ANTI-TIM-3 ANTIBODIES

The present invention is in the field of medicine. Particularly, the present invention relates to antibodies directed to T-cell immunoglobulin- and mucin-domain-containing protein-3 (Tim-3), compositions comprising such anti-Tim-3 antibodies, and methods of using such anti-Tim-3 antibodies for the treatment of solid and hematological tumors alone or in combination with chemotherapy and other cancer therapeutics.

Tumor cells escape detection and elimination by the immune system through a variety of mechanisms. One such mechanism is by the manipulation of immune checkpoint regulatory pathways that are normally used in the maintenance of self-tolerance and control of T cell activation. Cancer cells can commandeer these immune checkpoint regulatory pathways to suppress the anti-tumor response and prevent their destruction.

Although T cells recognizing tumor antigens can be isolated from patients and mouse models, such cells can exhibit an exhausted phenotype characterized by an impairment in cytotoxic functions, effector cytokine production, and proliferation. Moreover, such tumor-infiltrating T cells can express high levels of the checkpoint regulator Tim-3. In this regard, it has been shown that anti-Tim-3 antibodies can restore anti-tumor immunity in some murine cancer models.

Antibodies directed to human Tim-3 are known. Humanized antibodies against human Tim-3 are described in WO15117002. MBG453, an anti-human Tim-3 antibody, is also currently being tested in human clinical trials. However, no antibody targeting Tim-3 has been approved for therapeutic use in humans.

Tim-3 has been shown to interact with galectin-9 (SEQ ID NO:40), phosphaditylserine ($C_{13}H_{24}NO_{10}P$), high-mobility group Box 1 (HMGB1), and carcinoembryonic antigen cell adhesion molecule 1(CEACAM1) (SEQ ID NO:39). CEACAM1 expression in the primary tumors of melanoma patients has been shown to be associated with the subsequent development of metastatic disease (Thies et al., J. Clin. Oncol. 20, (2002), pp. 2530-2536). Additionally, CEACAM1 expression has been shown to be a prognosticator for unfavorable non-small cell lung cancer (NSCLC) related survival, an independent risk factor for lymph node metastasis of colon carcinomas,

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:

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;

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

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.

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:

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.

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;

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:

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

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:

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

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 preent 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

CD3-positive T cell infiltration or persistence 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.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively.

The present invention provides an antibody that binds human Tim-3, (SEQ ID NO:1), the antibody comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 wherein:

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;

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

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.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a HCDR1 of SEQ ID NO:2, HCDR2 of SEQ ID NO:3, HCDR3 of SEQ ID NO:4, LCDR1 of SEQ ID NO:5, LCDR2 of SEQ ID NO:6, and LCDR3 of SEQ ID NO:7.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a HCDR1 of SEQ ID NO:14, HCDR2 of SEQ ID NO:15,

HCDR3 of SEQ ID NO:16, LCDR1 of SEQ ID NO:17, LCDR2 of SEQ ID NO:18, and LCDR3 of SEQ ID NO:19.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a HCDR1 of SEQ ID NO:26, HCDR2 of SEQ ID NO:27, HCDR3 of SEQ ID NO:28, LCDR1 of SEQ ID NO:29, LCDR2 of SEQ ID NO:30, and LCDR3 of SEQ ID NO:31.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein: the HCVR has the amino acid sequence given in SEQ ID NO: 8, and the LCVR has the amino acid sequence given in SEQ ID NO: 9; the HCVR has the amino acid sequence given in SEQ ID NO: 20, and the LCVR has the amino acid sequence given in SEQ ID NO: 21; or the HCVR has the amino acid sequence given in SEQ ID NO: 32, and the LCVR has the amino acid sequence given in SEQ ID NO: 33.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein: the HCVR has the amino acid sequence given in SEQ ID NO: 8, and the LCVR has the amino acid sequence given in SEQ ID NO: 9.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein: the HCVR has the amino acid sequence given in SEQ ID NO: 20, and the LCVR has the amino acid sequence given in SEQ ID NO: 21.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein: the HCVR has the amino acid sequence given in SEQ ID NO: 32, and the LCVR has the amino acid sequence given in SEQ ID NO: 33.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences given in SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a heavy chain (HC) having the amino acid sequence of SEQ ID NO: 10,and a light chain (LC) having the amino acid of SEQ ID NO: 11.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a heavy chain (HC) having the amino acid sequence of SEQ ID NO: 22 and a light chain (LC) having the amino acid sequence of SEQ ID NO: 23.

The present invention provides an antibody that binds human Tim-3 (SEQ ID NO: 1), the antibody comprising a heavy chain (HC) having the amino acid sequence of SEQ ID NO: 34 and a light chain (LC) having the amino acid sequence of SEQ ID NO: 35.

The present invention provides an anti-human Tim-3 antibody, comprising two heavy chains and two light chains, wherein each heavy chain (HC) has the amino acid sequence of SEQ ID NO: 10 and each light chain (LC) has the amino acid sequence of SEQ ID NO: 11.

The present invention provides an anti-human Tim-3 antibody, comprising two heavy chains and two light chains, wherein each heavy chain (HC) has the amino acid sequence of SEQ ID NO:22 and each light chain (LC) has the amino acid sequence of SEQ ID NO:23.

The present invention provides an anti-human Tim-3 antibody, comprising two heavy chains and two light chains, wherein each heavy chain (HC) has the amino acid sequence of SEQ ID NO: 34 and each light chain (LC) has the amino acid sequence of SEQ ID NO: 35.

The present invention provides an antibody that binds the same epitope on human Tim-3 (SEQ ID NO: 1), as an antibody comprising a HCDR1 of SEQ ID NO:2, HCDR2 of SEQ ID NO:3, HCDR3 of SEQ ID NO:4, LCDR1 of SEQ ID NO:5, LCDR2 of SEQ ID NO:6, and LCDR3 of SEQ ID NO:7. The present invention provides an antibody that binds the same epitope on human Tim-3 (SEQ ID NO: 1), as antibody comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein: the HCVR has the amino acid sequence given in SEQ ID NO: 8, and the LCVR has the amino acid sequence given in SEQ ID NO: 9. The present invention provides an antibody that binds the same epitope on human Tim-3 (SEQ ID NO: 1), as an antibody comprising

a heavy chain (HC) having the amino acid sequence of SEQ ID NO: 10, and a light chain (LC) having the amino acid of SEQ ID NO: 11.

The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1), wherein said antibody blocks binding of human Tim-3 to human phosphatidylserine, but does not block binding of human Tim-3 to human CEACAM1 (SEQ ID: 39). The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1), wherein said antibody blocks binding of human Tim-3 to human phosphatidylserine and human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 to human CEACAM1 (SEQ ID: 39).

The present invention also provides an antibody that binds a human Tim-3 (SEQ ID NO:1) epitope, wherein the antibody contacts residues 50, 55-65, 72, 107, 111, 113-120, and 122 of human Tim-3 (SEQ ID NO:1). The present invention also provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts residues 50, 55-65, 72, 107, 111, 113-120, and 122 of human Tim-3 (SEQ ID NO:1); wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody. The present invention also provides an antibody that binds a human Tim-3 (SEQ ID NO:1) epitope, wherein the antibody contacts residues 50, 55-65, 72, 107, 111, 113-120, and 122 of human Tim-3 (SEQ ID NO:1); wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40) (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive). The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody. The present

invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues.

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40),

but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); and wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive) , and 122. The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); and wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122; wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; and wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122.

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least

four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122; wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; and wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive). An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; wherein the antibody further

contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive) , and 122; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts amino acid residues 50, 55-65, 72, 107, 111, 113-120, and 122. An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts amino acid residues 50, 55-65, 72, 107, 111, 113-120, and 122, as determined by X-ray crystallography. An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts amino acid residues 50, 55-65, 72, 107, 111, 113-120, and 122, as determined by X-ray crystallography; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues.

An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues;

more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography.

An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human

Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention provides an anti-human Tim-3 antibody, wherein the antibody is glycosylated.

The present invention provides a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO.10, 22, or 34. The present invention provides a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO. 11, 23, or 35. The present invention provides a DNA molecule comprising a pair of polynucleotide sequences encoding two distinct polypeptides having the amino acid sequence of SEQ ID NO. 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO. 10, 22, or 34, wherein the polynucleotide sequence comprises SEQ ID NO. 12, 24, or 36, respectively. The present invention provides a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO. 11, 23, or 35, wherein the polynucleotide sequence comprises SEQ ID NO.13, 25, or 37, respectively.

The present invention provides a mammalian cell capable of expressing an antibody comprising a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences given in SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides a mammalian cell capable of expressing an antibody comprising a heavy chain (HC) and a light chain (LC), wherein 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.

The present invention provides a mammalian cell capable of expressing an antibody comprising a heavy chain (HC) and a light chain (LC), 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.

The present invention provides a mammalian cell capable of expressing an antibody comprising a heavy chain (HC) and a light chain (LC), 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.

The present invention provides 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 and a light chain having the amino acid sequences given in SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides 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 having the amino acid sequence of SEQ ID NO: 10 and a light chain having the amino acid sequence of SEQ ID NO: 11.

The present invention provides 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 having the amino acid sequence of SEQ ID NO: 22 and a light chain having the amino acid sequences of SEQ ID NO: 23.

The present invention provides 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 having the amino acid sequence of SEQ ID NO: 34 and a light chain having the amino acid sequence of SEQ ID NO: 35.

The present invention provides an anti-human Tim-3 antibody disclosed herein produced by a process of the present invention.

The present invention provides a pharmaceutical composition, comprising an anti-human Tim-3 antibody of the present invention, and an acceptable carrier, diluent, or excipient.

The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention.

In some embodiments, the present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-

human Tim-3 antibody, wherein the cancer is melanoma, lung cancer, non-small cell 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.

In some embodiments, the present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody, wherein the cancer is melanoma, lung cancer, non-small cell 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; wherein the the antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences shown in SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively.

In some embodiments, the present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody, wherein the cancer is melanoma, lung cancer, non-small cell 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; wherein the the antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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; 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 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.

