[0007] Thus, provided in certain examples are **CD137 Binding Molecules**, such as monospecific antibodies, and molecules comprising epitope-binding fragments thereof, that are capable of binding to an epitope of CD137. The disclosure is further directed to multispecific **CD137 Binding Molecules** (e.g., bispecific antibodies, bispecific diabodies, BiTEs, trivalent binding molecules, etc.) that are capable of binding to both an epitope of CD137 and to an epitope of a second antigen, particularly a tumor antigen ("**TA**") (*e.g.*, a "**CD137 x TA Binding Molecule**"). The disclosure also provides novel **PD-L1 Binding Molecules**, such as monospecific antibodies, and molecules comprising epitope-binding fragments thereof, that are capable of binding to an epitope of PD-L1, as well as derivatives thereof and uses thereof. The present disclosure is also directed to pharmaceutical compositions that comprise such molecules. The disclosure also includes the use of such molecules in the treatment of disease, especially cancer or a disease or condition associated with or characterized by the presence of a suppressed immune system.

[0008] The present disclosure provides novel **CD137 Binding Molecules** that exhibit desirable characteristics particularly when incorporated into multispecific molecules. The present disclosure is also directed to multispecific **CD137 x TA Binding Molecules** that are composed of polypeptide chains that associate with one another to form two binding sites each specific for an epitope of CD137 and two binding sites each specific for an epitope of a **TA**. Such **CD137 x TA Binding Molecules** of the disclosure are termed "**bispecific tetravalent**." The present disclosure is also directed to **CD137 x TA Binding Molecules** that are composed of polypeptide chains that associate with one another to form two binding sites each specific for an epitope of CD137 and one binding site specific for an epitope of a **TA**. Such **CD137 x TA Binding Molecules** of the disclosure are termed "**bispecific trivalent**." The binding molecules of the disclosure (*e.g.*, **CD137 Binding Molecules)** sometimes include a first binding site without including a second binding site that immunospecifically binds to an antigen different than the antigen to which the first binding site binds. The binding molecules of the disclosure therefore sometimes include only a first binding site, and a first Light Chain Variable Domain and a first Heavy Chain Variable Domain, and not a second binding site, second Light Chain Variable Domain or second Heavy Chain Variable Domain that bind to a different antigen than the first binding site, and non-limiting examples of such binding molecules include scFv, antibody and Fab binding molecules.

[0009] The present disclosure provides **CD137 x TA Binding Molecules** that comprise four polypeptide chains (a "first," "second," "third," and "fourth" polypeptide chain), wherein

the first and second polypeptide chains are covalently bonded to one another, the third and fourth polypeptide chains are covalent bonded to one another, and the first and third polypeptide chains are covalently bonded to one another. Also provided are **CD137 x TA Binding Molecules** of the disclosure comprising five polypeptide chains (a "first," "second," "third," "fourth," and "fifth" polypeptide chain), wherein the first and second polypeptide chains are covalently bonded to one another, the third and fourth polypeptide chain are covalent bonded to one another, the third and fifth polypeptide chains are covalent bonded to one another, and the first and third polypeptide chains are covalently bonded to one another.

[0010] In one aspect, the present disclosure refers to a **CD137 Binding Molecule** comprising a first binding site that immunospecifically binds to an epitope of CD137, wherein said first binding site comprises a first Light Chain Variable Domain that comprises a CDR_L1, CDR_L2 and CDR_L3, and a first Heavy Chain Variable Domain that comprises a CDR_H1, CDR_H2 and CDR_H3; and wherein:

(A) said first Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **CD137 MAB-6 VL1** (**SEQ ID NO:50**); and

(B) said first Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **CD137 MAB-6 VH1** (**SEQ ID NO:46**).

[0011] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the first Heavy Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VH1** (**SEQ ID NO:46**).

[0012] The disclosure further concerns the examples of such a **CD137 Binding Molecule**, wherein the first Light Chain Variable Domain comprises the amino acid sequence of:

(A) **hCD137 MAB-6 VLx** (**SEQ ID NO:54**);

(B) **hCD137 MAB-6 VL1** (**SEQ ID NO:50**);

(B) **hCD137 MAB-6 VL2** (**SEQ ID NO:55**); or

(C) **hCD137 MAB-6 VL3** (**SEQ ID NO:56**).

