitutions selected from: L234A, L235A, D265A, N297Q, and N297G;

the CH2-CH3 Domain optionally comprises two or more amino acid substitutions selected from: T250Q, M252Y, S254T, T256E, K288D, T307Q, V308P, A378V, M428L, N434A, H435K, and Y436I;

the CH2-CH3 Domain optionally comprises a T366W amino acid substitution or T366S, L368A and Y407V amino acid substitutions; and/or the Hinge Domain optionally comprises a S228P amino acid substitution.

Claim 17. The pharmaceutical composition of any one of claims 14-16, wherein the second binding molecule is a bispecific diabody.

Claim 18. The pharmaceutical composition of any one of claims 14-17, wherein the first binding molecule is an antibody comprising a Heavy Chain of SEQ ID NO:186 and a Light Chain of SEQ ID NO:187.

Claim 19. The pharmaceutical composition of any one of claims 14-18, wherein the second binding molecule comprises:

(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a B7-H3 Cancer Antigen and comprising the six CDRs of SEQ ID NO:222 and 226, or the VH Domain of SEQ ID NO:222 and the VL Domain of SEQ ID NO:226; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

Claim 20. The pharmaceutical composition of claim 19, wherein the second binding molecule comprises a first polypeptide chain comprising the polypeptide of SEQ ID NO:271, a second polypeptide chain comprising the polypeptide of SEQ ID NO:272, and a third polypeptide chain comprising the polypeptide of SEQ ID NO:273.

Claim 21. The pharmaceutical composition of any one of claims 14-18, wherein the second binding molecule comprises:

(a) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD123 Cancer Antigen and comprising the six CDRs of SEQ ID NO:263 and 264, or the VH Domain of SEQ ID NO:263 and the VL Domain of SEQ ID NO:264; and

(b) an epitope-binding domain of an antibody capable of immunospecifically binding to a CD3 and comprising the six CDRs of SEQ ID NO:192 and 193, or 194 and 193, or the VH Domain of SEQ ID NO:192 and the VL Domain of SEQ ID NO:193, or the VH Domain of SEQ ID NO:194 and the VL Domain of SEQ ID NO:193.

Claim 22. The pharmaceutical composition of claim 21, wherein the second binding molecule is flotetuzumab.