

associated with urinary bladder cancer and muscle invasiveness, present on thyroid carcinoma cell lines derived from tumors showing aggressive behavior, and associated with a more malignant transformation in gastric carcinomas (Fiori et al., Ann. Ist. Super Sanita 48 (2012), pp. 161-171). With regards to galectin-9, tumor-derived galectin-9 has been shown to induce the apoptosis of tumor-infiltrating Tim-3⁺ CD8⁺ T cells in a CT26 mouse colon tumor model (Kang, C.W. et al., Sci. Rep. 5:15659 (2015)).

Because all of the aforementioned Tim-3 ligands are not exclusive ligands of Tim-3, it is desirable to provide therapeutic anti-Tim-3 antibodies that differentially block the activity of said ligands as these ligands can regulate the immune system independently of Tim-3. Such a strategy can provide alternative ways to more specifically modulate Tim-3 activity, allowing for tailored immuno-oncology based therapies for patients.

Furthermore, such anti-Tim-3 antibodies can provide options for combinatorial therapies with other checkpoint inhibitors, providing alternatives that may display improved efficacy and toxicity profiles when combined with other therapeutics. Thus, there remains a need to provide antibodies that bind human Tim-3 and inhibit Tim-3's interactions with some of Tim-3's ligands, but not others.

There also remain a need for alternative anti-human Tim-3 antibodies that may be clinically beneficial. In particular, there remains a need for alternative anti-Tim-3 antibodies that specifically bind human Tim-3 and alleviate immune exhaustion such as the failure of the T cell to produce cytokines. There also remains a need for alternative anti-Tim-3 antibodies that specifically bind human Tim-3 and enhance the anti-tumor immune response. There also remains a need for anti-human Tim-3 antibodies that display sufficient potency as a cancer monotherapy.

Summary

In one aspect of the present disclosure, there is provided an antibody that binds human Tim-3, (SEQ ID NO:1), the antibody comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 wherein:

- 5 a) HCDR1 has the amino acid sequence of SEQ ID: 2, HCDR2 has the amino acid sequence of SEQ ID NO: 3, HCDR3 has the amino acid sequence of SEQ ID NO: 4, LCDR1 has the amino acid sequence of SEQ ID NO:5, LCDR2 has the amino acid sequence of SEQ ID NO:6, and LCDR3 has the amino acid sequence of SEQ ID NO:7;
- 10 b) HCDR1 has the amino acid sequence of SEQ ID NO:14, HCDR2 has the amino acid sequence of SEQ ID NO:15, HCDR3 has the amino acid sequence of SEQ ID NO:16, LCDR1 has the amino acid sequence of SEQ ID NO:17, LCDR2 has the amino acid sequence of SEQ ID NO:18, and LCDR3 has the amino acid sequence of SEQ ID NO:19; or
- 15 c) HCDR1 has the amino acid sequence of SEQ ID NO:26, HCDR2 has the amino acid sequence of SEQ ID NO:27, HCDR3 has the amino acid sequence of SEQ ID NO:28, LCDR1 has the amino acid sequence of SEQ ID NO:29, LCDR2 has the amino acid sequence of SEQ ID NO:30, and LCDR3 has the amino acid sequence of SEQ ID NO:31.

20 In another aspect of the present disclosure, there is provided an antibody, comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein:

- 25 a) the HCVR has the amino acid sequence of SEQ ID NO: 8, and the LCVR has the amino acid sequence of SEQ ID NO: 9;
- b) the HCVR has the amino acid sequence of SEQ ID NO: 20, and the LCVR has the amino acid sequence of SEQ ID NO: 21; or
- c) the HCVR has the amino acid sequence of SEQ ID NO: 32, and the LCVR has the amino acid sequence of SEQ ID NO: 33.

30 In a further aspect of the present disclosure, there is provided an antibody, comprising a heavy chain (HC) and a light chain (LC), wherein:

- a) the HC has the amino acid sequence of SEQ ID NO: 10 and the LC has the amino acid sequence of SEQ ID NO: 11;

- 5 b) the HC has the amino acid sequence of SEQ ID NO: 22 and the LC has the amino acid sequence of SEQ ID NO: 23; or
- c) the HC has the amino acid sequence of SEQ ID NO: 34 and the LC has the amino acid sequence of SEQ ID NO: 35.