[0013] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein:

(A) the first Heavy Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VH1** (**SEQ ID NO:46**); and

(B) the first Light Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VL3** (**SEQ ID NO:56**).

[0014] The disclosure further concerns all the above examples of such **CD137 Binding Molecules**, wherein the molecule is a bispecific molecule comprising a second binding site that immunospecifically binds a **TA**, and wherein the second binding site comprises a second Light Chain Variable Domain that comprises a CDR_L1, CDR_L2 and CDR_L3, and a second Heavy Chain Variable Domain that comprises a CDR_H1, CDR_H2 and CDR_H3.

[0015] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the **TA** is selected from the tumor antigens presented in **Tables 1-2**.

[0016] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the **TA** is PD-L1 and wherein:

(A) the second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hPD-L1 MAB-2 VLx** (**SEQ ID NO:63**); and

(B) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VHx (SEQ ID NO:59**).

[0017] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein:

(A) (1) the second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hPD-L1 MAB-2 VL1** (**SEQ ID NO:58**); or

(2) the second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hPD-L1 MAB-2 VL2** (**SEQ ID NO:72**);

and

(B) (1) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH1** (**SEQ ID NO:57**);

(2) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2** (**SEQ ID NO:67**);

(3) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH3** (**SEQ ID NO:68**);

(4) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2** (**SEQ ID NO:69**);

(5) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2** (**SEQ ID NO:70**); or

(6) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2** (**SEQ ID NO:71**).

[0018] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the second Heavy Chain Variable Domain comprises the amino acid sequence of:

(A) **hPD-L1 MAB-2 VH1** (**SEQ ID NO:57**);

(B) **hPD-L1 MAB-2 VH2** (**SEQ ID NO:67**);

(C) **hPD-L1 MAB-2 VH3** (**SEQ ID NO:68**);

(D) **hPD-L1 MAB-2 VH4** (**SEQ ID NO:69**);

(E) **hPD-L1 MAB-2 VH5** (**SEQ ID NO:70**); or

(F) **hPD-L1 MAB-2 VH6** (**SEQ ID NO:71**).

[0019] The disclosure further concerns the examples of such **CD137 Binding Molecules**, wherein the second Light Chain Variable Domain comprises the amino acid sequence of:

(A) **hPD-L1 MAB-2 VL1** (**SEQ ID NO:58**); or

(B) **hPD-L1 MAB-2 VL2** (**SEQ ID NO:72**).

[0020] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the **TA** is 5T4 and wherein:

(A) (1) the second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **5T4 MAB-1 VL** (**SEQ ID NO:93**); and

(2) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **5T4 MAB-1 VH (SEQ ID NO:92**); or

(B) (1) the second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **5T4 MAB-2 VL** (**SEQ ID NO:95**); and

(2) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **5T4 MAB-2 VH (SEQ ID NO:96**).

[0021] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the second Heavy Chain Variable Domain comprises the amino acid sequence of: **5T4 MAB-1 VH** (**SEQ ID NO:92**).

[0022] The disclosure further concerns the examples of such **CD137 Binding Molecules**, wherein the second Light Chain Variable Domain comprises the amino acid sequence of: **5T4 MAB-1 VL** (**SEQ ID NO:93**).

[0023] The disclosure further concerns such a **CD137 Binding Molecule**, wherein the **TA** is HER2 and wherein:

(A) the second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hHER2-MAB-1 VLx** (**SEQ ID NO:79**); and

(B) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hHER2-MAB-1 VHx (SEQ ID NO:78**);

[0024] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein:

(A) (1) the second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hHER2-MAB-1 VL1** (**SEQ ID NO:83**);

(2) the second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hHER2-MAB-1 VL2** (**SEQ ID NO:84**); or

(3) the second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hHER2-MAB-1 VL3** (**SEQ ID NO:85**);

and

(B) (1) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hHER2-MAB-1 VH1** (**SEQ ID NO:80**);

(2) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hHER2-MAB-1 VH2 (SEQ ID NO:81**); or

(3) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hHER2-MAB-1 VH3 (SEQ ID NO:82**).

