

Wilker 2007), other molecules reported to be ligands for Tim-3, including Galectin-9 (Zhu 2005), Phosphatidylserine (DeKruyff 2010), HMGB1 (high-mobility group box 1) (Chiba 2012), and LILRB2 (Leukocyte immunoglobulin like receptor B2) (PCT Publ. No. WO16/111947).

SUMMARY OF THE INVENTION

[0005] In one aspect, the present disclosure refers to an antibody or antigen-binding fragment thereof which binds to an IgV domain of a human Tim-3 (T cell immunoglobulin and mucin-domain containing-3) or IgV mucin-stalk of a human Tim-3, and comprises a) a heavy chain comprising one or more of: GYSFTGYTIN (SEQ ID NO:1) (CDR1); LFNPYNGGTT (SEQ ID NO:2) (CDR2); ARYYGYDAMDY (SEQ ID NO:3) (CDR3); and b) a light chain comprising one or more of: KSSQSVLYSSNQKNHLA (SEQ ID NO:4) (CDR1); WASTRES (SEQ ID NO:5) (CDR2); HQYLSSYT (SEQ ID NO:6) (CDR3). In another aspect, the present disclosure refers to a nucleic acid encoding the isolated antibody or antigen-binding fragment thereof as disclosed herein. In yet another aspect, the present disclosure refers to a host cell comprising the nucleic acid disclosed herein. In a further example, the present disclosure refers to the use of the antibody or antigen-binding fragment thereof as disclosed herein in the manufacture of a medicament for inhibiting a human Tim-3 or inhibiting Tim-3-mediated T cell suppression in a subject. In another aspect, the present disclosure refers to the use of the antibody or antigen-binding fragment thereof as disclosed herein in the manufacture of a medicament for treating cancer in a subject. In yet another aspect, the present disclosure refers to the use of an antibody or fragment thereof as disclosed herein having a detectable marker conjugated thereto in the manufacture of a medicament for detecting a human Tim-3-positive cell in a subject, wherein the medicament is to be administered in an amount effective to label a human Tim-3-positive cell and then detecting the presence of the label in the subject, thereby detecting a human Tim-3-positive cell in a subject. In one example, there is disclosed
An antibody or antigen-binding fragment thereof is provided which binds to an IgV domain of a human Tim-3 (T cell immunoglobulin and mucin-domain containing-3) or IgV mucin-stalk of a human Tim-3, and comprises:

a) a heavy chain comprising one or more of:

GYSFTGYTIN (SEQ ID NO:1) (complementarity determining region (CDR) 1 (CDR1));

LFNPYNGGTT (SEQ ID NO:2) (CDR2);

ARRYYGYDAMDY (SEQ ID NO:3) (CDR3);

or

GFNIKDYYMH (SEQ ID NO:7) (CDR1);

WIDPENDNTIY (SEQ ID NO:8) (CDR2);

ARDFGYVAWLKY (SEQ ID NO:9) (CDR3); and

b) a light chain comprising one or more of:

KSSQSVLYSSNQKNHLA (SEQ ID NO:4) (CDR1);

WASTRES (SEQ ID NO:5) (CDR2);

HQYLSSYT (SEQ ID NO:6) (CDR3);

or

KASQNVDTAVA (SEQ ID NO:10) (CDR1);

SASNRYT (SEQ ID NO:11) (CDR2);

QQYSSYPT (SEQ ID NO:12) (CDR3).

[0006] An antibody or antigen-binding fragment thereof is provided which binds to an IgV domain of a human Tim-3 or IgV mucin-stalk of a human Tim-3, and comprises:
a heavy chain comprising

CLAIMS

What is claimed is:

1. An antibody or antigen-binding fragment thereof which binds to an IgV domain of a human Tim-3 (T cell immunoglobulin and mucin-domain containing-3) or IgV mucin-stalk of a human Tim-3, and comprises:

a) a heavy chain comprising one or more of:

GYSFTGYTIN (SEQ ID NO:1) (CDR1);

LFNPYNGGTT (SEQ ID NO:2) (CDR2);

ARRYYGYDAMDY (SEQ ID NO:3) (CDR3);

or

~~GFNIKDYYMH (SEQ ID NO:7) (CDR1);~~

~~WIDPENDNTIY (SEQ ID NO:8) (CDR2);~~

~~ARDFGYVAWLVI (SEQ ID NO:9) (CDR3); and~~

b) a light chain comprising one or more of:

KSSQSVLYSSNQKNHLA (SEQ ID NO:4) (CDR1);

WASTRES (SEQ ID NO:5) (CDR2);