In some embodiments, the present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody, wherein the cancer is melanoma, lung cancer, non-small cell 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; wherein the the antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is melanoma. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is lung cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the lung cancer is non-small cell lung cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is head and neck cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is colorectal cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is pancreatic cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is gastric cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is kidney cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is bladder cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is prostate cancer.

The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is breast cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is ovarian cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is esophageal cancer. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is soft tissue sarcoma. The present invention provides a method of treating cancer, comprising administering to a patient in need, thereof an effective amount of an anti-human Tim-3 antibody of the present invention, wherein the cancer is liver cancer.

In some embodiments, the methods comprise the administration of an effective amount of an anti-human Tim-3 antibody of the present invention in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include 5-fluorouracil, hydroxyurea, gemcitabine, methotrexate, pemetrexed, doxorubicin, etoposide, cetuximab, carboplatin, cisplatin, cyclophosphamide, melphalan, dacarbazine, taxol, camptothecin, FOLFIRI, docetaxel, daunorubicin, paclitaxel, oxaliplatin, and combinations thereof. In some embodiments, the methods comprise the administration of an effective amount of an anti-human Tim-3 antibody of the present invention in simultaneous, separate, or sequential combination with ionizing radiation.

The present invention provides an anti-human Tim-3 antibody, for use in therapy. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences shown in SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-

human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises HCDR1 having the amino acid sequence of SEQ ID NO: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 and comprises HCDR1 having the amino acid sequence of SEQ ID NO: 14, HCDR2 having the amino acid sequence of SEQ ID NO: 15, HCDR3 having the amino acid sequence of SEQ ID NO: 16, LCDR1 having the amino acid sequence of SEQ ID NO: 17, LCDR2 having the amino acid sequence of SEQ ID NO: 18, and LCDR3 having the amino acid sequence of SEQ ID NO: 19. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises a HCDR1 having the amino acid sequence of SEQ ID NO: 26, HCDR2 having the amino acid sequence of SEQ ID NO: 27, HCDR3 having the amino acid sequence of SEQ ID NO: 28, LCDR1 having the amino acid sequence of SEQ ID NO: 29, LCDR2 having the amino acid sequence of SEQ ID NO: 30, and LCDR3 having the amino acid sequence of SEQ ID NO: 31.

The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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; 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 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. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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.

The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3antibody binds human Tim-3 (SEQ ID NO: 1) and comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises a heavy chain (HC) and a light chain (LC), wherein 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. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises a heavy chain (HC) and a light chain (LC), 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. The present invention provides an anti-human Tim-3 antibody, for use in therapy; wherein the anti-human Tim-3 antibody binds human Tim-3 (SEQ ID NO: 1) and comprises a heavy chain (HC) and a light chain (LC), 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.

The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer. The present invention provides an anti-human Tim-3 antibody, for

use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences shown in SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID NO: 2, HCDR2 having the amino acid sequence of SEQ ID NO: 3, HCDR3 having the amino acid sequence of SEQ ID NO: 4, LCDR1 having the amino acid sequence of SEQ ID NO: 5, LCDR2 having the amino acid sequence of SEQ ID NO: 6, and LCDR3 having the amino acid sequence of SEQ ID NO: 7. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID NO: 14, HCDR2 having the amino acid sequence of SEQ ID NO: 15, HCDR3 having the amino acid sequence of SEQ ID NO: 16, LCDR1 having the amino acid sequence of SEQ ID NO:17, LCDR2 having the amino acid sequence of SEQ ID NO: 18, and LCDR3 having the amino acid sequence of SEQ ID NO: 19. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises HCDR1 having the amino acid sequence of SEQ ID NO: 26, HCDR2 having the amino acid sequence of SEQ ID NO: 27, HCDR3 having the amino acid sequence of SEQ ID NO: 28, LCDR1 having the amino acid sequence of SEQ ID NO: 29, LCDR2 having the amino acid sequence of SEQ ID NO: 30, and LCDR3 having the amino acid sequence of SEQ ID NO: 31.

The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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; 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 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. The present invention provides an anti-human Tim-3 antibody, for use

in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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.

The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences given in SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein 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. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), 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. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), 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.

The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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.

The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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; 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 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. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid

sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is melanoma. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is lung cancer. The present invention provides an anti-human Tim-3 antibody for use in the treatment of lung cancer, wherein the lung cancer is non-small cell lung cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is head and neck cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is colorectal cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is pancreatic cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is gastric cancer. The present invention provides an anti-human Tim-3, for use in the treatment of cancer, wherein the cancer is kidney cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is bladder cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is prostate cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is breast cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is ovarian cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is esophageal cancer. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is soft tissue sarcoma. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is liver cancer.

The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is melanoma; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present

invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is lung cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody for use in the treatment of lung cancer, wherein the lung cancer is non-small cell lung cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is head and neck cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is colorectal cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is pancreatic cancer; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is gastric cancer; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3, for use in the treatment of cancer, wherein the cancer is kidney cancer; wherein the anti-human Tim-3 antibody comprises a

HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is bladder cancer; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is prostate cancer; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is breast cancer; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is ovarian cancer; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is esophageal cancer; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is soft tissue sarcoma; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17,

18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is liver cancer; wherein the anti-human Tim-3 antibody comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively.

The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is melanoma; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is lung cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody for use in the treatment of lung cancer, wherein the lung cancer is non-small cell lung cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is head and neck cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is colorectal cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is pancreatic cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light

chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is gastric cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3, for use in the treatment of cancer, wherein the cancer is kidney cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is bladder cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is prostate cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is breast cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is ovarian cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is esophageal cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have

the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is soft tissue sarcoma; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides an anti-human Tim-3 antibody, for use in the treatment of cancer, wherein the cancer is liver cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the an anti-human Tim-3 antibody for use in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.

The present invention provides an anti-human Tim-3 antibody for use in simultaneous, separate, or sequential combination with with one or more chemotherapeutic agents in the treatment of cancer. The present invention provides an anti-human Tim-3 antibody for use in simultaneous, separate, or sequential combination with with one or more chemotherapeutic agents in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an anti-human Tim-3 antibody for use in simultaneous, separate, or sequential combination with with one or more chemotherapeutic agents in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides an effective amount of an anti-human Tim-3 antibody for use in simultaneous, separate, or sequential combination with ionizing radiation. The present invention provides an effective amount of an anti-human Tim-3

antibody for use in simultaneous, separate, or sequential combination with ionizing radiation in the treatment of cancer. The present invention provides an effective amount of an anti-human Tim-3 antibody for use in simultaneous, separate, or sequential combination with ionizing radiation in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences shown in SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides an effective amount of an anti-human Tim-3 antibody for use in simultaneous, separate, or sequential combination with ionizing radiation in the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer.

The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively. The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 14, 15, 16, 17, 18, and 19, respectively. The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody

comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 26, 27, 28, 29, 30, and 31, respectively.

The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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; 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 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. The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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. The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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. The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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.

The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the

LC have the amino acid sequences given in SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively. The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein 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. The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), 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. The present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), 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.

In a further embodiment, the present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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. In a further embodiment, the present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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; wherein the anti-Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. In a further embodiment, the present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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; wherein the anti-Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC comprises a heavy chain variable region (HCVR) and the LC comprises a light chain variable region (LCVR), wherein: 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; 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 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. In a further embodiment, the present invention provides the use of an anti-human Tim-3 antibody for the manufacture of a medicament for the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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; wherein the anti-Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences given in SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of melanoma; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of melanoma; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of lung cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1,

LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of lung cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of non-small cell lung cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of non-small cell lung cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of head and neck cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of head and neck cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of colorectal

cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of colorectal cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of pancreatic cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of pancreatic cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of gastric cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of gastric cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of kidney cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1,

LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of kidney cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of bladder cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of bladder cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of prostate cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of prostate cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of breast cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5,

6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of breast cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of ovarian cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of ovarian cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of esophageal cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of esophageal cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of soft tissue sarcoma; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2,

3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of soft tissue sarcoma; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of liver cancer; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of liver cancer; wherein the anti-human Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of cancer wherein said medicament is to be administered simultaneously, separately, or sequentially with one or more chemotherapeutic agents. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of cancer wherein said medicament is to be administered simultaneously, separately, or sequentially with one or more chemotherapeutic agents; wherein the anti-Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an anti-human Tim-3 antibody of the present invention in the manufacture of a medicament for the treatment of cancer wherein said medicament is to be administered simultaneously, separately, or sequentially with one or more chemotherapeutic agents; wherein the anti-Tim-3 antibody comprises a heavy chain

(HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides the use of an effective amount of an anti-human Tim-3 antibody for the manufacture of a medicament in simultaneous, separate, or sequential combination with ionizing radiation. The present invention provides the use of an effective amount of an anti-human Tim-3 antibody for the manufacture of a medicament in simultaneous, separate, or sequential combination with ionizing radiation; wherein the anti-Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. The present invention provides the use of an effective amount of an anti-human Tim-3 antibody for the manufacture of a medicament in simultaneous, separate, or sequential combination with ionizing radiation; wherein the anti-Tim-3 antibody comprises a heavy chain (HC) and a light chain (LC), wherein the HC and the LC have the amino acid sequences of SEQ ID NOs: 10 and 11, respectively; 22 and 23, respectively; or 34 and 35, respectively.

The present invention provides an anti-human Tim-3 antibody for use in the treatment of cancer, wherein the anti-human Tim-3 antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), preferably blocks binding of human Tim-3 (SEQ ID NO:1) to phosphatidylserine, but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for use in therapy. The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer. The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein said binding blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine, but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39). The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein said binding blocks binding of human Tim-3 (SEQ ID

NO:1) to human phosphatidylserine and human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for use in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents in the treatment of cancer. The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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. The present invention provides a monoclonal antibody that binds an epitope of human Tim-3 (SEQ ID NO:1) for use in simultaneous, separate, or sequential combination with ionizing radiation in the treatment of cancer. The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer. The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein said binding blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine, but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39). The present invention provides a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) (SEQ ID NO:1) for use in the treatment of cancer, wherein said binding blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention also provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts residues 50, 55-65, 72, 107, 111, 113-120, and 122. The present invention also provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts residues 50, 55-65, 72, 107, 111, 113-120, and 122; wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine

and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive). The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues.