[0025] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the second Heavy Chain Variable Domain comprises the amino acid sequence of:

(A) **hHER2-MAB-1 VHx (SEQ ID NO:78**);

(B) **hHER2-MAB-1 VH1** (**SEQ ID NO:80**);

(C) **hHER2-MAB-1 VH2** (**SEQ ID NO:81**); or

(D) **hHER2-MAB-1 VH3** (**SEQ ID NO:82**).

[0026] The disclosure further concerns the examples of such **CD137 Binding Molecules**, wherein the second Light Chain Variable Domain comprises the amino acid sequence of:

(A) **hHER2-MAB-1 VLx** (**SEQ ID NO:79**);

(B) **hHER2-MAB-1 VL1** (**SEQ ID NO:83**);

(C) **hHER2-MAB-1 VL2** (**SEQ ID NO:84**); or

(D) **hHER2-MAB-1 VL3** (**SEQ ID NO:85**).

[0027] The disclosure further concerns all the above examples of such **CD137 Binding Molecules**, wherein the molecule is an antibody, a bispecific tetravalent Fc-bearing diabody, or a bispecific trivalent molecule.

[0028] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the molecule is bispecific and tetravalent, and comprises a first, a second, a third, a fourth, and optionally a fifth polypeptide chain, wherein the polypeptide chains form a covalently bonded complex.

[0029] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the molecule is bispecific and trivalent, and comprises a first, a second, a third, and a fourth, polypeptide chain, wherein the polypeptide chains form a covalently bonded complex.

[0030] The disclosure additionally concerns the example of all such **CD137 Binding Molecules** wherein the molecule comprises an Fc Region of the IgG1, IgG2, IgG3, or IgG4 isotype and optionally wherein the molecule further comprises a Hinge Domain.

[0031] The disclosure additionally concerns the example of all such **CD137 Binding Molecules** wherein the Fc Region is a variant Fc Region that comprises one or more amino acid modifications that reduces the affinity of the variant Fc Region for an FcγR and/or enhances the serum half-life, and more particularly, wherein the modifications comprise at least one amino acid substitution selected from the group consisting of:

(A) L234A; L235A;

(B) L234A and L235A;

(C) M252Y; M252Y and S254T;

(D) M252Y and T256E;

(E) M252Y, S254T and T256E; or

(F) K288D and H435K;

wherein the numbering is that of the EU index as in Kabat.

[0032] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the **TA** is PD-L1 and wherein:

(A) the first and third polypeptide chains comprise the amino acid sequence of **SEQ ID NO:116**, **SEQ ID NO:118**, **SEQ ID NO:120**; and

(B) the second and fourth polypeptide chains comprise the amino acid sequence of **SEQ ID NO:117**, **SEQ ID NO:119**, **SEQ ID NO:121**, **SEQ ID NO:122**, **SEQ ID NO:123**, **SEQ ID NO:124**, **SEQ ID NO:125**, **SEQ ID NO:126**, or **SEQ ID NO:139**.

[0033] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the molecule comprises:

(A) **SEQ ID NO:116** and **SEQ ID NO:117**;

(B) **SEQ ID NO:118** and **SEQ ID NO:119**;

(C) **SEQ ID NO:120** and **SEQ ID NO:119**;

(D) **SEQ ID NO:118** and **SEQ ID NO:121**;

(E) **SEQ ID NO:120** and **SEQ ID NO:121**;

(F) **SEQ ID NO:120** and **SEQ ID NO:122**;

(G) **SEQ ID NO:120** and **SEQ ID NO:123**;

(H) **SEQ ID NO:120** and **SEQ ID NO:124**;

(I) **SEQ ID NO:120** and **SEQ ID NO:125**;

(J) **SEQ ID NO:120** and **SEQ ID NO:126**; or

(K) **SEQ ID NO:120** and **SEQ ID NO:139**.

[0034] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the **TA** is PD-L1 and wherein:

(A) the first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:127**, **SEQ ID NO:133**, or **SEQ ID NO:135**;

(B) the second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:128**, **SEQ ID NO:134**, or **SEQ ID NO:136**;

(C) the third polypeptide chain comprises the amino acid sequence of **SEQ ID NO:129**, or **SEQ ID NO:131**; and

(D) the fourth polypeptide chain comprises the amino acid sequence of **SEQ ID NO:130**, **SEQ ID NO:132**.

