

SUMMARY

[006] The present disclosure provides a variety of agents that bind T-cell immunoreceptor with Ig and ITIM domains (TIGIT), including, but not limited to, antibodies that specifically bind the extracellular domain of TIGIT. In certain embodiments, the agent is a TIGIT antagonist. The disclosure provides methods of using the agents. In some embodiments, the disclosure provides methods of using the agents for immunotherapy. In some embodiments, the disclosure provides methods of using the agents for cancer immunotherapy. In some embodiments, the agents are used in methods of inducing, activating, promoting, increasing, enhancing, or prolonging an immune response. In some embodiments, the agents are used in methods of inducing, activating, promoting, increasing, enhancing, or prolonging an immune response to cancer and/or a tumor. In some embodiments, the agents are used in methods of inhibiting the growth of a tumor or tumor cells. In some embodiments, the agents are used in methods for the treatment of cancer. In some embodiments, the methods comprise inhibiting the growth of cancer cells. In some embodiments, the agents are used in combination with at least one additional therapeutic agent.

[007] The disclosure also provides compositions, such as pharmaceutical compositions, comprising the agents described herein. Polynucleotides and/or vectors encoding the agents and methods of making the agents are also provided. Cells comprising or producing the agents described herein are provided as well as cells comprising the polynucleotides and/or the vectors described herein.

[008] Disclosed are agents that bind TIGIT. In some embodiments, the agent binds mouse TIGIT. In some embodiments, the agent binds human TIGIT. In some embodiments, the agent binds mouse TIGIT and human TIGIT. In some embodiments, the agent is an antibody. In some embodiments, the agent is an antibody that binds mouse TIGIT. In some embodiments, the agent is an antibody that binds human TIGIT. In some embodiments, the agent is an antibody that binds mouse TIGIT and human TIGIT. In some embodiments, the agent is an antibody that binds human TIGIT and does not bind mouse TIGIT.

[009] In some embodiments, the agent is an antibody that specifically binds the extracellular domain of TIGIT, which comprises a heavy chain CDR1 comprising GSSLSSSYMS (SEQ ID NO:7) or GFSLSSSYMS (SEQ ID NO:13), a heavy chain CDR2 comprising IIGSNGNTYYANWAKG (SEQ ID NO:8), and a heavy chain CDR3 comprising GGYRTSGMDP (SEQ ID NO:9), and/or a light chain CDR1 comprising QASQSISSYLNW (SEQ ID NO:10), QASQSNIIYSDLAW (SEQ ID NO:14), or QASQNIYSDLAW (SEQ ID NO:81), a light chain CDR2 comprising DALKLAS (SEQ ID NO:11) or RASTLAS (SEQ ID NO:15), and a light chain CDR3 comprising QQEHSVGNVDN (SEQ ID NO:12) or QQEHLVAWIYN (SEQ ID NO:16). In some embodiments, the agent is an antibody that comprises a heavy chain CDR1 comprising GSSLSSSYMS (SEQ ID NO:7), a heavy chain CDR2 comprising

IIGSNNGNTYYANWAKG (SEQ ID NO:8), and a heavy chain CDR3 comprising GGYRTSGMDP (SEQ ID NO:9), and/or a light chain CDR1 comprising QASQSISSYLNW (SEQ ID NO:10), a light chain CDR2 comprising DALKLAS (SEQ ID NO:11), and a light chain CDR3 comprising QQEHSVGNVDN (SEQ ID NO:12). In other embodiments, the agent is an antibody that comprises a heavy chain CDR1 comprising GFSLSSSYMS (SEQ ID NO:13), a heavy chain CDR2 comprising IIGSNNGNTYYANWAKG (SEQ ID NO:8), and a heavy chain CDR3 comprising GGYRTSGMDP (SEQ ID NO:9); and/or a light chain CDR1 comprising QASQSNYSDLAW (SEQ ID NO:14), a light chain CDR2 comprising RASTLAS (SEQ ID NO:15), and a light chain CDR3 comprising QQEHLVAWIYN (SEQ ID NO:16). In other embodiments, the agent is an antibody that comprises a heavy chain CDR1 comprising GFSLSSSYMS (SEQ ID NO:13), a heavy chain CDR2 comprising IIGSNNGNTYYANWAKG (SEQ ID NO:8), and a heavy chain CDR3 comprising GGYRTSGMDP (SEQ ID NO:9); and/or a light chain CDR1 comprising QASQNIYSDLAW (SEQ ID NO:14), a light chain CDR2 comprising RASTLAS (SEQ ID NO:15), and a light chain CDR3 comprising QQEHLVAWIYN (SEQ ID NO:16).