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); and wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive) , and 122. The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; and wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122.

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); and wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive) , and 122. The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; and wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122.

The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39); and optionally, wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive) , and 122. The present invention provides an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more

preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39); and optionally,wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122.

An antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive). An antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the residues in contact

are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive) , and 122; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts amino acid residues 50, 55-65, 72, 107, 111, 113-120, and 122, as determined by X-ray crystallography. An antibody that binds human Tim-3 (SEQ ID NO:1)) for use in the treatment of cancer, wherein the antibody contacts amino acid residues 50, 55-65, 72, 107, 111, 113-120, and 122, as determined by X-ray crystallography; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues.

An antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least

eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography.

An antibody that binds human Tim-3 (SEQ ID NO:1) for use in the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive). An antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one amino

acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive) , and 122; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts amino acid residues 50, 55-65, 72, 107, 111, 113-120, and 122, as determined by X-ray crystallography. An antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts amino acid residues 50, 55-65, 72, 107, 111, 113-120, and 122, as determined by X-ray crystallography; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

An antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the

residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues.

An antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography.

An antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one amino acid residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; optionally, wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39).

The present invention provides the use of a monoclonal antibody that binds an epitope of human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer. The present invention provides the use of a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein said binding blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine, but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39). The present invention provides the use of a monoclonal antibody that binds an epitope of human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein said binding blocks the binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39). The present invention provides the use of a monoclonal antibody that binds an epitope of human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer in simultaneous, separate, or sequential combination with one or more chemotherapeutic agents.

The present invention provides the use of a monoclonal antibody that binds an epitope of human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the cancer is melanoma, lung cancer, non-small cell 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. The present invention provides the use of a monoclonal antibody that binds an epitope of human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer in simultaneous, separate, or sequential combination with ionizing radiation.

The present invention provides the use of a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein said binding blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine, but does not block binding of human Tim-3 (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39). The present invention provides the use of a monoclonal antibody that binds human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein said binding blocks binding of human Tim-3 (SEQ

ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1) to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1) (SEQ ID NO:1) to human CEACAM1 (SEQ ID: 39). The present invention also provides the use of an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts residues 50, 55-65, 72, 107, 111, 113-120, and 122. The present invention also provides the use of an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts residues 50, 55-65, 72, 107, 111, 113-120, and 122; wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1) to human phosphatidylserine and human Tim-3 (SEQ ID NO:1)to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1)to human CEACAM1 (SEQ ID: 39).

The present invention provides the use of an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive). The present invention provides the use of an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues.

The present invention provides the use of an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65

(inclusive), 72, 111, and 113-118 (inclusive); and wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive) , and 122. The present invention provides the use of an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues; more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; and wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122.

The present invention provides the use of an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive); wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1)to human phosphatidylserine and human Tim-3 (SEQ ID NO:1)to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1)to human CEACAM1 (SEQ ID: 39); and optionally, wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive) , and 122. The present invention provides the use of an antibody that binds an epitope on human Tim-3 (SEQ ID NO:1) for the manufacture of a medicament for the treatment of cancer, wherein the antibody contacts at least one residue of the following: 50, 55, 62-65 (inclusive), 72, 111, and 113-118 (inclusive), wherein the antibody contacts: at least two of the residues; preferably at least three of the residues; more preferably at least four of the residues; more preferably at least five of the residues; more preferably at least six of the residues; more preferably at least seven of the residues; more preferably at least eight of the residues;

more preferably at least nine of the residues; more preferably at least ten of the residues; more preferably at least eleven of the residues; more preferably at least twelve of the residues; more preferably at least thirteen of the residues; or more preferably all of the residues; wherein the epitope is determined by X-ray crystallography and wherein the residues in contact are within six (6) angstroms or less of the antibody; wherein said antibody blocks binding of human Tim-3 (SEQ ID NO:1)to human phosphatidylserine and human Tim-3 (SEQ ID NO:1)to human galectin-9 (SEQ ID: 40), but does not block binding of human Tim-3 (SEQ ID NO:1)to human CEACAM1 (SEQ ID: 39); and optionally, wherein the antibody further contacts at least one residue of the following: 56-61 (inclusive), 107, 119-120 (inclusive), and 122.

A pharmaceutical composition for the treatment of cancer, comprising an antibody that binds human Tim-3 (SEQ ID NO:1), the antibody comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 wherein: 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; 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 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.

A pharmaceutical composition for the treatment of cancer, comprising an antibody that binds human Tim-3 (SEQ ID NO:1), the antibody comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein: 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; 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 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.

A pharmaceutical composition for the treatment of cancer, comprising an antibody that binds human Tim-3 (SEQ ID NO:1), the antibody comprising a heavy chain (HC) and a light chain (LC), wherein: 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; 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 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.

A pharmaceutical composition for the treatment of cancer, comprising an antibody that binds human Tim-3 (SEQ ID NO:1), the antibody comprising a heavy chain (HC) and a light chain (LC), wherein: 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; 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 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; 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.

A pharmaceutical composition for the treatment of cancer, comprising an antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts residues 50, 55-65, 72, 107, 111, 113-120, and 122 of human Tim-3 (SEQ ID NO:1); wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography.

A pharmaceutical composition for the treatment of cancer, comprising an antibody that binds human Tim-3 (SEQ ID NO:1), wherein the antibody contacts residues 50, 55-65, 72, 107, 111, 113-120, and 122 of human Tim-3 (SEQ ID NO:1); wherein the residues in contact are within six (6) angstroms or less of the antibody, as determined by X-ray crystallography; 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.

In some embodiments, a method of evaluating the efficacy of an anti-human Tim-3 (SEQ ID NO:1) antibody is provided, the method comprising (a) combining a murine T cell hybridoma expressing human Tim-3 (SEQ ID NO:1), a murine antigen-presenting cell, a peptide recognized by the murine T cell hybridoma, and an anti-human Tim-3 antibody, and (b) measuring murine cytokine production. In some embodiments, a method of evaluating the efficacy of an anti-human Tim-3 antibody is provided, the method comprising (a) combining a murine T cell hybridoma expressing human Tim-3 (SEQ ID NO:1), a murine antigen presenting cell, a peptide recognized by the murine T cell hybridoma, and an anti-human Tim-3 antibody, and (b) measuring murine cytokine production; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively.

In some embodiments, a method of evaluating the efficacy of an anti-human Tim-3 (SEQ ID NO:1) antibody is provided, the method comprising (a) combining a murine T cell hybridoma expressing human Tim-3 (SEQ ID NO:1), a murine antigen-presenting cell, a peptide recognized by the murine T cell hybridoma, and an anti-human Tim-3 antibody, and (b) measuring murine cytokine production; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively; wherein the peptide recognized by the murine T cell hybridoma is ISQAVHAAHAEINEAGR (SEQ ID NO: 38); wherein the murine cytokine is IL-2, interferon-gamma, TNF-alpha, or combinations thereof.

In some embodiments, a method of evaluating the efficacy of an anti-human Tim-3 antibody is provided, the method comprising (a) combining a murine T cell hybridoma expressing human Tim-3 (SEQ ID NO:1), a murine antigen-presenting cell, a peptide recognized by the murine T cell hybridoma,and an anti-human Tim-3 antibody, and (b) measuring murine cytokine production; wherein the anti-human Tim-3 antibody

comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively; wherein the peptide recognized by the murine T cell hybridoma is ISQAVHAAHAEINEAGR (SEQ ID NO: 38); wherein the murine cytokine is IL-2, interferon-gamma, TNF-alpha, or combinations thereof; wherein the murine cytokine production is measured by enzyme-linked immunospot assay, enzyme-linked immunosorbent assay, or flow cytometry; and wherein the murine antigen presenting cell is an A20 cell.

In some embodiments, a method of evaluating the efficacy of an anti-human Tim-3 antibody is provided, the method comprising (a) combining a murine T cell hybridoma expressing human Tim-3 (SEQ ID NO:1) and an anti-human Tim-3 antibody, and (b) measuring the binding of the anti-human Tim-3 antibody to the murine T cell hybrioma expressing Tim-3; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively. In some embodiments, a method of evaluating the efficacy of an anti-human Tim-3 antibody is provided, the method comprising (a) combining a murine T cell hybridoma expressing human Tim-3 (SEQ ID NO:1) and an anti-human Tim-3 antibody, and (b) measuring the binding of the anti-human Tim-3 antibody to the murine T cell hybrioma expressing Tim-3; wherein the anti-human Tim-3 antibody comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences of SEQ ID NOs: 2, 3, 4, 5, 6, and 7, respectively; 14, 15, 16, 17, 18, and 19, respectively; or 26, 27, 28, 29, 30, and 31, respectively; wherein the binding of the anti-human Tim-3 antibody is measured by flow cytometry.

The murine antigen presenting preferably is syngeneic with the murine T cell hybridoma prior to introducing the human Tim-3 gene into the murine T cell hybridoma. The murine antigen presenting cells are murine cells that express the major histocompatibility complex II gene(s); non-limiting examples of which include I-A^d. Non-limiting examples of murine antigen presenting cells include B cells, dendritic cells, and monocytes/macrophages. The murine antigen present cell can be a primary cell or a cell line, a non-limiting example of which includes an A20 cell (ATCC® TIB-208™; a

murine B lymphocyte cell line derived from a BALB/cAnN mouse). Non-limiting examples of murine T cell hybridomas include DO11.10 T cell hybridomas as described by Shimonkevitz et al., Antigen Recognition by H-2-Restricted T cells, Journal of Immunology 133(4), pp. 2067-2074. In some embodiments, the murine cytokine production is measured at the RNA level by methods including, but not limited to real-time PCR, multiplex real time PCR, and PCR. In some embodiments, the murine cytokines include other cytokines, non-limiting examples of which include IL-10, TNF-beta/LT-alpha, IL-3, IL-4, IL-5, IL-6, IL-13, IL-17A, IL-17E, IL-17F, IL-17AF heterodimer, IL-21, IL-22, IL-26, IL-31, GM-CSF, and MIP-3alpha.