In another aspect of the present disclosure, there is provided a mammalian cell capable of expressing an antibody comprising a heavy chain (HC) and a light chain (LC), wherein:

- 10 a) the HC has the amino acid sequence of SEQ ID NO: 10 and the LC has the amino acid sequence of SEQ ID NO: 11;
- b) the HC has the amino acid sequence of SEQ ID NO: 22 and the LC has the amino acid sequence of SEQ ID NO: 23; or
- 15 c) the HC has the amino acid sequence of SEQ ID NO: 34 and the LC has the amino acid sequence of SEQ ID NO: 35.

In a further aspect of the present disclosure, there is provided a process for producing an antibody comprising cultivating a mammalian cell capable of expressing the antibody and recovering the antibody; wherein the antibody comprises a heavy chain (HC) and a light chain (LC), wherein:

- 20 a. the HC has the amino acid sequence of SEQ ID NO: 10 and the LC has the amino acid sequence of SEQ ID NO: 11;
- b. the HC has the amino acid sequence of SEQ ID NO: 22 and the LC has the amino acid sequence of SEQ ID NO: 23; or
- 25 c. the HC has the amino acid sequence of SEQ ID NO: 34 and the LC has the amino acid sequence of SEQ ID NO: 35.

In another aspect of the present disclosure, there is provided the antibody produced by a process disclosed herein.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition, comprising the antibody as disclosed herein and an acceptable carrier, diluent, or excipient.

In another aspect of the present disclosure, there is provided the antibody as disclosed herein, for use in therapy.

In a further aspect of the present disclosure, there is provided the antibody as disclosed herein, for use in the treatment of cancer.

In another aspect of the present disclosure, there is provided a use of the antibody as disclosed herein for the manufacture of a medicament for the treatment of cancer.

Detailed description

Anti-Tim-3 antibodies of the present invention can block human Tim-3's binding with human galectin-9 and phosphatidylserine while simultaneously not blocking the binding of human Tim-3 and human CEACAM1. Surprisingly, the anti-Tim-3 antibodies of the present invention enhance T cell responses to tumors as measured by tumor size in established tumor models by blocking the interaction of human Tim-3 with human phosphatidylserine and human galectin-9 while not blocking the interaction of human CEACAM1 with human Tim-3. Surprisingly, certain anti-Tim-3 antibodies of the present invention mediate enhanced T cell responses to a tumor as measured by CD8-positive

22. The process of claim 20, wherein the HC has the amino acid sequence of SEQ ID NO: 22 and the LC has the amino acid sequence of SEQ ID NO: 23.
23. The process of claim 20, wherein the HC has the amino acid sequence of SEQ ID NO: 34 and the LC has the amino acid sequence of SEQ ID NO: 35.
- 5 24. The antibody produced by the process of any one of claims 20-23.
25. A pharmaceutical composition, comprising the antibody of any one of claims 1-15 and an acceptable carrier, diluent, or excipient.
26. The antibody of any one of claims 1-15, for use in therapy.
27. The antibody of any one of claims 1-15, for use in the treatment of cancer.
- 10 28. The antibody for use of claim 27, wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.
29. The antibody for use of claim 28, wherein the lung cancer is non-small cell lung cancer.
- 15 30. The antibody for use of any one of claims 27-29, wherein the antibody is to be administered in simultaneous, separate, or sequential combination with ionizing radiation.

31. The antibody for use of any one of claims 27-30, wherein the antibody is to be administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.
32. Use of the antibody of claims 1-15 for the manufacture of a medicament for the treatment of cancer.
33. The use of claim 32, wherein the cancer is melanoma, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, gastric cancer, kidney cancer, bladder cancer, prostate cancer, breast cancer, ovarian cancer, esophageal cancer, soft tissue sarcoma, or liver cancer.
34. The use of claim 33, wherein the lung cancer is non-small cell lung cancer.
35. The use of any one of claims 32-34, wherein the medicament is to be administered in simultaneous, separate, or sequential combination with ionizing radiation.
36. The use of any one of claims 32-35, wherein the medicament is to be administered in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.