[010] In some embodiments, the agent is an antibody that specifically binds the extracellular domain of TIGIT, wherein the antibody comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:17, SEQ ID NO:19, or SEQ ID NO:32; and/or a light chain variable region having at least 90% sequence identity to SEQ ID NO:18 or SEQ ID NO:20. In some embodiments, the antibody comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:17, SEQ ID NO:19, or SEQ ID NO:32; and/or a light chain variable region having at least 95% sequence identity to SEQ ID NO:18 or SEQ ID NO:20. In some embodiments, the antibody comprises a heavy chain variable region comprising SEQ ID NO:17 and a light chain variable region comprising SEQ ID NO:18; a heavy chain variable region comprising SEQ ID NO:19 and a light chain variable region comprising SEQ ID NO:20; or a heavy chain variable region comprising SEQ ID NO:32 and a light chain variable region comprising SEQ ID NO:20.

[011] In some embodiments, the agent is an antibody that specifically binds the extracellular domain of human TIGIT, which comprises a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:57), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:58), and a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:59), and/or a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:60), a light chain CDR2 comprising SASYRYT (SEQ ID NO:61), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:62).

[011a] In one aspect, there is provided an isolated antibody that specifically binds the extracellular domain of TIGIT, which comprises: a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:57), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:58), and a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:59), and a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:60), a light chain CDR2 comprising SASYRYT (SEQ ID NO:61), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:62).

[012] In some embodiments, the agent is an antibody that specifically binds the extracellular domain of TIGIT, wherein the antibody comprises a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:63 or SEQ ID NO:67; and/or a light chain variable region having at least 90%

sequence identity to SEQ ID NO:64 or SEQ ID NO:68. In some embodiments, an antibody comprises a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:63 or SEQ ID NO:67; and/or a light chain variable region having at least 95% sequence identity to SEQ ID NO:64 or SEQ ID NO:68. In some embodiments, an antibody comprises a heavy chain variable region comprising SEQ ID NO:63 and a light chain variable region comprising SEQ ID NO:64, or a heavy chain variable region comprising SEQ ID NO:67 and a light chain variable region comprising SEQ ID NO:68.

[012a] In another aspect, there is provided a polypeptide comprising a sequence selected from the group consisting of: SEQ ID NO:63, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72.

[013] In some embodiments, the agent is an antibody which is a monoclonal antibody, a humanized antibody, a human antibody, a recombinant antibody, a chimeric antibody, a bispecific antibody, an antibody fragment comprising an antigen-binding site, an IgG antibody, an IgG1 antibody, an IgG2 antibody, or an IgG4 antibody. In some embodiments, the antibody is monovalent. In some embodiments, the antibody is bivalent. In some embodiments, the antibody is monospecific. In some embodiments, the antibody is bispecific.

[014] In some embodiments, the agent is an antibody that specifically binds TIGIT, wherein the antibody comprises a heavy chain amino acid sequence selected from the group consisting of: SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:34, and SEQ ID NO:56; and a light chain amino acid sequence selected from the group consisting of: SEQ ID NO:28 and SEQ ID NO:30. In some embodiments, the antibody comprises a heavy chain amino acid sequence of SEQ ID NO:26 and a light chain amino acid sequence of SEQ ID NO:28; a heavy chain amino acid sequence of SEQ ID NO:27 and a light chain amino acid sequence of SEQ ID NO:28; a heavy chain amino acid sequence of SEQ ID NO:29 and a light chain amino acid sequence of SEQ ID NO:30; a heavy chain amino acid sequence of SEQ ID NO:34 and a light chain amino acid sequence of SEQ ID NO:30; or a heavy chain amino acid sequence of SEQ ID NO:56 and a light chain amino acid sequence of SEQ ID NO:30.

[015] In some embodiments, an antibody that specifically binds human TIGIT comprises a heavy chain amino acid sequence of SEQ ID NO:70 and a light chain amino acid sequence of SEQ ID NO:72. In some embodiments, an antibody that specifically binds human TIGIT comprises a heavy chain amino acid sequence of SEQ ID NO:82 and a light chain amino acid sequence of SEQ ID NO:72.

[016] In some embodiments an antibody that specifically binds human TIGIT, does not bind mouse TIGIT. In some embodiments an antibody that specifically binds human TIGIT, does not bind rat TIGIT. In some embodiments an antibody that specifically binds human TIGIT, does not bind rabbit TIGIT. In some embodiments an antibody that specifically binds human TIGIT, does not bind marmoset TIGIT. In some embodiments an antibody that specifically binds human TIGIT, does not bind dog TIGIT. In some embodiments an antibody that specifically binds human TIGIT, does not bind pig TIGIT. In some embodiments an antibody that specifically binds human TIGIT, does not bind cynomolgus monkey

TIGIT. In some embodiments an antibody that specifically binds human TIGIT, does not bind rhesus monkey TIGIT.