An antibody of the present invention is an engineered, non-naturally occurring polypeptide complex. A DNA molecule of the present invention is a non-naturally occurring DNA molecule that comprises a polynucleotide sequence encoding a polypeptide having the amino acid sequence of one of the polypeptides in an antibody of the present invention.

The antibody of the present invention is an IgG type antibody and has "heavy" chains and "light" chains that are cross-linked via intra- and inter-chain disulfide bonds. Each heavy chain is comprised of an N-terminal HCVR and a heavy chain constant region ("HCCR"). Each light chain is comprised of a LCVR and a light chain constant region ("LCCR"). When expressed in certain biological systems, antibodies having native human Fc sequences are glycosylated in the Fc region. Typically, glycosylation occurs in the Fc region of the antibody at a highly conserved N-glycosylation site. N-glycans typically attach to asparagine. Antibodies may be glycosylated at other positions as well.

Optionally, certain anti-Tim-3 antibodies described herein contain an Fc portion that is derived from human IgG_1. IgG1 is well known to bind to the proteins of the Fc-gamma receptor family (FcγR) as well as C1q. Interaction with these receptors can induce antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Therefore, optionally, certain anti-Tim-3 antibodies described herein are a fully human monoclonal antibody lacking Fc effector function (IgG1, Fc-null). To achieve an Fc-null IgG1 antibody, selective mutagenesis of residues is necessary within the CH2 region of its IgG1 Fc region. Amino acid substitutions L234A, L235E, and

G237A are introduced into IgG1 Fc to reduce binding to FcγRI, FcγRIIa, and FcγRIII, and substitutions A330S and P331S are introduced to reduce C1q-mediated complement fixation. To reduce the potential induction of an immune response when dosed in humans, certain amino acids may require back-mutations to match antibody germline sequences.

The HCVR and LCVR regions can be further subdivided into regions of hyper-variability, termed complementarity determining regions ("CDRs"), interspersed with regions that are more conserved, termed framework regions ("FR"). Each HCVR and LCVR is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Herein, the three CDRs of the heavy chain are referred to as "HCDR1, HCDR2, and HCDR3" and the three CDRs of the light chain are referred to as "LCDR1, LCDR2 and LCDR3". The CDRs contain most of the residues which form specific interactions with the antigen. There are currently three systems of CDR assignments for antibodies that are used for sequence delineation. The North CDR definition (North *et al.*, "A New Clustering of Antibody CDR Loop Conformations", Journal of Molecular Biology, 406, 228-256 (2011)) is based on affinity propagation clustering with a large number of crystal structures. For the purposes of the present invention, the North CDR definitions are used.

An isolated DNA encoding a HCVR region can be converted to a full-length heavy chain gene by operably linking the HCVR-encoding DNA to another DNA molecule encoding heavy chain constant regions. The sequences of human, as well as other mammalian, heavy chain constant region genes are known in the art. DNA fragments encompassing these regions can be obtained *e.g.,* by standard PCR amplification.

An isolated DNA encoding a LCVR region may be converted to a full-length light chain gene by operably linking the LCVR-encoding DNA to another DNA molecule encoding a light chain constant region. The sequences of human, as well as other mammalian, light chain constant region genes are known in the art. DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light chain constant region can be a human kappa or lambda constant region. Preferably for

antibodies of the present invention, the light chain constant region is a human kappa constant region.

The polynucleotides of the present invention will be expressed in a host cell after the sequences have been operably linked to an expression control sequence. The expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors will contain selection markers, e.g., tetracycline, neomycin, and dihydrofolate reductase, to permit detection of those cells transformed with the desired DNA sequences.

The antibody of the present invention may readily be produced in mammalian cells, non-limiting examples of which includes CHO, NS0, HEK293 or COS cells. The host cells are cultured using techniques well known in the art.

The vectors containing the polynucleotide sequences of interest (e.g., the polynucleotides encoding the polypeptides of the antibody and expression control sequences) can be transferred into the host cell by well-known methods, which vary depending on the type of cellular host.

Various methods of protein purification may be employed and such methods are known in the art and described, for example, in Deutscher, *Methods in Enzymology* 182: 83-89 (1990) and Scopes, *Protein Purification: Principles and Practice*, 3rd Edition, Springer, NY (1994).

In other embodiments of the present invention, the antibody, or the nucleic acids encoding the same, is provided in isolated form. As used herein, the term "isolated" refers to a protein, peptide, or nucleic acid which is free or substantially free from any other macromolecular species found in a cellular environment. "Substantially free" as used herein means the protein, peptide, or nucleic acid of interest comprises more than 80% (on a molar basis) of the macromolecular species present, preferably more than 90%, and more preferably more than 95%.

The antibody of the present invention, or pharmaceutical compositions comprising the same, may be administered by parenteral routes (e.g., subcutaneous and intravenous). An antibody of the present invention may be administered to a patient along with pharmaceutically acceptable carriers, diluents, or excipients in single or multiple doses. Pharmaceutical compositions of the present invention can be prepared by methods well

known in the art (e.g., *Remington: The Science and Practice of Pharmacy*, 22nd ed. (2012), A. Loyd et al., Pharmaceutical Press) and comprise an antibody, as disclosed herein, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

Dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic effect). Treatment dosages may be titrated to optimize safety and efficacy. Dosing schedules, for intravenous (*i.v.*) or non-intravenous administration, localized or systemic, or combinations, thereof will typically range from a single bolus dosage or continuous infusion to multiple administrations per day (e.g., every 4-6 hours), or as indicated by the treating physician and the patient's condition.

The term "treating" (or "treat" or "treatment") refers to slowing, interrupting, arresting, alleviating, stopping, reducing, or reversing the progression or severity of an existing symptom, disorder, condition, or disease.

"Effective amount" means the amount of an antibody of the present invention or pharmaceutical composition comprising an antibody of the present invention that will elicit the biological or medical response of or desired therapeutic effect on a tissue, system, animal, mammal or human that is being sought by the researcher, medical doctor, or other clinician. An effective amount of the antibody may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effect of the antibody is outweighed by the therapeutically beneficial effects.

WINN Assay

The antibodies of the present invention can be tested for *in vivo* immunomodulatory activity with the WINN assay. In the WINN assay, human NSCLC tumor cells NCI-H292 and human immune cells (allogeneic) are mixed and co-implanted into an immunodeficient mouse, and then followed by dosing with an immunomodulatory agent. The ability of the immunomodulatory agent to inhibit or delay tumor formation or support intra-tumroal persistence can be assessed as follows.

On day 0, NSG mice from Jackson Laboratories (7 weeks of age, female, in groups of 8-10 mice) are implanted into the flank subcutaneously with either 2 $x10^6$ H292 cells, or a mixture of 2 $x10^6$ H292 cells and 1 x 10^6 human PBMCs in HBSS (0.2 ml total

volume). Starting on Day 0, mice are treated with an i.p. injection of control human IgG at 10 mg/kg or Antibody A at 1 mg/kg or 10 mg/kg , one time per week for six weeks. Animal well-being and behavior, including grooming and ambulation, are monitored at least twice per week.

Tumor sections from the model can be analyzed for CD3-positive and CD8-positive T cell persistence by measuring the presence of CD3-positive and CD8-positive T cells by staining for CD3 and CD8 and analyzing with the Aperio ScanScope™. The IHC Nuclear Image Analysis macro detects nuclear staining for a target chromogen for the individual cells in those regions that are chosen by the user and quantifies their intensities. Three to five annotations are made from viable tumor area and used in adjusting the parameters until the algorithm results generate consistent cell identification. The macro is then saved and the slides logged in for analysis. The % CD3-positive and CD8-positive cells as a percent of the total number of cells are calculated by the Aperio software.

In experiments performed essentially as described in this WINN assay, by IHC analysis, mice co-implanted with NCI-H292 tumors and PBMCs and dosed with Antibody A at 10 mg/kg results in a significant increase (30%) of human CD3-positive CD8-positive intratumoral T cells as compared to mice co-implanted with NCI-H292 tumors and PBMCs and treated with the control IgG (6.5 %) ($P = 0.03$).

<u>Established human tumor xenograft model in NSG mice humanized with primary human T cells</u>

The efficacy of the antibodies of the present invention can be tested in the NCI-HCC827 human NSCLC (non-small cell lung cancer) xenograft model to assess the ability to delay or destroy established tumors in the model. On day 0, $1x10^7$ NCI-HCC827 cells are implanted subcutaneously into the flank of NSG mice (7 weeks of age, female, 8 mice per group). When tumors reach a volume of ~400 mm^3 (~days 30-32), the mice are infused (i.v.) with 2.5 $x10^6$ previously expanded human T cells. Previously expanded human T cells are generated by isolating human T cells from whole blood and expanding using Dynabeads® Human T-Activator CD3/CD28 for 10 days. Previously expanded human T cells may be cryopreserved for later use. One day after T cell infusion, mice are dosed at 10 mg/kg by weekly (4 total doses) i.p. injection with human

IgG or Antibody A. Animal well-being and behavior, including grooming and ambulation are monitored at least twice per week.

Body weight and tumor volume are measured twice a week. Tumor volumes were measured twice per week starting on day 4 post-cell implantation using electronic calipers as described above. Tumor Volume (mm^3) = $\pi/6$ * Length * $Width^2$. The antitumor efficacy is expressed as T/C ratio in percent and calculated as summarized below: %T/C is calculated by the formula 100 $\Delta T / \Delta C$ if $\Delta T > 0$ of the geometric mean values. ΔT = mean tumor volume of the drug-treated group on the final day of the study – mean tumor volume of the drug-treated group on initial day of dosing; ΔC = mean tumor volume of the control group on the final day of the study – mean tumor volume of the control group on initial day of dosing. Additionally, % Regression is calculated using the formula = 100 x $\Delta T/T_{initial}$ if $\Delta T < 0$. Animals with no measurable tumors are considered as Complete Responders (CR) and tumors with >50% regressions are Partial Responders (PR).

In experiments performed essentially as described above, treatment with Antibody A (anti-human Tim-3) significantly inhibits tumor growth in the humanized NSG mice, compared to treatment with human IgG (Table 1). On day 76, treatment with Antibody A results in a T/C = 2%. On day 110, Antibody A treatment results in a 3/8 CR.