[0035] The disclosure further concerns the example of such a **CD137 Binding Molecule**, wherein the molecule comprises:

(A) **SEQ ID NO:127**, **SEQ ID NO:128**, **SEQ ID NO:129**, and **SEQ ID NO:130**;

(B) **SEQ ID NO:127**, **SEQ ID NO:128**, **SEQ ID NO:131**, and **SEQ ID NO:132**;

(C) **SEQ ID NO:133**, **SEQ ID NO:134**, **SEQ ID NO:131**, and **SEQ ID NO:132**; or

(D) **SEQ ID NO:135**, **SEQ ID NO:136**, **SEQ ID NO:131**, and **SEQ ID NO:132**.

[0036] The disclosure additionally concerns a pharmaceutical composition comprising any of the above-described **CD137 Binding Molecules**, and a physiologically acceptable carrier.

[0037] The disclosure additionally concerns the use of such **CD137 Binding Molecules**, or such a pharmaceutical composition, in the treatment of cancer characterized by the expression of the **TA**.

[0037a] In one aspect, the present disclosure refers to a **PD-L1 Binding Molecule**, comprising a Light Chain Variable Domain that comprises a CDR_L1, CDR_L2 and CDR_L3, and a Heavy Chain Variable Domain that comprises a CDR_H1, CDR_H2 and CDR_H3; wherein:

(A) said Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hPD-L1 MAB-2 VLx** (**SEQ ID NO:63**); and

(B) said Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VHx (SEQ ID NO:59**).

[0038] The disclosure additionally concerns a **PD-L1 Binding Molecule** that comprises a Light Chain Variable Domain that comprises a CDR_L1, CDR_L2 and CDR_L3, and a Heavy Chain Variable Domain that comprises a CDR_H1, CDR_H2 and CDR_H3; wherein:

(A) the Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hPD-L1 MAB-2 VL2** (**SEQ ID NO:72**);

and

(B) (1) the Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH2** (**SEQ ID NO:67**);

(2) the Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH3 (SEQ ID NO:68**)

(3) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH4 (SEQ ID NO:69**)

(4) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH5 (SEQ ID NO:70**); or

(5) the second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VH6 (SEQ ID NO:71**).

[0039] The disclosure further concerns the example of such a **PD-L1 Binding Molecule**, wherein the Heavy Chain Variable Domain comprises the amino acid sequence of:

(A) **hPD-L1 MAB-2 VH2** (**SEQ ID NO:67**);
(B) **hPD-L1 MAB-2 VH3** (**SEQ ID NO:68**);
(C) **hPD-L1 MAB-2 VH4** (**SEQ ID NO:69**);
(D) **hPD-L1 MAB-2 VH5** (**SEQ ID NO:70**); or
(E) **hPD-L1 MAB-2 VH6** (**SEQ ID NO:71**).

[0040] The disclosure further concerns the example of such a **PD-L1 Binding Molecule**, wherein the Light Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VL2** (**SEQ ID NO:72**).

[0041] The disclosure further concerns the example of such **PD-L1 Binding Molecules**, wherein the molecule is an antibody or an antigen binding fragment thereof.

[0042] The disclosure additionally concerns a pharmaceutical compositions comprising any of the above-described **PD-L1 Binding Molecules**, and a physiologically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the **CD137 Binding Molecule** as disclosed herein or the **PD-L1 Binding Molecule** as disclosed herein, and a physiologically acceptable carrier.

[0042a] In one aspect, the present disclosure refers to the **CD137 Binding Molecule** as disclosed herein, the **PD-L1 Binding Molecule** as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in the preparation of a medicament.

[0043] The disclosure additionally concerns the use of such **PD-L1 Binding Molecules**, or such pharmaceutical compositions, in the treatment of a disease or condition associated with a suppressed immune system or characterized by the expression of PD-L1.