[017] In some embodiments, the agent is an antibody that specifically binds TIGIT, wherein the antibody comprises the heavy chain variable region and the light chain variable region from an antibody selected from the group consisting of: 313R11, 313R12, 313R14, 313R19, and 313R20. In some embodiments, the antibody is selected from the group consisting of: 313R11, 313R12, 313R14, 313R19, and 313R20. In some embodiments, the antibody is 313R19. In some embodiments, the antibody comprises the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-122180. In some embodiments, the antibody comprises the light chain variable region encoded by the plasmid deposited with ATCC as PTA-122181. In some embodiments, the antibody comprises a heavy chain comprising the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-122180. In some embodiments, the antibody comprises a light chain comprising the light chain variable region encoded by the plasmid deposited with ATCC as PTA-122181. In some embodiments, the antibody comprises the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-122180 and the light chain variable region encoded by the plasmid deposited with ATCC as PTA-122181. In some embodiments, the antibody comprises a polypeptide encoded by the plasmid deposited with ATCC as PTA-122180 and a polypeptide encoded by the plasmid deposited with ATCC as PTA-122181.

[018] Disclosed are a plasmid deposited with ATCC and assigned designation number PTA-122180 and a plasmid deposited with ATCC and assigned designation number PTA-122181.

[019] In some embodiments, an antibody that specifically binds human TIGIT comprises the heavy chain variable region and the light chain variable region from antibody 313M32. In some embodiments, the antibody comprises the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-122346. In some embodiments, the antibody comprises a polypeptide comprising the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-122346. In some embodiments, the antibody comprises the light chain variable region encoded by the plasmid deposited with ATCC as PTA-122347. In some embodiments, the antibody comprises the light chain encoded by the plasmid deposited with ATCC as PTA-122347. In some embodiments, the antibody comprises the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-122346 and the light chain variable region encoded by the plasmid deposited with ATCC as PTA-122347. In some embodiments, the antibody comprises a polypeptide encoded by the plasmid deposited with ATCC as PTA-122346 and a polypeptide encoded by the plasmid deposited with ATCC as PTA-122347.

[019a] In another aspect, there is provided an antibody comprising: the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-122346 and the light chain variable region encoded by the plasmid deposited with ATCC as PTA-122347.

[020] Disclosed are a plasmid deposited with ATCC and assigned designation number PTA-122346 and a plasmid deposited with ATCC and assigned designation number PTA-122347.

[020a] In another aspect, there is provided a plasmid deposited with ATCC and selected from the group consisting of assigned designation numbers PTA-122346 and PTA-122347.

[021] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the agent is monovalent. In some embodiments, the agent is bivalent. In some embodiments, the agent is monospecific. In some embodiments, the agent is bispecific. In some embodiments, the bispecific agent is a heterodimeric agent or heterodimeric molecule. In some embodiments, a heterodimeric agent comprises an antibody described herein that specifically binds TIGIT.

[021a] In another aspect, there is provided a heterodimeric agent comprising an antibody as described herein.

[022] Disclosed is an isolated antibody that competes for specific binding to human TIGIT with an agent (e.g., antibody) described herein. In some embodiments, an isolated antibody binds the same epitope on human TIGIT as an agent (e.g., antibody) described herein. In some embodiments, an isolated antibody binds an epitope on human TIGIT that overlaps with the epitope on TIGIT bound by an agent (e.g., antibody) described herein. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids within SEQ ID NO:79. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids within SEQ ID NO:80. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids within SEQ ID NO:79 and SEQ ID NO:80. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids Q62 and I109 of SEQ ID NO:4. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids Q62 and T119 of SEQ ID NO:4. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids Q64 and I109 of SEQ ID NO:4. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids Q64 and T119 of SEQ ID NO:4. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids Q62, Q64, and I109 of SEQ ID NO:4. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids Q62, Q64, and T119 of SEQ ID NO:4. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids Q62, I109, and T119 of SEQ ID NO:4. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids Q64, I109, and T119 of SEQ ID NO:4. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising amino acids Q62, Q64, I109, and T119 of SEQ ID NO:4. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope comprising at least one amino acid selected from the group consisting of: N58, E60, Q62, Q64, L65, F107, I109, H111, T117, T119, G120, and R121 of SEQ ID NO:4. In some embodiments, the epitope is a

conformational epitope. In some embodiments, an antibody that specifically binds human TIGIT binds an epitope that does not comprise amino acid V100 of SEQ ID NO:4.