Table 1: Tumor volume (mm^3) in the NCI-HCC827 human NSCLC xenograft model

	Human IgG Control		Antibody A	
Day	Mean	SEM	Mean	SEM
21	152	13	164	85
28	289	24	309	160
30	332	28	358	186
34	388	32	403	209
36	414	34	505	262
40	706	59	628	326
43	752	62	733	380
47	858	71	763	396
50	932	77	747	387

	Human IgG Control		Antibody A	
Day	Mean	SEM	Mean	SEM
55	982	81	807	418
57	1212	100	843	437
62	1324	110	553	287
65	1524	126	726	376
69	1492	124	602	312
72	1827	151	539	279
76	2030	168	375	196
79			375	196
83			414	218
85			331	175
90			192	103
93			235	128
97			173	95
100			118	65
103			125	69
106			120	67
110			131	73

Mixed Lymphocyte Reaction

The function of blocking Tim-3 signals by antibodies of the present invention may be evaluated by measuring the release of cytokines during T cell activation. The levels of certain cytokines, such as IFN-γ, are expected to increase if T cell activation is promoted by treatment with antibodies of the present invention.

$CD14^+$ monocytes are isolated by negative selection from fresh human PBMC obtained from a healthy donor (AllCells) using human monocyte isolation kit II (Miltennyi Biotec). Human monocyte-derived dendritic cells are generated by culturing the $CD14^+$ monocytes in complete RPMI-1640 medium in the presence of 62.5 ng/ml hGM-CSF and 20 ng/ml hIL-4 for 7 days. $CD4^+$ T cells are purified from fresh human PBMC of a different healthy donor (AllCells) by negative selection using the CD4 T cell isolation kit (Miltenyi). The two types of cells are then mixed in individual wells of a 96-well plate with 100 µl complete AIM-V medium containing $1x10^5$ $CD4^+$ T cells and $2x10^4$ immature DC per well. 100 µl complete AIM-V medium is added containing 100

nM human IgG1 or Antibody A in 6 replicates. After incubation for 3 days at 37°C at 5% CO_2, supernatants are harvested and measured for human IFN-γ with an ELISA kit (R&D Systems). An unpaired t-test is used to compare groups.

In experiments performed essentially as described above, the addition of Antibody A significantly increases the secretion of IFN-γ as compared to the addition of control human IgG1 (3,036 ± 367 vs. 1,644 ± 261 pg/mL of hIFN-γ; p=0.0384).

ELISA analysis: Antibody A binds to recombinant Tim-3

The ability for antibodies of the present invention to bind human Tim-3 can be measured with an ELISA assay. For the Tim-3 binding assay, a 96-well plate (Nunc) is coated with human Tim-3-Fc (R&D Systems) overnight at 4°C. Wells are blocked for 2 h with blocking buffer (PBS containing 3% bovine serum albumin). Wells are washed three times with PBS containing 0.1% Tween-20. Antibody A or control IgG (100 µl) is then added and incubated at room temperature for 1 h. After washing, the plate is incubated with 100 µl of goat anti-human IgG F(ab')2-HRP conjugate (Jackson Immuno Research) at room temperature for 1 h. The plates are washed and then incubated with 100 µl of 3,3', 5,5'-tetra-methylbenzidine. The absorbance at 450 nm is read on a microplate reader. The half maximal effective concentration (EC50) is calculated using GraphPad Prism 6 software.

In experiments performed essentially as described above, Antibody A binds human Tim-3 with an EC50 of 2.07 x 10^{-11} M.

Flow cytometric analysis: Antibody A binds to cell surface Tim-3

The ability for antibodies of the present invention to bind to cell surface human Tim-3 can be measured with a flow cytometric assay. Tim-3 DO11.10 cells, a human Tim-3 expressing DO11.10 cell line, are used for this assay.

Tim-3 DO11.10 cells can be obtained as follows. Full-length Tim-3 gene can be purchased from Origene Technologies, Inc. and cloned into a pLVX-IRES-Neo lentivirus vector from Clonetech Laboraties, Inc. using PCR. Lenti-X™ system from Clonetech Laboraties, Inc. is used to generate high titers of recombinant, replication-incompetent virions. The virions are either used to infect the target cells immediately or are aliquoted and frozen at -80 until use. The murine T cell hybridoma, DO11.10 cell line, can be obtained from the National Jewish Health®. The DO11.10s are cultured and maintained

according to a protocol accompanying this cell line. On day 0, DO11.10 cells are counted and spun down to remove culture media. Cell pellets are mixed with virions containing the human TIM-3 gene or vector control and incubated at 37°C for 24 hours. Polybrene is added when mixing cells and virions until a final concentration of 8 ug/ml is achieved. After 24 hours, DO11.10 cells are pelleted again and resuspended in fresh culture media and incubated at 37°C for 3 days. Next, the DO11.10 cells are pelleted every 3 days and resuspended in selection media containing 1 mg/ml Geneticin® to select stably transduced cells. Tim-3 expression is monitored by flow cytometry using antibodies obtained from R&D Systems. After 2 to 3 weeks in selection media, the resulting Tim-3 expressing DO11.10 cells are sorted to establish a single cell clone.

DO11.10 and Tim-3 DO11.10 cells are added to a 96 well V-bottom plate at $1.x10^5$ cells per well (100 µl/well) in staining buffer (DPBS containing 3% BSA). Cells are Fc blocked on ice for 1 hour in staining buffer with 30 µg/mL human IgG. Antibody A or control human IgG is labelled with A488 (Molecular Probes®) and 12 point titrations (1:3 serial dilutions) of both antibodies are prepared in staining buffer with a starting concentration of 66.7 nM. Labelled antibodies are added to the cells and incubated for 1 hour at 4°C in the dark. Cells are washed two times with PBS by spinning for 5 min at 1200 RPM and decanting the supernatant. Live/Dead cell dye 7-AAD (1:1000 in PBS) is added to each well at 3 µl/well and cells are incubated for 15 min on ice. Cells are washed two times with PBS and resuspended in 100 µl DPBS containing 0.5% BSA and analyzed on an Intellictye iQue. All stainings are done in triplicate. Data are analyzed with FlowJo software to identify populations of live cells and determine the median fluorescence intensity of each sample using the AF488 (FL1) detection channel. The individual MFI (i.e. mean fluorescence intensity) values are placed into GraphPad Prism software to generate concentration response curves from which EC50 values are extrapolated.

In experiments performed essentially as described above, Antibody A binds to cellular bound human Tim-3 on Tim-3 DO11.10 cells in a dose dependent manner with an EC50 value of 0.09 nM.

Flow cytometric analysis: Antibody A blocks the interaction of phosphatidylserine with human Tim-3 The ability for certain antibodies of the present invention to block

phosphatidylserine binding to Tim-3 can be measured by FACS analysis. For this receptor-ligand blocking assay, $1x10^6$/ml of DO11.10 cells are treated with 12 µM camptothecin (Sigma®) for 3 hours at 37°C to induce apoptosis. FITC-Annexin V (Becton Dickinson®) is used as a positive control to detect the existence of phosphatidylserine. Biotinylated hTIM-3-Fc binds strongly to camptothecin-treated cells but does not bind to non-treated cells. Camptothecin-treated cells are washed with cold PBS and resuspended in binding buffer (Becton Dicknson®) at $1x10^6$ cells/ml. Fc receptors are blocked by adding 50 µg/ml mouse IgG and rat IgG to the cells and incubating at room temperature for 30 min. 6 point titrations (1:3 serial dilutions) of Antibody A are prepared in binding buffer with a starting concentration of 90 nM and added to 1 ml of cells and cells are then incubated for 60 min at room temperature. hTIM-3-Fc Biotin is then added at 0.05 µg/well to the appropriate samples in a 200 µl volume and incubated for 30 min at room temperature. Cells are then washed twice with binding buffer by centrifugation at 1200 RPM for 5 min. 2.4 µl/well of a streptavidin-FITC (Biolegend®) containing solution (1:10 dilution in DPBS) and 5 µl/well of propidium iodide are added to each well and incubated for 30 min at room temperature in the dark. Cells are washed twice with binding buffer and resuspended in 100 µl of PBS. Samples are read on the IntelliCyt iQue Flow Cytometer and Data were analyzed with FlowJo software. The individual MFI (i.e. mean fluorescence intensity) values are placed into GraphPad Prism software to generate concentration response curves from which IC50 values are extrapolated.

In experiments performed essentially as described above, Antibody A blocks the interaction of human Tim-3 with phosphatidylserine in a dose-dependent manner with an IC50 value of 0.32 nM and as further illustrated in Table 2.

Table 2

	Untreated DO11.10 + hTIM-3-Fc Biotin	Camptothecin-treated DO11.10+ hTIM-3-Fc Biotin						
Antibody A (nM)	0	90	30	10	3.3	1.1	0.37	0

MFI	1747	1815	19655	32574	52885	96566	197146	214044

Galectin-9 Blocking Assay: Antibody A blocks the interaction of human galectin-9 with human Tim-3

The ability for antibodies of the present invention to block human galectin-9 binding to human Tim-3 can be measured as follows. For this receptor-ligand blocking assay, a 96-well streptavidin-coated MSD plate (Meso Scale Diagnostics) is blocked for 2 hours with 150 µl blocking buffer (PBST containing 5% bovine serum albumin). Wells are washed three times with 200 µl PBS containing 0.2% Tween-20. Recombinant human galectin-9 (R&D Systems) is biotinylated using EZ-Link™ biotin (Thermo Scientific™) and then 25 µl of 0.21 µg/ml of the human recombinant galectin-9-biotin is then added and incubated at room temperature for 2 hours. Plates are washed three times with PBS containing 0.2% Tween-20. Human Tim-3-Fc protein (R&D Systems) is ruthinylated using sulfo-tag NHS-ester reagent (Meso Scale Discovery®) and a small aliquot is stored at -80 until use. Antibodies are serially diluted (starting at 13.5 µg/ml) and 50 µl of each antibody combined with 50 µl of diluted hTim-3-Fc-ruth at 0.05 µg/ml and incubated for 1 hour at room temperature. 50 µl of each combination is then added to the plate and incubated for 1.5 hours at room temperature. Plates are washed three times with PBS containing 0.2% Tween-20. 150 µl of 1X read buffer (Meso Scale Diagnostics) is then added to each well of the plate and the plate is read on a Sector Imager 2400 (Meso Scale Diagnostics).

