

the first and second polypeptide chains are covalently bonded to one another, the third and fourth polypeptide chains are covalently 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 covalently bonded to one another, the third and fifth polypeptide chains are covalently 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)**, wherein the CDRs are identified in accordance with Kabat.

[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

[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**.

[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, and a physiologically acceptable carrier.

[0042a] In one aspect, the present disclosure refers to the **CD137 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, 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, 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, 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)**, wherein the CDRs are identified in accordance with Kabat.
- 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 VL_x** (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 VH_x** (SEQ ID NO:59)

wherein the CDRs are identified in accordance with Kabat.

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 VL_x (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 VH_x (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)**

wherein the CDRs are identified in accordance with Kabat.

- 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 pharmaceutical composition comprising the **CD137 Binding Molecule** of any one of claims 1-13 and a physiologically acceptable carrier.
- Claim 15. The **CD137 Binding Molecule** of any one of claims 1-13 or the pharmaceutical composition of claim 14 for use in the preparation of a medicament.
- Claim 16. The **CD137 Binding Molecule** of any one of claims 1-13 or the pharmaceutical composition of claim 14 for use in the treatment of a cancer.
- Claim 17. Use of the **CD137 Binding Molecule** of any one of claims 1-13 or the pharmaceutical composition of claim 14 in the manufacture of a medicament for the treatment of a cancer.

- Claim 18. The **CD137 Binding Molecule** or the pharmaceutical composition for use of claim 16, or the use of claim 17, 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 19. A nucleic acid encoding the **CD137 Binding Molecule** of any one of claims 1-13.