[023] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the agent that specifically binds TIGIT is an antibody, wherein the antibody is part of a bispecific agent. In some embodiments, a bispecific agent comprises a first arm which binds TIGIT and a second arm which binds a second target. In some embodiments, a bispecific agent comprises a first arm that specifically binds TIGIT and a second arm, wherein the first arm comprises an anti-TIGIT antibody described herein. In some embodiments, a bispecific agent comprises a first arm that binds TIGIT and a second arm which comprises an antigen-binding site from an antibody. In some embodiments, a bispecific agent comprises a first arm that binds TIGIT and a second arm that specifically binds PD-1, PD-L1, CTLA4, TIM-3, LAG-3, OX-40, or GITR. In some embodiments, a bispecific agent comprises a first arm that binds TIGIT and a second arm that specifically binds a tumor antigen. In some embodiments, a bispecific agent comprises a first arm that binds TIGIT and a second arm that comprises an immune response stimulating agent. In some embodiments, the immune response stimulating agent is selected from the group consisting of: granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage colony stimulating factor (M-CSF), granulocyte colony stimulating factor (G-CSF), interleukin 2 (IL-2), interleukin 3 (IL-3), interleukin 12 (IL-12), interleukin 15 (IL-15), B7-1 (CD80), B7-2 (CD86), 4-1BB ligand, GITRL, OX-40L, anti-CD3 antibody, anti-CTLA4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-GITR antibody, anti-OX-40 antibody, anti-LAG-3 antibody, and anti-TIM-3 antibody.

[023a] In another aspect, there is provided a bispecific agent comprising: a) a first arm that specifically binds TIGIT, and b) a second arm, wherein the first arm comprises an antibody as described herein.

[024] In some embodiments, the bispecific agent is a heterodimeric agent or heterodimeric molecule. In some embodiments, the bispecific agent is a homodimeric agent or homodimeric molecule. In some embodiments, a heterodimeric molecule comprises a first arm which binds human TIGIT and a second arm which binds a second target. In some embodiments, a heterodimeric molecule comprises a first arm that specifically binds human TIGIT and a second arm, wherein the first arm comprises an anti-TIGIT antibody described herein. In some embodiments, a heterodimeric molecule comprises a first arm that binds human TIGIT and a second arm which comprises an antigen-binding site from an antibody that specifically binds a second target. In some embodiments, a heterodimeric molecule is a bispecific antibody. In some embodiments, a heterodimeric molecule comprises a first arm that binds human TIGIT and a second arm that specifically binds a tumor antigen. In some embodiments, a heterodimeric molecule comprises a first arm that binds human TIGIT and a second arm that specifically binds PD-1, PD-L1, CTLA-4, TIM-3, LAG-3, OX-40, 4-1BB, or GITR. In some embodiments, a heterodimeric molecule comprises a first arm that binds TIGIT and a second arm that comprises an immunotherapeutic agent. In some embodiments, the immunotherapeutic agent is selected from the group consisting of:

increases cell-mediated immunity. In some embodiments, the agent increases T-cell activity. In some embodiments, the agent increases cytolytic T-cell (CTL) activity. In some embodiments, the agent increases natural killer (NK) cell activity. In some embodiments, the agent increases IL-2 production and/or the number of IL-2-producing cells. In some embodiments, the agent increases IFN-gamma production and/or the number of IFN-gamma-producing cells. In some embodiments, the agent increases a Th1-type immune response. In some embodiments, the agent decreases IL-4 production and/or the number of IL-4-producing cells. In some embodiments, the agent decreases IL-10 and/or the number of IL-10-producing cells. In some embodiments, the agent decreases IL-6 production and/or the number of IL-6-producing cells. In some embodiments, the agent decreases IL-5 production and/or the number of IL-5-producing cells. In some embodiments, the agent decreases a Th2-type immune response. In some embodiments, the agent decreases the number of Treg cells. In some embodiments, the agent decreases Treg activity. In some embodiments, the agent inhibits and/or decreases the suppressive activity of Tregs. In some embodiments, the agent decreases the number of MDSCs. In some embodiments, the agent inhibits and/or decreases the suppressive activity of myeloid-derived suppressor cells (MDSCs).

[029] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, an agent described herein specifically binds TIGIT and inhibits tumor growth. In some embodiments, the agent reduces tumor growth. In some embodiments, the agent reduces tumor growth to an undetectable size. In some embodiments, the agent induces long-term anti-tumor immunity.

[030] Disclosed are compositions comprising an agent described herein. Methods of using a composition comprising an agent described herein are also provided.