[0044] The disclosure further concerns such a use, wherein the condition associated with a suppressed immune system or characterized by the expression of PD-L1 is cancer. In one aspect, the present disclosure refers to the **CD137 Binding Molecule** as disclosed herein, the **PD-L1 Binding Molecule** as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in the treatment of a cancer. In one aspect, the present disclosure refers to use of the **CD137 Binding Molecule** as disclosed herein, the **PD-L1 Binding Molecule** as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a cancer.

[0045] The disclosure additionally concerns the example of all such uses, wherein the cancer is selected from the group consisting: bladder cancer, bone cancer, a brain and spinal cord cancer, breast cancer, cervical cancer, colorectal cancer, gallbladder or bile duct cancer, gastric cancer, glioblastoma, head and neck cancer, hepatocellular carcinoma, kidney cancer, leukemia, liver cancer, lung cancer, melanoma, neuroblastoma, non-small cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, pharyngeal cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, squamous cell cancer of the head and neck (SCCHN), stomach cancer, testicular cancer, thymic carcinoma, and uterine cancer.

[0046] The disclosure further concerns a method of enhancing the activity of a tumor targeting agent comprising administering the tumor target agent in combination with any of the above-described **CD137 Binding Molecules**, any of the above-described **PD-L1 Binding Molecules**, or any of the above-described pharmaceutical compositions.

[0047] The disclosure additionally concerns a method of treating a disease or condition associated with a suppressed immune system or characterized by the expression of a **TA** comprising administering to a subject in need thereof and of the above-described **CD137 Binding Molecules**, any of the above-described **PD-L1 Binding Molecules**, or any of the above-described pharmaceutical compositions.

[0048] The disclosure further concerns such a method, further comprising administering a tumor targeting agent.

[0049] The disclosure further concerns such a method, wherein the condition associated with a suppressed immune system or characterized by the expression of the tumor **TA** is cancer.

[0050] The disclosure further concerns all the above examples of such a method, wherein the tumor target agent is an antibody, an epitope binding fragment of an antibody, or an agent that mediates T-cell redirected killing of a target cell.

[0051] The disclosure additionally concerns the example such methods, wherein the cancer is selected from the group consisting: bladder cancer, bone cancer, a brain and spinal cord cancer, breast cancer, cervical cancer, colorectal cancer, gallbladder or bile duct cancer, gastric cancer, glioblastoma, head and neck cancer, hepatocellular carcinoma, kidney cancer, leukemia, liver cancer, lung cancer, melanoma, neuroblastoma, non-small cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, pharyngeal cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, squamous cell cancer of the head and neck (SCCHN), stomach cancer, testicular cancer, thymic carcinoma, and uterine cancer.

[0052] In one aspect, the present disclosure refers to a nucleic acid encoding the **CD137 Binding Molecule** as disclosed herein, or the **PD-L1 Binding Molecule** as disclosed herein.

[0053] The disclosure further concerns an expression vector comprising such nucleic acid.

[0054] The disclosure additionally concerns a cell comprising a nucleic acid according to any of the above examples or an expression vector of any of the above examples.

[0055] The disclosure further concerns a such cell, wherein said cell is a mammalian cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0056] **Figure 1A-1D** provides schematics showing representative covalently bonded diabodies comprising Fc Regions. **Figures 1A-1D** show tetravalent diabodies having four epitope-binding sites composed of two pairs of polypeptide chains, (*i.e.*, four polypeptide

WHAT IS CLAIMED IS:

Claim 1. A **CD137 Binding Molecule** comprising a first binding site that immunospecifically binds to an epitope of CD137, wherein said first binding site comprises a first Light Chain Variable Domain that comprises a CDR_L1, CDR_L2 and CDR_L3, and a first Heavy Chain Variable Domain that comprises a CDR_H1, CDR_H2 and CDR_H3; and wherein:

(A) said first Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **CD137 MAB-6 VL1** (**SEQ ID NO:50**); and

(B) said first Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **CD137 MAB-6 VH1** (**SEQ ID NO:46**).