In experiments performed essentially as described above, Antibody A blocks the interaction of human Tim-3 with human galectin-9 with an IC50 value of 5.6 nM as compared to control a polyclonal anti-human Tim-3 antibody (R&D Systems) with an IC50 value of 7.8 nM. However, The polyclonal anti-human Tim-3 antibody can block up to 100% human Tim-3's interactions with human galectin-9 while Antibody A only achieve partial blockage in this assay.

CEACAM-1 Blocking Assay: Antibody A does not block the interaction of human CEACAM1 with human Tim-3

The ability for antibodies of the present invention to block human CEACAM1 binding to human Tim-3 can be measured as follows. For this receptor-ligand blocking assay, a 96-well Immulon 4HBX plate (Thermo Scientific) is coated with 100 µl/well of 1ug/ml human Tim-3-Fc at 4°C. The plate is washed three times with PBS containing 0.2% Tween-20 and blocked with 200 µl/well of PBS with 3% BSA for 1 hour at room temperature. Blocking buffer is then removed and 50 µl of titrated Abs (including polyclonal anti-human Tim-3, R&D Systems, Antibody A, and control human IgG), starting at 600 nM are added to the plate and incubated for 1 hour at room temperature. 50 µl of 20 µg/ml of CEACAM1 (BIOTANG) is then added directly to the wells and incubated for 1 hour at room temperature (final concentration of antibody is 300 nM and of CEACAM1 is 10 µg/ml). The plate is washed three times with PBS containing 0.2% Tween-20 and 100 µl of 0.2 µg/ml of biotinylated human CEACAM1 antibody (R&D Systems) is added and then incubated for 1 hour at room temperature. The plate is washed three times with PBS containing 0.2% Tween-20 and then 100 µl of streptavidin peroxidase (Jackson ImmunoResearch Laboratories) is added and then incubated for 1 hour at room temperature. The plate is washed six times with PBS containing 0.2% Tween-20 and developed using 100 µl/well of a 1:1 TMB substrate solution A and B (KPL) for 10 min at room temperature. The reaction is then stopped with 100 µl/well of 0.1N H_2SO_4 and the plate is read on a SpectraMax® plate reader at 450 nm.

In experiments performed essentially as described above, Antibody A does not significantly block the binding of CEACAM1 to human Tim-3, as illustrated in Table 3 below.

Table 3

Concentration of Antibody (nM)	0.015	0.046	0.137	0.41	1.24	3.71	11.1	33.3	100	300
Human IgG Control (O.D.)	2.05	2.02	2.13	2.03	2.04	2.03	2.05	2.07	2.12	2.08

Polyclonal Anti-Tim-3 (O.D.)	1.96	1.88	1.89	1.88	1.85	1.80	1.51	1.16	0.99	0.99
Antibody A (O.D.)	1.87	1.88	1.87	1.82	1.80	1.78	1.79	1.79	1.73	1.74

Epitope

A Fab for Antibody A is generated by by enzymatically clipping Antibody A with immobilized (agarose resin) papain (ThermoFisher Scientific) followed by a standard ProA column (GE Healthcare Life Sciences) purification to pull out the free, soluble Fc and the unclipped IgG. Flow through containing the Fab is collected to concentrate and buffer exchange. The hTim-3-IgV-FLAG is purified from the 293HEK supernatant with a standard anti-FLAG resin (Sigma-Aldrich) protocol. The hTim-3-IgV domain represents amino acid residues S22 to K130 of human Tim-3 (SEQ ID:1). Flow through is rerun in the resin column multiple times. After each run, SDS-PAGE (NuPAGE Novex 4-12% Bis-Tris Gels; Invitrogen) and HPLC (TSKgel G3000 SW XL (Dimensions: 7.8mm, ID 30 CM, 5 μM; TOSHO BioSCIENCE) is utilized to determine quality of the hTim-3-FLAG protein. Proteins of the best rounds are combined together to generate the final batch.

hTim-3-IgV-FLAG, at 2.17 mg/mL in TBS buffer pH 7.2, and Antibody A-Fab, at 6.79 mg/mL, are combined in a 1:1 molar ratio and the complex is isolated via size exclusion chromatography with a final concentration of 6.9 mg/mL in 20 mM hepes pH 7.4 and 150 mM sodium chloride. The Tim-3-anti-Tim-3 complex is screened in five Qiagen grid screens at both 8°C and 21°C using the sitting drop vapor diffusion method. Drops are set up using an Art Robbins Phoenix liquid handling robot which dispenses 0.3 μL crystallization solution on top of 0.3 μL protein. 100-200 μm intergrown prisms are obtained at 21°C in 20% PEG 3350 and 0.2 M lithium chloride. Crystals are harvested and cryoprotected in a solution made of the crystallization condition supplemented with 20% ethylene glycol prior to flash freezing in liquid nitrogen. A dataset is collected at Argonne National Laboratory diffracting to 2.2 Å in space group P21 with cell parameters a = 74.62 Å, b = 57.85 Å, and c = 74.71 Å.

The structure of the Antibody A-Fab in complex with human Tim-3 is determined by Molecular Replacement using the program Phaser. High resolution and publicly available Fab structures and the published structure of murine Tim-3 can be used as Molecular Replacement models. The structure is refined using the program Refmac and the model rebuilt using the program COOT. Final refinement R-factors are Rwork=20.2%, Rfree=23.4%. There are no Ramachandran violators, and 96.4% of the residues are in the favored region of the Ramachandran plot. There is density indicating glycosylation at Asn99 of Tim-3 (SEQ ID NO:1).

Biacore T200 is utilized to determine the binding kinetics of hTim-3-IgV-FLAG to the captured AntibodyA-Fab. In HBS-EP as a running buffer, 1:1 binding of this complex at 25°C has a k_{on} of 3.62E+05 1/Ms, k_{off} of 2.86E-03 1/s, and a K_D of 7.92E-09 M.

In experiments performed essentially as described in this assay, Antibody A-Fab/hTim-3 complex is resolved and the epitope/paratope is illustrated in Table 4 below. Table 4 below lists the residues on Antibody A-Fab that are within 6Å of the listed residues on hTim-3 (SEQ ID NO:1). The heavy chain of the Antibody A-Fab has 62 contacts (cutoff 6 Å) with hTim-3 while the light chain has 34 contacts (cutoff 6 Å).

Table 4

Tim-3 (Epitope)	Antibody A Heavy Chain (Paratope)	Antibody A Light Chain (Paratope)
P50	S54	--
K55	--	Y32
G56	--	Y32
A57	--	Y30, Y32, N92
C58	--	Y32, A91, N92, S93
P59	Y99, T102	Y32, A91, N92, S93
V60	Y59, Y99, T102	Y32, Q89,

		Q90,A91, N92, S93, F94, P95, P96
F61	Y33, S35, W47, A50, Y59, Y99, A100, T102, F104	A91, F94, P96
E62	S31, Y33, Y59, Y99, R101	--
C63	Y99, R101, T102	Y32
G64	T102	Y32
N65	T102	N31, Y32, A50
E72	S54	--
I107	--	T30
R111	Y33, Y59	--
Q113	Y33, S52, G53, S54, G55, G56, S57,Y59	--
I114	G56, S57	--
P115	G56, S57	--
G116	G56, S57, T58, Y59	--
I117	G56, S57, T58, Y59, Y60, K65	--
M118	S57, T58, Y59, Y60, A61, D62, K65	F94
N119	T58, Y59	--
D120	Y33, S57, Y59	--
K122	--	N92, F94

Competition assay

A competition assay can be performed to determine whether Antibody B and Antibody C compete with Antibody A for binding to human Tim-3. An Octet® Red384 instrument and AR2G (Amine Reactive Second Generation) Biosensors from ForteBIO can be used for this assay. Biosensors are rehydrated in H_2O for a minimum of 30 minutes before being activated with 20 mM 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and 10 mM *N*-hydroxysuccinimide (NHS) for 300 seconds. Antibodies at 2 ug/ml in 10 mM sodium acetate buffer, pH 4.5 are coupled to the sensor through free amines for 500 sec and the coupling reaction is quenched with 1M ethanolamine for 400 seconds. Sensors are dipped in kinase buffer (obtained from the AR2G reagent kit (ForteBIO)) for baseline measurement for 300 seconds. Sensors are then dipped into a 100 nM human Tim-3-IgV-Fc single arm antigen (SAG in kinase buffer for 500 sec to enable the binding of the antigen to amine coupled antibodies on the sensor. Next, sensors are dipped into 100 nM of test antibodies in kinase buffer for 300 seconds to test for competition. Sensograms are visualized using the ForteBio Data Analysis 8.0 software. Each trace is visually compared to its respective "self-self" control. If additional binding is observed when sensors are dipped into the test antibodies, the test antibody is considered not to compete with the antibody coupled to the sensor for binding to the antigen. If no additional binding is observed, the test antibody is considered to be blocked by or to compete with the fixed antibody for binding to the antigen.

In experiments performed essentially as described here, no additional binding is observed for either Antibody B or Antibody C when Antibody A is coupled to the sensor, and vice versa. These data demonstrate that Antibody B and Antibody C compete with Antibody A for binding to human Tim-3.

hTIM-3 DO11.10 cell based assay using Antibody A, Antibody B, and Antibody C

The ability for antibodies of the present invention to bind to cellular bound human Tim-3 and promote T cell activation can be measured using a human Tim-3 expressing DO11.10 cell line and measuring for IL-2 production. For the huma Tim-3 DO11.10 cell based assay, $2x10^4$ cells/well (in 50 microliters) of either DO11.10 or DO11.10 cells expressing human Tim-3 are plated with $2x10^4$ cells/well of A20 cells (in 50 microliters)

in a 96 well U bottom tissue culture plate (Greiner CELLSTAR®) with RPMI 1640 media (Gibco®). 50 µl of OVA peptide (323-339) (Sigma-Aldrich®) is added to achieve a final concentration of 0.2 uM (diluted in media). Antibody A, Antibody B, Antibody C, or control human IgG is diluted into RPMI 1640 media starting from 200 nM with a dilution factor of 3 to give concentrations of 0.09, 0.27, 0.82, 2.47, 7.41, 22.2, 66.7 and 200 nM. 50 µl of the diluted Antibody A, Antibody B, Antibody C, or control human IgG is added to each well. RPMI 1640 media is then added as needed to achieve a final volume of 200 µl/well. Supernatants are collected 18-22 hours after stimulation and IL-2 levels in the supernatants are measured by ELISA (R&D Systems®). The EC50 is calculated with GraphPad software.