[031] Disclosed are pharmaceutical compositions comprising an agent described herein and a pharmaceutically acceptable carrier. Methods of treating cancer and/or inhibiting tumor growth in a subject (e.g., a human) comprising administering to the subject an effective amount of a composition comprising an agent described herein are also provided. Methods of treating a viral infection in a subject (e.g., a human) comprising administering to the subject an effective amount of a composition comprising an agent described herein are also provided.

[031a] In another aspect, there is provided a pharmaceutical composition comprising the antibody as described herein, the heterodimeric agent as described herein, or the bispecific agent as described herein and a pharmaceutically acceptable carrier.

[032] In certain embodiments of each of the aforementioned aspects, as well as other aspects and/or embodiments described elsewhere herein, the agent is isolated. In certain embodiments, the agent is substantially pure.

[033] Disclosed are polynucleotides comprising a polynucleotide that encodes an agent described herein. In some embodiments, the polynucleotide is isolated. In some embodiments, the disclosure provides vectors that comprise the polynucleotides, as well as cells that comprise the vectors and/or the polynucleotides. In some embodiments, the disclosure also provides cells

comprising or producing an agent described herein. In some embodiments, the cell is a monoclonal cell line.

[033a] In another aspect, there is provided a cell comprising or producing the antibody as described herein, the heterodimeric agent as described herein, or the bispecific agent as described herein.

[033b] In another aspect, there is provided an isolated polynucleotide molecule comprising a polynucleotide that encodes the antibody as described herein, the heterodimeric agent as described herein, or the bispecific agent as described herein.

[033c] In another aspect, there is provided an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of: SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.

[033d] In another aspect, there is provided a vector comprising the polynucleotide as described herein.

[034] Disclosed are methods of modulating the immune response of a subject. In some embodiments, the method of modulating the immune response comprises a method of inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject. In some embodiments, a method of inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject, comprises administering a therapeutically effective amount of an antibody, bispecific agent, or polypeptide described herein. In some embodiments, a method of inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject, comprises administering a therapeutically effective amount of a heterodimeric bispecific agent or a homodimeric bispecific agent described herein. In some embodiments, a method of inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject, comprises administering a therapeutically effective amount of an antibody that specifically binds TIGIT described herein. In some embodiments, a method of inducing an immune response in a subject comprises administering an agent described herein. In some embodiments, a method of activating an immune response in a subject comprises administering an agent described herein. In some embodiments, a method of promoting an immune response in a subject comprises administering an agent described herein. In some embodiments, a method of increasing an immune response in a subject comprises administering an agent described herein. In some embodiments, a method of enhancing an immune response in a subject comprises administering an agent described herein. In some embodiments, a method of prolonging an immune response in a subject comprises administering an agent described herein. In some embodiments, the immune response is to an antigenic stimulation. In some embodiments, the antigenic stimulation is a tumor or a tumor cell. In some embodiments, the antigenic stimulation is a pathogen. In some embodiments, the antigenic stimulation is a virus. In some embodiments, the antigenic stimulation is a virally-infected cell. In some embodiments, the immune response is against a tumor or cancer.

[035] In some embodiments, the disclosure provides methods of increasing the activity of immune cells. In some embodiments, a method of increasing the activity of immune cells comprises contacting the cells with an effective amount of an agent described herein. In some embodiments, the immune cells are T-cells, NK cells, monocytes, macrophages, myeloid-derived cells, antigen-presenting cells (APCs), and/or B-cells. In some embodiments, a method of increasing the activity of NK cells in a subject comprises administering to the subject a therapeutically effective amount of an agent described herein. In some embodiments, a method of increasing the activity of T-cells in a subject comprises administering to the subject a therapeutically effective amount of an agent described herein. In some embodiments, a method of increasing the activation of T-cells and/or NK cells in a subject comprises administering to the subject

a therapeutically effective amount of an agent described herein. In some embodiments, a method of increasing the T-cell response in a subject comprises administering to the subject a therapeutically effective amount of an agent described herein. In some embodiments, a method of increasing the activity of CTLs in a subject comprises administering to the subject a therapeutically effective amount of an agent described herein. In some embodiments, a method of inhibiting the activity of Tregs in a subject comprises administering to the subject a therapeutically effective amount of an agent described herein. In some embodiments, a method of inhibiting the suppressive activity of Tregs in a subject comprises administering to the subject a therapeutically effective amount of an agent described herein. In some embodiments, a method of inhibiting the activity of MDSCs in a subject comprises administering to the subject a therapeutically effective amount of an agent described herein. In some embodiments, a method of inhibiting the suppressive activity of MDSCs in a subject comprises administering to the subject a therapeutically effective amount of an agent described herein.