Claim 2. The **CD137 Binding Molecule** of claim 1, wherein:

(A) said first Heavy Chain Variable Domain comprises the amino acid sequence of **hCD137 MAB-6 VH1** (**SEQ ID NO:46**); and

(B) said first Light Chain Variable Domain comprises the amino acid sequence of:

(1) **hCD137 MAB-6 VL1** (**SEQ ID NO:50**);

(2) **hCD137 MAB-6 VL2** (**SEQ ID NO:55**); or

(3) **hCD137 MAB-6 VL3** (**SEQ ID NO:56**).

Claim 3. The **CD137 Binding Molecule** of claim 1 or claim 2, wherein:

(A) said first Heavy Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VH1** (**SEQ ID NO:46**); and

(B) said first Light Chain Variable Domain comprises the amino acid sequence of: **hCD137 MAB-6 VL3** (**SEQ ID NO:56**).

Claim 4. The **CD137 Binding Molecule** of any one of claims 1-3, comprising a second binding site that immunospecifically binds to an epitope of PD-L1, wherein said second binding site comprises a second Light Chain Variable Domain that comprises a CDR_L1, CDR_L2 and CDR_L3, and a second Heavy Chain Variable Domain that comprises a CDR_H1, CDR_H2 and CDR_H3; and wherein:

(A) said second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hPD-L1 MAB-2 VLx** (**SEQ ID NO:63**); and

(B) said second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VHx (SEQ ID NO:59**).

Claim 5. The **CD137 Binding Molecule** of claim 4, wherein:

(A) said second Heavy Chain Variable Domain comprises the amino acid sequence of:

(1) **hPD-L1 MAB-2 VH1** (**SEQ ID NO:57**);

(2) **hPD-L1 MAB-2 VH2** (**SEQ ID NO:67**);

(3) **hPD-L1 MAB-2 VH3** (**SEQ ID NO:68**);

(4) **hPD-L1 MAB-2 VH4** (**SEQ ID NO:69**);

(5) **hPD-L1 MAB-2 VH5** (**SEQ ID NO:70**); or

(6) **hPD-L1 MAB-2 VH6** (**SEQ ID NO:71**); and

(B) said second Light Chain Variable Domain comprises the amino acid sequence of:

(1) **hPD-L1 MAB-2 VL1** (**SEQ ID NO:58**); or

(2) **hPD-L1 MAB-2 VL2** (**SEQ ID NO:72**).

Claim 6. The **CD137 Binding Molecule** of claim 5, wherein:

(A) said second Heavy Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VH4** (**SEQ ID NO:69**); and

(B) said second Light Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VL2** (**SEQ ID NO:72**).

Claim 7. The **CD137 Binding Molecule** of any one of claims 1-3, comprising a second binding site that immunospecifically binds to an epitope of HER2, wherein said second binding site comprises a second Light Chain Variable Domain that comprises a CDR_L1, CDR_L2 and CDR_L3, and a second Heavy Chain Variable Domain that comprises a CDR_H1, CDR_H2 and CDR_H3; and wherein:

(A) (1) said second Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hHER2-MAB-1 VLx** (**SEQ ID NO:79**); and

(2) said second Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hHER2-MAB-1 VHx (SEQ ID NO:78**);

or

(B) (1) said second Heavy Chain Variable Domain comprises the amino acid sequence of **hHER2-MAB-1 VH1 (SEQ ID NO:80)**; **hHER2-MAB-1 VH2 (SEQ ID NO:81)**; or **hHER2-MAB-1 VH3 (SEQ ID NO:82)**; and

(2) said second Light Chain Variable Domain comprises the amino acid sequence of: **hHER2-MAB-1 VL1** (**SEQ ID NO:83**); **hHER2-MAB-1 VL2** (**SEQ ID NO:84**); or **hHER2-MAB-1 VL3** (**SEQ ID NO:85**);

or

(C) said second Heavy Chain Variable Domain comprises the amino acid sequence of **hHER2-MAB-1 VH1 (SEQ ID NO:80)** and said second Light Chain Variable Domain comprises the amino acid sequence of **hHER2-MAB-1 VL3** (**SEQ ID NO:85**).

Claim 8. The **CD137 Binding Molecule** of any one of claims 1-7, which is an antibody or a bispecific tetravalent Fc-bearing diabody, or a bispecific trivalent molecule.