In experiments performed essentially as described above, Antibody A, Antibody B, and Antibody C enhance OVA-specific T cell activation in a dose-dependent manner with the EC50 values shown in Table 5.

Table 5

	Antibody A	Antibody B	Antibody C
EC50 (nM)	3.707	6.079	3.352

Kinetics/Affinity study for Antibody A, Antibody B, and Antibody C

A Biacore T100 instrument can be used to measure the kinetics of human Tim-3-IgV-Fc single arm antigen (SAG) binding to captured Antibody A, Antibody B, or Antibody C. Human Fab Binder surfaces are prepared by amine-coupling Human Fab Binder (GE Healthcare) to a Biacore CM5 sensor chip surface. Test antibodies are captured by the chip using HBS-EP buffer (GE Healthcare) as the running buffer. Tim-3 SAG is diluted into running buffer starting at 30 nM with a dilution factor of 3 to give concentrations of 0.04, 0.12, 0.37, 1.11, 3.33, 10 and 30 nM. Diluted Tim-3 SAG analyte or buffer is injected at 30 µl/min for 180 seconds and the complex dissociation is monitored for 1200 seconds. The binding surface is regenerated with injection of 10mM Glycine-HCl pH 2.1 at 30 µl/min, 30 seconds of two injections for five lower concentrations, and two injections at 60 seconds for two higher concentrations between

each analyte binding cycle. Experimental data for a given antigen/Ab interaction are fit using a *1:1 Langmuir with mass transport* Model.

In experiments performed essentially as described above, Antibody A, Antibody B, and Antibody C bind to human Tim-3 with the kinetics and affinity constants illustrated in Table 6.

Table 6

Antibody	K_{on} (1/Ms)	K_{off} (1/s)	K_D (M)	R_{max}	Chi^2
Antibody B	6.75E+05	1.06E-04	1.58E-10	17.36	0.115
Antibody C	7.97E+05	1.38E-04	1.73E-10	32.56	0.404
Antibody A	2.33E+06	9.27E-04	3.98E-10	17.09	0.319

Antibody generation, expression, and purification

The antibodies of the present invention may be generated by known methods including use of, but not limited to, phage display, transgenic animals, and humanization. Additionally, the antibodies derived as described above may be further screened using the assays described herein.

The polypeptides of the variable regions of the heavy chain and light chain, the complete heavy chain and light chain amino acid sequences of Antibodies A through C, and the nucleotide sequences encoding the same, are listed in the section entitled "Amino Acid and Nucleotide Sequences." In addition, the SEQ ID NOs for the light chain, heavy chain, light chain variable region, and heavy chain variable region of Antibodies A through C are shown in Table 7.

The antibodies of the present invention, including, but not limited to, Antibodies A through C can be made and purified essentially as follows. An appropriate host cell, such as HEK 293 or CHO, can be either transiently or stably transfected with an expression system for secreting antibodies using an optimal predetermined HC:LC vector ratio or a single vector system encoding both HC and LC. Clarified media, into which the antibody has been secreted, may be purified using any of many commonly-used techniques. For example, the medium may be conveniently applied to a MabSelect column (GE Healthcare), or KappaSelect column (GE Healthcare) for Fab fragment, that has been equilibrated with a compatible buffer, such as phosphate buffered saline (pH

7.4). The column may be washed to remove nonspecific binding components. The bound antibody may be eluted, for example, by pH gradient (such as 20 mM Tris buffer pH 7 to 10 mM sodium citrate buffer pH 3.0, or phosphate buffered saline pH 7.4 to 100 mM glycine buffer pH 3.0). Antibody fractions may be detected, such as by UV absorbance or SDS-PAGE, and then may be pooled. Further purification is optional, depending on the intended use. The antibody may be concentrated and/or sterile filtered using common techniques. Soluble aggregate and multimers may be effectively removed by common techniques, including size exclusion, hydrophobic interaction, ion exchange, multimodal, or hydroxyapatite chromatography. The purity of the antibody after these chromatography steps is greater than 95%. The product may be immediately frozen at -70°C or may be lyophilized.

Table 7

Corresponding SEQ ID	Antibody A	Antibody B	Antibody C
HCDR1	2	14	26
HCDR2	3	15	27
HCDR3	4	16	28
LCDR1	5	17	29
LCDR2	6	18	30
LCDR3	7	19	31
HCVR	8	20	32
LCVR	9	21	33
Heavy chain	10	22	34
Light chain	11	23	35
DNA Heavy Chain	12	24	36
DNA Light Chain	13	25	37

Amino Acid and Nucleotide Sequences

SEQ ID NO: 1 (human Tim-3)

MFSHLPFDCVLLLLLLLLTRSSEVEYRAEVGQNAYLPCFYTPAAPGNLVPVCWG
KGACPVFECGNVVLRTDERDVNYWTSRYWLNGDFRKGDVSLTIENVTLADSGIY
CCRIQIPGIMNDEKFNLKLVIK

SEQ ID NO: 2 (HCDR1 of Antibody A)

AASGFTFSSYYMS

SEQ ID NO: 3 (HCDR2 of Antibody A)

AISGSGGSTYYADSVKG

SEQ ID NO: 4 (HCDR3 of Antibody A)

ARYARTAFDL

SEQ ID NO: 5 (LCDR1 of Antibody A)

QASQDIYNYLN

SEQ ID NO: 6 (LCDR2 of Antibody A)

YAASSLQS

SEQ ID NO: 7 (LCDR3 of Antibody A)

QQANSFPPT

SEQ ID NO: 8 (HCVR of Antibody A)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYYMSWVRQAPGKGLEWVSAISGS
GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYARTAFDLW
GQGTLVTVSS

SEQ ID NO: 9 (LCVR of Antibody A)

DIVMTQSPSSLSASVGDGVTITCQASQDIYNYLNWYQQKPGKAPKLLIYAASSLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPPTFGQGTKLEIK

SEQ ID NO: 10 (HC of Antibody A)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYYMSWVRQAPGKGLEWVSAISGS
GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYARTAFDLW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK
SCDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPSSIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK

SEQ ID NO: 11 (LC of Antibody A)

DIVMTQSPSSLSASVGDGVTITCQASQDIYNYLNWYQQKPGKAPKLLIYAASSLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPPTFGQGTKLEIKRTVAA
PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 12 (DNA of HC of Antibody A)

GAGGTGCAGCTGTTGGAGTCTGGCGGAGGGCTGGTGCAGCCGGGAGGCAGCC
TCAGGCTGAGCTGCGCTGCGAGCGGGTTTACTTTCTCGTCGTACTATATGTCG
TGGGTGAGACAAGCACCAGGTAAAGGACTTGAGTGGGTGTCCGCTATCTCAG
GCAGCGGAGGATCCACCTACTACGCGGATTCAGTCAAGGGAAGATTCACTAT
CTCGCGCGACAATTCCAAGAACACCCTGTACCTCCAGATGAACTCGCTGCGG
GCAGAAGATACGGCCGTGTACTACTGTGCCCGCTACGCCCGGACCGCCTTCG
ACTTGTGGGGTCAGGGAACCCTGGTCACTGTCTCCTCAGCTAGCACCAAGGG
CCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAG
CGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC
GTGGAACTCAGGCGCACTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTA
CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAG
CTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACC
AAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCC
CACCGTGCCCAGCACCTGAAGCCGAGGGGGCACCGTCAGTCTTCCTCTTCCCC
CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCG
TGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTATGT
GGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA
CAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAAGACTGG
CTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCATCCT
CCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
GTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAAGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTC
CGACGGCTCCTTCTTCCTCTATTCCAAGCTCACCGTGGACAAGAGCAGGTGGC

AGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCA
CTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGCAAA

SEQ ID NO: 13 (DNA of LC of Antibody A)

GACATCGTGATGACTCAAAGCCCTTCAAGCCTCTCGGCGTCAGTCGGTGATGG
CGTGACCATTACCTGTCAAGCATCCCAAGACATCTACAACTACTTGAATTGGT
ACCAGCAGAAGCCAGGGAAAGCCCCGAAGCTGCTGATCTACGCCGCCTCCTC
ACTTCAGAGCGGAGTGCCATCCCGCTTTTCCGGATCGGGGAGCGGAACGGAT
TTCACTCTGACCATCTCGTCGCTGCAACCGGAGGACTTCGCGACTTACTATTG
CCAGCAGGCTAACTCGTTCCCGCCCACTTTCGGACAGGGCACCAAGCTCGAA
ATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
CCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAA
CTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC
AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTAC
GCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCA
ACAGGGGAGAGTGT

SEQ ID NO: 14 (HCDR1 of Antibody B)

AASGFSFSSFYFS

SEQ ID NO: 15 (HCDR2 of Antibody B)

AISGNGRSTYYADSVKG

SEQ ID NO: 16 (HCDR3 of Antibody B)

ARYYNTGFDL

SEQ ID NO: 17 (LCDR1 of Antibody B)

QASEAIYGYLN

SEQ ID NO: 18 (LCDR2 of Antibody B)

YAASSLPI

SEQ ID NO: 19 (LCDR3 of Antibody B)

QQAYGFPPT

SEQ ID NO: 20 (HCVR of Antibody B)

EVQLLESGGGLVQPGGSLRLSCAASGFSFSSFYFSWVRQAPGKGLEWVSAISGNG
RSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYYNTGFDLWG
QGTLVTVSS

SEQ ID NO: 21 (LCVR of Antibody B)

DIVMTQSPSSLSASVGDGVTITCQASEAIYGYLNWYQQKPGKAPKLLIYAASSLPI
GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAYGFPPTFGQGTKLEIK

SEQ ID NO: 22 (HC of Antibody B)