[036] In some embodiments, the disclosure provides methods of inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject, comprising administering to the subject a therapeutically effective amount of an agent that binds human TIGIT. In some embodiments, a method of inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject comprises administering to the subject a therapeutically effective amount of an agent that inhibits or reduces TIGIT activity. In some embodiments, a method of inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject comprises administering to the subject a therapeutically effective amount of an agent that inhibits or reduces TIGIT signaling. In some embodiments, the immune response is against a tumor cell, a tumor, or cancer. In some embodiments, the immune response is against a viral infection, a viral antigen, or a virally-infected cell.

[036a] In another aspect, there is provided the antibody as described herein, the heterodimeric agent as described herein, or the bispecific agent as described herein for use in inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject, wherein a therapeutically effective amount of the antibody, the heterodimeric agent, or the bispecific agent is to be administered to the subject.

[037] Disclosed are methods of inhibiting growth of tumor cells or a tumor comprising contacting the tumor or tumor cell with an effective amount of an agent described herein. In some embodiments, a method of inhibiting growth of a tumor comprises contacting a tumor or tumor cell with an effective amount of an agent that binds human TIGIT.

[038] Disclosed are methods of inhibiting growth of a tumor in a subject comprising administering to the subject a therapeutically effective amount of an agent described herein. In some embodiments, a method of inhibiting growth of a tumor in a subject comprises administering to the subject a therapeutically effective amount of an agent that binds human TIGIT. In some embodiments, a method of inhibiting growth of a tumor in a subject comprises administering to the subject a therapeutically effective amount of an antibody that binds human TIGIT. In some embodiments, a method of inhibiting growth of a tumor in a subject comprises administering to the subject a therapeutically effective amount of a bispecific agent that binds human TIGIT. In some

embodiments, the tumor is selected from the group consisting of colorectal tumor, colon tumor, ovarian tumor, pancreatic tumor, lung tumor, liver tumor, breast tumor, kidney tumor, prostate tumor, gastrointestinal tumor, melanoma, cervical tumor, bladder tumor, glioblastoma, and head and neck tumor. **[038a]** In another aspect, there is provided use of the antibody as described herein, the heterodimeric agent as described herein, or the bispecific agent as described herein in the manufacture of a medicament to inhibit growth of a tumor in a subject, wherein a therapeutically effective amount of the antibody, the heterodimeric agent, or the bispecific agent is to be administered to the subject.

[039] Disclosed are methods of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of an agent described herein. In some embodiments, a method of treating cancer in a subject comprises administering to the subject a therapeutically effective amount of an agent that binds TIGIT. In some embodiments, a method of treating cancer in a subject comprises administering to the subject a therapeutically effective amount of an antibody that binds human TIGIT. In some embodiments, a method of treating cancer in a subject comprises administering to the subject a therapeutically effective amount of a bispecific agent that binds human TIGIT. In some embodiments, the cancer is selected from the group consisting of colorectal cancer, ovarian cancer, pancreatic cancer, lung cancer, liver cancer, breast cancer, kidney cancer, prostate cancer, gastrointestinal cancer, melanoma, cervical cancer, bladder cancer, glioblastoma, and head and neck cancer.

[039a] In another aspect, there is provided use of the antibody as described herein, the heterodimeric agent as described herein, or the bispecific agent as described herein in the manufacture of a medicament to treat cancer in a subject, wherein a therapeutically effective amount of the antibody, the heterodimeric agent, or the bispecific agent is to be administered to the subject.

[040] Disclosed are methods of stimulating and/or inducing long-term anti-tumor immunity in a subject comprising administering to the subject a therapeutically effective amount of an agent described herein.

[041] Disclosed are methods of stimulating a protective response in a subject comprising administering to the subject a therapeutically effective amount of an agent described herein in combination with an antigen of interest. In some embodiments, the antigen of interest is a tumor antigen. In some embodiments, the antigen of interest is a cancer cell biomarker. In some embodiments, the antigen of interest is a cancer stem cell marker.

[042] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the methods comprise administering to the subject an immune response stimulating agent. In some embodiments, the immune response stimulating agent is selected from the group consisting of GM-CSF, M-CSF, G-CSF, IL-3, IL-12, IL-1, IL-2, B7-1 (CD80), B7-2 (CD86), anti-CD3 antibodies, anti-CTLA-4 antibodies, anti-CD28 antibodies, anti-PD-L1 antibodies, and anti-PD1 antibodies.