HQYLSSYT (SEQ ID NO:6) (CDR3);

or

~~KASQNVDTAVA (SEQ ID NO:10) (CDR1);~~

~~SASNRYT (SEQ ID NO:11) (CDR2);~~

~~QQYSSYPT (SEQ ID NO:12) (CDR3).~~

~~2. An antibody or antigen-binding fragment thereof which binds to an IgV domain of a human Tim-3 or IgV mucin-stalk of a human Tim-3, and comprises:~~

~~a heavy chain comprising~~

~~GYSFTGYTIN (SEQ ID NO:1) (CDR1);~~

~~LFNPYNGGTT (SEQ ID NO:2) (CDR2);~~

~~ARRYYGYDAMDY (SEQ ID NO:3) (CDR3); and~~

~~a light chain comprising~~

~~KSSQSVLYSSNQKNHLA (SEQ ID NO:4) (CDR1);~~

~~WASTRES (SEQ ID NO:5) (CDR2);~~

~~HQYLSSYT (SEQ ID NO:6) (CDR3).~~

~~3. An antibody or antigen-binding fragment thereof which binds to an IgV domain of a human Tim-3 or IgV mucin-stalk of a human Tim-3, and comprises:~~

~~a heavy chain comprising~~

~~GFNIKDYYMH (SEQ ID NO:7) (CDR1);~~

~~WIDPENDNTIY (SEQ ID NO:8) (CDR2);~~

~~ARDFGYVAWLVI (SEQ ID NO:9) (CDR3); and~~

~~a light chain comprising~~

~~KASQNVDTAVA (SEQ ID NO:10) (CDR1);~~

~~SASNRYT (SEQ ID NO:11) (CDR2);~~

~~QQYSSYPT (SEQ ID NO:12) (CDR3).~~

~~4.2. The antibody or antigen-binding fragment thereof of ~~any of~~ Claims 1-3, wherein framework regions of the light chain and the heavy chain are human framework regions, or have 85% or more identity thereto.~~

~~5. The antibody or fragment thereof of Claim 4, wherein framework regions of the light chain and the heavy chain are human framework regions.~~

~~6.3. An isolated~~The antibody or antigen-binding fragment thereof of any of Claims 1-2 which binds to an IgV domain of a human Tim-3 or IgV mucin-stalk of a human Tim-3, with an affinity of 10.0 nM K_D or stronger.

~~7.4. The isolated~~ antibody or antigen-binding fragment thereof of Claim ~~6~~3, which binds to an IgV domain of a human Tim-3 or IgV mucin-stalk of a human Tim-3, with an affinity of 0.5 nM K_D or stronger.

~~8.5. The isolated~~ antibody or antigen-binding fragment thereof of any of Claims 1-~~7~~4, which has a human sequence Fc region.

~~9.6.~~ The ~~isolated~~ antibody or antigen-binding fragment thereof of any of Claims ~~6, 7 or 8~~3, 4 or 5, which inhibits binding of human Tim-3 to phosphatidylserine expressed on a dexamethasone-treated Jurkat T cell.

~~10.~~ The ~~isolated~~ antibody or antigen-binding fragment thereof of any of Claims ~~6 to 9~~, which comprises a heavy chain comprising one or more of:

~~GYSFTGYTIN (SEQ ID NO:1) (CDR1)~~

~~LFNPYNGGTT (SEQ ID NO:2) (CDR2)~~

~~ARRYYGYDAMDY (SEQ ID NO:3) (CDR3).~~

~~11.~~ The ~~isolated~~ antibody or antigen-binding fragment thereof of any of Claims ~~6 to 10~~, which comprises a light chain comprising one or more of:

~~KSSQSVLYSSNQKNHLA (SEQ ID NO:4) (CDR1)~~

~~WASTRES (SEQ ID NO:5) (CDR2)~~

~~HQYLSSYT (SEQ ID NO:6) (CDR3).~~

~~12.~~ The ~~isolated~~ antibody or antigen-binding fragment thereof of any of Claims ~~6 to 9~~, which comprises a heavy chain comprising one or more of:

~~GFNIKDYYMH (SEQ ID NO:7) (CDR1)~~

~~WIDPENDNTIY (SEQ ID NO:8) (CDR2)~~

~~ARDFGYVAWLKY (SEQ ID NO:9) (CDR3).~~

~~13.~~ The ~~isolated~~ antibody or antigen-binding fragment thereof of any of Claims ~~6 to 9 or 12~~, which comprises a light chain comprising one or more of

~~KASQNVDTAVA (SEQ ID NO:10) (CDR1)~~

~~SASNRYT (SEQ ID NO:11) (CDR2)~~

~~QQYSSYPT (SEQ ID NO:12) (CDR3).~~

~~14.7.~~ The ~~isolated~~ antibody or antigen-binding fragment thereof of any one of claims 1-~~13~~6, wherein the antibody or antigen-binding fragment thereof is chimeric or humanized.