EVQLLESGGGLVQPGGSLRLSCAASGFSFSSFYFSWVRQAPGKGLEWVSAISGNG
RSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYYNTGFDLWG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS
CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF
NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPSSIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK

SEQ ID NO: 23 (LC of Antibody B)

DIVMTQSPSSLSASVGDGVTITCQASEAIYGYLNWYQQKPGKAPKLLIYAASSLPI
GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAYGFPPTFGQGTKLEIKRTVAA
PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 24 (DNA of HC of Antibody B)

GAGGTGCAGCTGCTGGAATCCGGAGGAGGACTGGTCCAGCCAGGAGGCAGC
CTGCGACTGTCCTGTGCCGCTTCTGGCTTCAGTTTTTCTAGTTTCTATTTTTCCT
GGGTGCGGCAGGCTCCCGGCAAGGGACTGGAGTGGGTCTCTGCAATCAGCGG
CAACGGGCGTTCTACATACTATGCCGACAGTGTGAAAGGCAGGTTTACCATT
AGCCGGGACAACTCAAAGAATACACTGTACCTGCAGATGAACTCTCTGCGAG
CCGAAGACACTGCCGTGTACTATTGCGCCCGGTATTATAATACCGGGTTCGAT
CTGTGGGGACAGGGCACCCTGGTGACAGTCTCATCTGCTAGCACCAAGGGCC
CATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCG
GCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTG
GAACTCAGGCGCACTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAG
TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT
GGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAG
GTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCAC
CGTGCCCAGCACCTGAAGCCGAGGGGGCACCGTCAGTCTTCCTCTTCCCCCCA
AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGG

TGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTATGTGGA
CGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAA
CAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAAGACTGGCTGA
ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCATCCTCCAT
CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTA
CACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAAGTCAGCCTGACC
TGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCA
ATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGA
CGGCTCCTTCTTCCTCTATTCCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGCAAA

SEQ ID NO: 25 (DNA of LC of Antibody B)

GACATCGTGATGACCCAGTCCCCAAGCTCCCTGAGCGCCAGCGTGGGAGACG
GCGTCACCATCACATGCCAGGCCTCTGAAGCCATCTACGGCTATCTGAATTGG
TACCAGCAGAAGCCAGGGAAAGCCCCCAAGCTGCTGATCTATGCCGCTTCTA
GTCTGCCGATCGGAGTGCCCAGTAGGTTCTCTGGGAGTGGATCAGGCACAGA
CTTTACTCTGACCATTTCAAGCCTGCAGCCTGAGGATTTCGCTACTTACTATTG
CCAGCAGGCTTATGGGTTCCCCCCTACATTTGGGCAGGGAACTAAACTGGAG
ATCAAGCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
CCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAA
CTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC
AGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTAC
GCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCA
ACAGGGGAGAGTGT

SEQ ID NO: 26 (HCDR1 of Antibody C)

AASGFTFSSYYMS

SEQ ID NO: 27 (HCDR2 of Antibody C)

AISGNGKSTYYADSVKG

SEQ ID NO: 28 (HCDR3 of Antibody C)

ARYYNTGFDL

SEQ ID NO: 29 (LCDR1 of Antibody C)

QASQDIYNYLN

SEQ ID NO: 30 (LCDR2 of Antibody C)

YYASSIVS

SEQ ID NO: 31 (LCDR3 of Antibody C)

QQANSFPPT

SEQ ID NO: 32 (HCVR of Antibody C)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYYMSWVRQAPGKGLEWVSAISGN
GKSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYYNTGFDLW
GQGTLVTVSS

SEQ ID NO: 33 (LCVR of Antibody C)

DIVMTQSPSSLSASVGDGVTITCQASQDIYNYLNWYQQKPGKAPKLLIYYASSIVS
GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPPTFGQGTKLEIK

SEQ ID NO: 34 (HC of Antibody C)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYYMSWVRQAPGKGLEWVSAISGN
GKSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYYNTGFDLW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK
SCDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPSSIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK

SEQ ID NO: 35 (LC of Antibody C)

DIVMTQSPSSLSASVGDGVTITCQASQDIYNYLNWYQQKPGKAPKLLIYYASSIVS
GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPPTFGQGTKLEIKRTVAAP
SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 36 (DNA of HC of Antibody C)

GAGGTGCAGCTGCTGGAATCCGGAGGAGGACTGGTCCAGCCAGGAGGCAGC
CTGCGACTGTCCTGTGCCGCTTCTGGCTTCACTTTTTCTAGTTACTATATGTCC
TGGGTGCGGCAGGCTCCCGGCAAGGGACTGGAGTGGGTCTCTGCAATCAGCG
GCAACGGAAAATCTACATACTATGCCGACAGTGTGAAAGGCAGGTTTACCAT
TAGCCGGGACAACTCAAAGAATACACTGTACCTGCAGATGAACTCTCTGCGA
GCCGAAGACACTGCCGTGTACTATTGCGCCCGGTATTATAATACGGGGTTCGA

TCTGTGGGGACAGGGCACCCTGGTGACAGTCTCATCTGCTAGCACCAAGGGC
CCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGC
GGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGT
GGAACTCAGGCGCACTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACA
GTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCT
TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAA
GGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCA
CCGTGCCCAGCACCTGAAGCCGAGGGGGCACCGTCAGTCTTCCTCTTCCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTG
GTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTATGTGG
ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACA
ACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAAGACTGGCTG
AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCATCCTCCA
TCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTA
CACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAAGTCAGCCTGACC
TGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCA
ATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGA
CGGCTCCTTCTTCCTCTATTCCAAGCTCACCGTGGACAAGAGCAGGTGGCAGC
AGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACGCAGAAGAGCCTCTCCCTGTCTCCGGGCAAA

SEQ ID NO: 37 (DNA of LC of Antibody C)

GACATCGTGATGACCCAGTCCCCAAGCTCCCTGAGCGCCAGCGTGGGAGACG
GCGTCACCATCACATGCCAGGCCTCTCAGGATATCTACAACTATCTGAATTGG
TACCAGCAGAAGCCAGGGAAAGCCCCCAAGCTGCTGATCTATTACGCTTCTA
GTATTGTCTCTGGAGTGCCCAGTAGGTTCTCTGGGAGTGGATCAGGCACAGAC
TTTACTCTGACCATTTCAAGCCTGCAGCCTGAGGATTTCGCTACTTACTATTGC
CAGCAGGCAAACAGCTTCCCCCCTACATTTGGGCAGGGAACTAAACTGGAGA
TCAAGCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCC
CAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC
TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCA
GCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGC
CTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAAC
AGGGGAGAGTGT

SEQ ID NO: 38 (Ovalbumin peptide 323-339)

ISQAVHAAHAEINEAGR

SEQ ID NO: 39 (Human CEACAM1)

MGHLSAPLHRVRVPWQGLLLTASLLTFWNPPTTAQLTTESMPFNVAEGKEVLLL
VHNLPQQLFGYSWYKGERVDGNRQIVGYAIGTQQATPGPANSGRETIYPNASLLI
QNVTQNDTGFYTLQVIKSDLVNEEATGQFHVYPELPKPSISSNNSNPVEDKDAVA
FTCEPETQDTTYLWWINNQSLPVSPRLQLSNGNRTLTLLSVTRNDTGPYECEIQNP
VSANRSDPVTLNVTYGPDTPTISPSDTYYRPGANLSLSCYAASNPPAQYSWLINGT
FQQSTQELFIPNITVNNSGSYTCHANNSVTGCNRTTVKTIIVTELSPVVAKPQIKAS
KTTVTGDKDSVNLTCSTNDTGISIRWFFKNQSLPSSERMKLSQGNTTLSINPVKRE
DAGTYWCEVFNPISKNQSDPIMLNVNYNALPQENGLSPGAIAGIVIGVVALVALI
AVALACFLHFGKTGRASDQRDLTEHKPSVSNHTQDHSNDPPNKMNEVTYSTLNF
EAQQPTQPTSASPSLTATEIIYSEVKKQ

SEQ ID NO:40 (Human Galectin-9)

MAFSGSQAPYLSPAVPFSGTIQGGLQDGLQITVNGTVLSSSGTRFAVNFQTGFSGN
DIAFHFNPRFEDGGYVVCNTRQNGSWGPEERKTHMPFQKGMPFDLCFLVQSSDF
KVMVNGILFVQYFHRVPFHRVDTISVNGSVQLSYISFQPPGVWPANPAPITQTVIH
TVQSAPGQMFSTPAIPPMMYPHPAYPMPFITTILGGLYPSKSILLSGTVLPSAQRFH
INLCSGNHIAFHLNPRFDENAVVRNTQIDNSWGSEERSLPRKMPFVRGQSFSVWIL
CEAHCLKVAVDGQHLFEYYHRLRNLPTINRLEVGGDIQLTHVQT

WE CLAIM:

1. An antibody that binds human Tim-3, (SEQ ID NO:1), the antibody comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 wherein:
   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;
   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
   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.
2. The antibody of claim 1, wherein 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.
3. The antibody of claim 1, wherein 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.
4. The antibody of claim 1, wherein 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.

5. An antibody, comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein:
    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.
6. The antibody of claim 5, wherein 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.
7. The antibody of claim 5, wherein 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.
8. The antibody of claim 5, wherein 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.
9. 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;
    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.
10. The antibody of claim 9, wherein 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.
11. The antibody of claim 9, 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.
12. The antibody of claim 9, 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.
13. The antibody of any one of claims 9-12, wherein the antibody has two of the heavy chains and two of the light chains.

14. The antibody of claim 13, wherein one of the heavy chains forms an inter-chain disulfide bond with one of the light chains, and the other heavy chain forms an inter-chain disulfide bond with the other light chain, and one of the heavy chains forms two inter-chain disulfide bonds with the other heavy chain.
15. The antibody of any one of claims 1-14, wherein the antibody is glycosylated.
16. A mammalian cell capable of expressing 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;
    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.
17. The mammalian cell of claim 16, wherein 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.
18. The mammalian cell of claim 16, 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.
19. The mammalian cell of claim 16, 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.
20. 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:
    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
    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.
21. The process of claim 20, wherein 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.

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.

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.

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.

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.