Claim 9. The **CD137 Binding Molecule** of any one of claims 1-8, wherein said molecule is bispecific and tetravalent, and comprises a first polypeptide chain, a second polypeptide chain, a third polypeptide chain, and a fourth polypeptide chain, wherein said polypeptide chains form a covalently bonded complex.

Claim 10. The **CD137 Binding Molecule** of claim 9, wherein the first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:120**; the second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:139**; the third polypeptide chain comprises the amino acid sequence of **SEQ ID NO:120** and the fourth polypeptide chain comprises the amino acid sequence of **SEQ ID NO:139.**

Claim 11. The **CD137 Binding Molecule** of any one of claims 1-8, wherein said molecule is bispecific and trivalent, and comprises a first polypeptide chain, a second polypeptide chain, a third polypeptide chain, and a fourth polypeptide chain, wherein said polypeptide chains form a covalently bonded complex.

Claim 12. The **CD137 Binding Molecule** of claim 11, wherein the first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:135**; the second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:136**; the third polypeptide chain comprises the amino acid sequence of **SEQ ID NO:131** and the fourth polypeptide chain comprises the amino acid sequence of **SEQ ID NO:132**.

Claim 13. The **CD137 Binding Molecule** of claim 11, wherein the first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:127**; the second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:128**; the third polypeptide chain comprises the amino acid sequence of **SEQ ID NO:129** and the fourth polypeptide chain comprises the amino acid sequence of **SEQ ID NO:130**.

Claim 14. A **PD-L1 Binding Molecule**, comprising a Light Chain Variable Domain that comprises a CDR_L1, CDR_L2 and CDR_L3, and a Heavy Chain Variable Domain that comprises a CDR_H1, CDR_H2 and CDR_H3; wherein:

(A) said Light Chain Variable Domain CDR_L1, CDR_L2, and CDR_L3 are the Light Chain CDRs of **hPD-L1 MAB-2 VLx** (**SEQ ID NO:63**); and

(B) said Heavy Chain Variable Domain CDR_H1, CDR_H2, and CDR_H3 are the Heavy Chain CDRs of **hPD-L1 MAB-2 VHx (SEQ ID NO:59**).

Claim 15. The **PD-L1 Binding Molecule** of claim 14, wherein:

(A) said Heavy Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VH4** (**SEQ ID NO:69**); and

(B) said Light Chain Variable Domain comprises the amino acid sequence of **hPD-L1 MAB-2 VL2** (**SEQ ID NO:72**).

Claim 16. A pharmaceutical composition comprising the **CD137 Binding Molecule** of any one of claims 1-13 or the **PD-L1 Binding Molecule** of claim 14 or claim 15, and a physiologically acceptable carrier.

Claim 17. The **CD137 Binding Molecule** of any one of claims 1-13, the **PD-L1 Binding Molecule** of claim 14 or claim 15, or the pharmaceutical composition of claim 16, for use in the preparation of a medicament.

Claim 18. The **CD137 Binding Molecule** of any one of claims 1-13, the **PD-L1 Binding Molecule** of claim 14 or claim 15, or the pharmaceutical composition of claim 16, for use in the treatment of a cancer.

Claim 19. Use of the **CD137 Binding Molecule** of any one of claims 1-13, the **PD-L1 Binding Molecule** of claim 14 or claim 15, or the pharmaceutical composition of claim 16, in the manufacture of a medicament for the treatment of a cancer.

Claim 20. The **CD137 Binding Molecule**, the **PD-L1 Binding Molecule** or the pharmaceutical composition for use of claim 18, or the use of claim 19, wherein said cancer is selected from the group consisting: bladder cancer, bone cancer, a brain and spinal cord cancer, breast cancer, cervical cancer, colorectal cancer, gallbladder or bile duct cancer, gastric cancer, glioblastoma, head and neck cancer, hepatocellular carcinoma, kidney cancer, leukemia, liver cancer, lung cancer, melanoma, neuroblastoma, non-small cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, pharyngeal cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, squamous cell cancer of the head and neck (SCCHN), stomach cancer, testicular cancer, thymic carcinoma, and uterine cancer.

Claim 21. A nucleic acid encoding the **CD137 Binding Molecule** of any one of claims 1-13, or the **PD-L1 Binding Molecule** of claim 14 or claim 15.