~~15.8.~~ The ~~isolated~~ antibody or antigen-binding fragment thereof of any one of claims 1-~~14~~7, wherein the antibody or antigen-binding fragment thereof is selected from

the group consisting of a monoclonal antibody, an scFv, an Fab fragment, an Fab' fragment, and an F(ab)' fragment.

~~16.9.~~ A nucleic acid encoding the isolated antibody or antigen-binding fragment thereof of any one of claims 1-8. ~~a heavy chain of an antibody which comprises one or more of:~~

~~GYSFTGYTIN (SEQ ID NO:1) (CDR1);~~

~~LFNPYNGGTT (SEQ ID NO:2) (CDR2);~~

~~ARRYYGYDAMDY (SEQ ID NO:3) (CDR3).~~

~~17.~~ A nucleic acid encoding a heavy chain of an antibody which comprises one or more of:

~~GFNIKDYYMH (SEQ ID NO:7) (CDR1);~~

~~WIDPENDNTIY (SEQ ID NO:8) (CDR2);~~

~~ARDFGYVAWLVI (SEQ ID NO:9) (CDR3).~~

~~18.~~ A nucleic acid encoding a light chain of an antibody which comprises one or more of:

~~KSSQSVLYSSNQKNHLA (SEQ ID NO:4) (CDR1);~~

~~WASTRES (SEQ ID NO:5) (CDR2);~~

~~HQYLSSYT (SEQ ID NO:6) (CDR3).~~

~~19.~~ A nucleic acid encoding a light chain of an antibody which comprises one or more of:

~~KASQNVDTAVA (SEQ ID NO:10) (CDR1);~~

~~SASNRYT (SEQ ID NO:11) (CDR2)~~

~~QQYSSYPT (SEQ ID NO:12) (CDR3).~~

~~20.10.~~ A host cell comprising one or more of the nucleic acids of any of Claims 14-179.

~~21.11.~~ An The antibody or antigen-binding fragment thereof according to any of Claims 1-158, which is linked or conjugated to a therapeutic agent selected from the

group consisting of a cytotoxic drug, a radioactive isotope, an immunomodulator, or a second antibody.

~~22. The antibody or fragment thereof according to Claim 21, wherein the therapeutic agent is a cytotoxic drug, a radioactive isotope, an immunomodulator, or a second antibody.~~

~~23.12. Use of the antibody or antigen-binding fragment thereof according to any of Claims 1-8 in the manufacture of a medicament for~~A method of inhibiting a human Tim-3 or inhibiting Tim-3-mediated T cell suppression in a subject comprising administering an amount of an antibody or fragment thereof of any of Claims 1-15, or a human Tim3-binding fragment thereof, effective to inhibit a human Tim-3.

~~24.13. The method use of Claim 2312, wherein the subject has a cancer.~~

~~25. A method of inhibiting Tim-3-mediated T cell suppression in a subject comprising administering an amount of an antibody or fragment thereof of any of Claims 1-15, or a human Tim3-binding fragment thereof, effective to inhibit Tim-3-mediated T cell suppression.~~

~~26.14. Use of the antibody or antigen-binding fragment thereof according to any of Claims 1-8 in the manufacture of a medicament for~~A method of treating a cancer in a subject comprising administering an amount of an antibody or fragment thereof of any of Claims 1-15, effective to treat a cancer in a subject.

~~27.15. The method use of Claim 2614, wherein the cancer is a human Tim-3-positive cancer.~~

16. The use according to any one of Claim 13-15, wherein the cancer is a hematologic malignancy.

17. The use according to any one of Claim 13-15, wherein the cancer comprises a solid tumor.

18. The use according to any one of Claim 12-14, wherein the subject is receiving an anti-PD-1 or anti-PD-L1 or anti-CTLA4 therapy.

~~28.19. Use of an antibody or fragment thereof of any of Claims 1-8 having a detectable marker conjugated thereto in the manufacture of a medicament for~~A method of detecting a human Tim-3-positive cell in a subject, comprising wherein the

~~medicament is to be administered administering an amount of an antibody or fragment thereof of any of Claims 1-15 having a detectable marker conjugated thereto, in an amount effective to label a human Tim-3-positive cell and then detecting the presence of the label in the subject, thereby detecting a human Tim-3-positive cell in a subject.~~

~~29-20. The method use of Claim 28~~19~~, wherein the label is detected by imaging.~~

~~30. The method of Claim 28 or 29, wherein the cell is a cancer cell.~~

~~31. The method of Claim 24, 26, 27 or 30, wherein the cancer is a hematologic malignancy.~~

~~32. The method of Claim 24, 26, 27, or 30, wherein the cancer comprises a solid tumor.~~

~~33. The method of Claim 24, 26, 27, or 30-32, wherein the subject is receiving an anti-PD-1 or anti-PD-L1 or anti-CTLA4 therapy.~~