[043] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, a method further comprises administering at least one additional therapeutic agent. In some embodiments, the additional therapeutic agent is a chemotherapeutic agent. In some embodiments, the additional therapeutic agent is an antibody. In some embodiments, the additional therapeutic agent is an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-CTLA4 antibody, an anti-LAG-3 antibody, or an anti-TIM-3 antibody. In some embodiments, the

additional therapeutic agent is an inhibitor of the Notch pathway, the Wnt pathway, or the RSPO/LGR pathway.

[044] In some embodiments, the additional therapeutic agent is an immunotherapeutic agent. As used herein, the phrase “immunotherapeutic agent” is used in the broadest sense and refers to a substance that directly or indirectly affects or modulates the immune system. In some embodiments, an immunotherapeutic agent is an agent that directly or indirectly stimulates the immune system by inducing activation or increasing activity of any of the immune system’s components. As the TIGIT-binding agents are considered immunotherapeutic agents, this additional immunotherapeutic agent may be considered a “second” immunotherapeutic agent. In some embodiments, the second immunotherapeutic agent is selected from the group consisting of: GM-CSF, M-CSF, G-CSF, IL-2, IL-3, IL-12, IL-15, B7-1 (CD80), B7-2 (CD86), 4-1BB ligand, GITRL, OX-40 ligand, anti-CD3 antibody, anti-CTLA-4 antibody, anti-CD28 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-4-1BB antibody, anti-GITR antibody, anti-OX-40 antibody, anti-LAG-3 antibody, and anti-TIM-3 antibody. In some embodiments, the second immunotherapeutic agent is a fusion protein comprising: GM-CSF, M-CSF, G-CSF, IL-2, IL-3, IL-12, IL-15, B7-1 (CD80), B7-2 (CD86), 4-1BB ligand, GITRL, OX-40 ligand, or a fragment thereof. In some embodiments, the second immunotherapeutic agent is a fusion protein comprising at least one copy of the extracellular domain of GITRL, OX40 ligand, or 4-1BB ligand.

[045] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the subject is human. In some embodiments, the subject has had a tumor or a cancer, at least partially, removed.

[046] In some embodiments of each of the aforementioned aspects and embodiments, as well as other aspects and embodiments described herein, the tumor or the cancer expresses PD-L1. In some embodiments, a method further comprises a step of determining the level of PD-L1 expression in the tumor or cancer. In some embodiments, determining the level of PD-L1 expression is done prior to treatment or contact with an agent described herein. In some embodiments, if the tumor or cancer has an elevated expression level of PD-L1, an agent described herein is administered to the subject. In some embodiments, if the tumor or cancer has an elevated expression level of PD-L1, the tumor or cancer is contacted with an agent described herein..

[047] Where aspects or embodiments of the disclosure are described in terms of a Markush group or other grouping of alternatives, the present disclosure encompasses not only the entire group listed as a whole, but also each member of the group individually and all possible subgroups of the main group, and also the main group absent one or more of the group members. The present disclosure also envisages the explicit exclusion of one or more of any of the group members in the claimed disclosure.

WHAT IS CLAIMED IS:

1. An isolated antibody that specifically binds the extracellular domain of TIGIT, which comprises: a heavy chain CDR1 comprising TSDYAWN (SEQ ID NO:57), a heavy chain CDR2 comprising YISYSGSTSYNPSLRS (SEQ ID NO:58), and a heavy chain CDR3 comprising ARRQVGLGFAY (SEQ ID NO:59), and a light chain CDR1 comprising KASQDVSTAVA (SEQ ID NO:60), a light chain CDR2 comprising SASYRYT (SEQ ID NO:61), and a light chain CDR3 comprising QQHYSTP (SEQ ID NO:62).
2. The antibody of claim 1, which comprises: a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:67 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:68.
3. The antibody of claim 1, which comprises: a heavy chain variable region having at least 95% sequence identity to SEQ ID NO:63 and a light chain variable region having at least 95% sequence identity to SEQ ID NO:64.
4. The antibody according to any one of claims 1-3, which is a monoclonal antibody, a humanized antibody, a human antibody, a chimeric antibody, a bispecific antibody, an IgG1 antibody, an IgG2 antibody, an IgG4 antibody, or an antibody fragment comprising an antigen binding site.
5. The antibody of claim 1, which comprises: a heavy chain amino acid sequence of SEQ ID NO:70 and a light chain amino acid sequence of SEQ ID NO:72.
6. An antibody comprising: the heavy chain variable region encoded by the plasmid deposited with ATCC as PTA-122346 and the light chain variable region encoded by the plasmid deposited with ATCC as PTA-122347.
7. The antibody according to any one of claims 1-6, which binds human TIGIT, but does not bind:
 - (a) mouse TIGIT;
 - (b) rat TIGIT;
 - (c) cynomolgus monkey TIGIT; and/or
 - (d) rhesus monkey TIGIT.

8. The antibody according to any one of claims 1-7, which:
 - (a) inhibits binding of TIGIT to poliovirus receptor (PVR);
 - (b) inhibits or blocks the interaction between TIGIT and PVR;
 - (c) inhibits TIGIT signaling;
 - (d) inhibits TIGIT activation;
 - (e) inhibits phosphorylation of TIGIT; and/or
 - (f) decreases cell surface expression of TIGIT.
9. The antibody according to any one of claims 1-8, which induces and/or enhances an immune response.
10. The antibody of claim 9, wherein the immune response is directed to a tumor or tumor cell.
11. The antibody according to any one of claims 1-7, which:
 - (a) increases cell-mediated immunity;
 - (b) increases T-cell activity;
 - (c) increases cytolytic T-cell (CTL) activity;
 - (d) increases natural killer (NK) cell activity;
 - (e) increases IL-2 production and/or the number of IL-2-producing cells;
 - (f) increases IFN-gamma production and/or the number of IFN-gamma-producing cells;
 - (g) increases a Th1-type immune response;
 - (h) decreases IL-4 production and/or the number of IL-4-producing cells;
 - (i) decreases IL-10 and/or the number of IL-10-producing cells;
 - (j) decreases a Th2-type immune response;
 - (k) inhibits and/or decreases the suppressive activity of regulatory T-cells (Tregs); and/or
 - (l) inhibits and/or decreases the suppressive activity of myeloid-derived suppressor cells (MDSCs).
12. A polypeptide comprising a sequence selected from the group consisting of: SEQ ID NO:63, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72.

13. A heterodimeric agent comprising an antibody according to any one of claims 1-11.
14. A bispecific agent comprising:
 - a) a first arm that specifically binds TIGIT, and
 - b) a second arm,wherein the first arm comprises an antibody according to any one of claims 1-11.
15. The bispecific agent of claim 14, wherein the second arm comprises an antigen-binding site from an antibody.
16. A cell comprising or producing the antibody according to any one of claims 1-11, the heterodimeric agent of claim 13, or the bispecific agent of claim 14 or claim 15.
17. A pharmaceutical composition comprising the antibody according to any one of claims 1-11, the heterodimeric agent of claim 13, or the bispecific agent of claim 14 or claim 15 and a pharmaceutically acceptable carrier.
18. An isolated polynucleotide molecule comprising a polynucleotide that encodes the antibody according to any one of claims 1-11, the heterodimeric agent of claim 13, or the bispecific agent of claim 14 or claim 15.
19. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of: SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, and SEQ ID NO:76.
20. A vector comprising the polynucleotide of claim 18 or claim 19.
21. The antibody according to any one of claims 1-11, the heterodimeric agent of claim 13, or the bispecific agent of claim 14 or claim 15 for use in inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject, wherein a therapeutically effective amount of the antibody, the heterodimeric agent, or the bispecific agent is to be administered to the subject.

22. The antibody, the heterodimeric agent, or the bispecific agent for use according to claim 21, wherein the immune response is against a tumor or cancer.
23. Use of the antibody according to any one of claims 1-11, the heterodimeric agent of claim 13, or the bispecific agent of claim 14 or claim 15 in the manufacture of a medicament to inhibit growth of a tumor in a subject, wherein a therapeutically effective amount of the antibody, the heterodimeric agent, or the bispecific agent is to be administered to the subject.
24. The use of claim 23, wherein the tumor is selected from the group consisting of colorectal tumor, ovarian tumor, pancreatic tumor, lung tumor, liver tumor, breast tumor, kidney tumor, prostate tumor, gastrointestinal tumor, melanoma, cervical tumor, bladder tumor, glioblastoma, and head and neck tumor.
25. Use of the antibody according to any one of claims 1-11, the heterodimeric agent of claim 13, or the bispecific agent of claim 14 or claim 15 in the manufacture of a medicament to treat cancer in a subject, wherein a therapeutically effective amount of the antibody, the heterodimeric agent, or the bispecific agent is to be administered to the subject.
26. The use of claim 25, wherein the cancer is selected from the group consisting of colorectal cancer, ovarian cancer, pancreatic cancer, lung cancer, liver cancer, breast cancer, kidney cancer, prostate cancer, gastrointestinal cancer, melanoma, cervical cancer, bladder cancer, glioblastoma, and head and neck cancer.
27. The antibody, the heterodimeric agent, or the bispecific agent for use according to claim 21 or 22, or the use according to any one of claims 23-26, wherein at least one additional therapeutic agent is to be further administered.
28. A plasmid deposited with ATCC and selected from the group consisting of assigned designation numbers PTA-122346 and PTA-122347.