

also modulate immune responses by direct interaction with ligands on dendritic cells (DCs), such as CD40L ligation and CTLA4 interaction with B7 molecules on DCs that elicits the induction of indoleamine 2,3-dioxygenase (IDO). DCs are professional APCs capable of inducing immunity or tolerance against self or non-self antigens. DC-expanded Tregs suppress alloreactivity responses in vitro, and when
5 adoptively transferred, appropriate Tregs inhibited diabetes in NODscid mice or experimentally induced asthma. Specific interactions of ligands on DC with Tregs can also abrogate their suppressive function, such as engagement of GITR in mice, suggesting DC may have a pluralistic role in modulating Treg function.

The molecules CTLA4 and GITR are representative of ligands defined within the CD28-B7 and
10 TNF-superfamilies of co-stimulatory/-inhibitory molecules, respectively. These molecules are highly expressed on Tregs but are typically upregulated on activated T cells. More recently, a protein designated TIGIT (for T-cell immunoreceptor with Ig and ITIM domains) was identified as a cell surface-bound protein specifically expressed in T cells that possessing an IgV domain, a transmembrane domain, and two putative immunoreceptor tyrosine inhibitory (ITIM) motifs. TIGIT was shown to be particularly
15 expressed on Treg and memory T cell subsets, as well as NK cells. As there is an unmet need for new therapeutics and methods of treatment of immune-related disorders and particularly cancers, described herein are unexpectedly efficacious therapeutic compositions, such as the anti-TIGIT antibodies and compositions thereof, and methods of treatment of immune-related disorders and cancers, which involve modulating the interaction of TIGIT with its binding partners.

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SUMMARY

The present disclosure provides anti-TIGIT (T-cell immunoreceptor with Ig and ITIM domains) antibodies and variants thereof with improved properties, including, for example, binding affinity, cross-reactivity, pharmacokinetics, and/or expression. In particular, the present disclosure provides anti-TIGIT
25 antibodies and variants thereof that possess, for example, high binding affinity to human TIGIT; cross-reactivity between human TIGIT, cynomolgus monkey (cyno) TIGIT, and/or rabbit TIGIT; desirable clearance properties in cyno; and biochemical and biophysical properties that confer the antibodies and variants thereof with high stability.

In one example, the disclosure features an antibody that specifically binds to human TIGIT,
30 wherein the antibody binds to an epitope on human TIGIT comprising one or more of amino acid residues Ser78, Ser80, and Lys82 of human TIGIT. In one example, the epitope comprises amino acid residues Ser80 and Lys82 of human TIGIT. In another example, the epitope comprises amino acid residues Ser78, Ser80, and Lys82 of human TIGIT. In another example, the epitope further comprises amino acid residue Ala67 of human TIGIT. In another example, the epitope further comprises one or more additional
35 amino acid residues selected from the group consisting of Glu60, Leu65, and Ile68 of human TIGIT. In another example, the epitope further comprises one or more additional amino acid residues selected from the group consisting of Gln56, Asn70, Leu73, and His111 of human TIGIT. In another example, the epitope further comprises one or more additional amino acid residues selected from the group consisting of Thr55, Asn58, Asp63, Gln64, His76, Ile77, and Pro79 of human TIGIT. In another example, the
40 epitope consists of amino acid residues Thr55, Gln56, Asn58, Glu60, Asp63, Gln64,

Leu65, Ala67, Ile68, Asn70, Leu73, His76, Ile77, Ser78, Pro79, Ser80, Lys82, and His111 of human TIGIT.

In another example, the disclosure features an antibody that specifically binds to human TIGIT, wherein the antibody binds to an epitope on human TIGIT comprising one or more of amino acid residues
5 Thr55, Ser80, and Lys82 of human TIGIT. In one example, the epitope comprises amino acid residue Lys82 of human TIGIT. In another example, the epitope comprises amino acid residues Thr55, Ser80, and Lys82 of human TIGIT. In another example, the epitope further comprises amino acid residue Gln56 of human TIGIT. In another example, the epitope further comprises amino acid residue Ile77 or Pro79 of human TIGIT. In another example, the epitope further comprises amino acid residues Ile77 and Pro79 of
10 human TIGIT. In another example, the epitope further comprises amino acid residue Asn58 or Glu60 of human TIGIT. In another example, the epitope further comprises amino acid residues Asn58 and Glu60 of human TIGIT. In another example, the epitope further comprises one or more additional amino acid residues selected from the group consisting of Leu65, Ile68, Leu73, His76, Ser78, and His111 of human TIGIT. In another example, the epitope further comprises amino acid residues Leu65, Ile68, Leu73,
15 His76, Ser78, and His111 of human TIGIT. In yet another example, the epitope consists of Thr55, Gln56, Asn58, Glu60, Leu65, Ile68, Leu73, His76, Ile77, Ser78, Pro79, Ser80, Lys82, and His111 of human TIGIT.

In another example, the disclosure features an antibody that specifically binds to human TIGIT, wherein the antibody comprises a paratope comprising one or more amino acid residues selected from
20 the group consisting of heavy chain variable region amino acid residues Asn32, Tyr52, Arg52b, Phe53, Lys54, Tyr56, Asp58, Tyr99, Asp100, Leu100a, Leu100b, and Ala100c and light chain variable region amino acid residues Tyr27d, Tyr92, Ser93, Thr94, and Phe96. In one example, the paratope consists of heavy chain variable region amino acid residues Asn32, Tyr52, Arg52b, Phe53, Lys54, Tyr56, Asp58, Tyr99, Asp100, Leu100a, Leu100b, and Ala100c and light chain variable region amino acid residues
25 Tyr27d, Tyr92, Ser93, Thr94, and Phe96. In any of the above examples, the antibody may be capable of binding to rabbit TIGIT.

In another example, the disclosure features an antibody that specifically binds to human TIGIT, wherein the antibody binds to an epitope on human TIGIT comprising one or more amino acid residues selected from the group consisting of Gln53, His111, and Tyr113 of human TIGIT. In some examples, the
30 epitope further comprises Gln56 of human TIGIT. In some examples, the epitope further comprises Glu60, Leu65, Ile68, Asn70, Leu73, and His76 of human TIGIT.

In another example, the disclosure features an antibody that specifically binds to human TIGIT, wherein the antibody comprises the following six hypervariable regions (HVRs): an HVR-H1 comprising the amino acid sequence of SNSAAWN (SEQ ID NO: 1); an HVR-H2 comprising the amino acid
35 sequence of KTYRFRKWYSDYAVSVKG (SEQ ID NO: 2); an HVR-H3 comprising the amino acid sequence of ESTTYDLLAGPFDY (SEQ ID NO: 3); an HVR-L1 comprising the amino acid sequence of KSSQTVLYSSNNKKYLA (SEQ ID NO: 4); an HVR-L2 comprising the amino acid sequence of WASTRES (SEQ ID NO: 5); and an HVR-L3 comprising the amino acid sequence of QQYYSTPFT (SEQ ID NO: 6). In some examples, the antibody further comprises the following light chain variable region
40 framework regions (FRs): an FR-L1 comprising the amino acid sequence of

DIVMTQSPDSLAVSLGERATINC (SEQ ID NO: 7); an FR-L2 comprising the amino acid sequence of WYQQKPGQPPLLIIY (SEQ ID NO: 8); an FR-L3 comprising the amino acid sequence of GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC (SEQ ID NO: 9); and an FR-L4 comprising the amino acid sequence of FGPGTKVEIK (SEQ ID NO: 10). In some examples, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of X₁VQLQQSGPGLVKPSQTLSTLCAISGDSVS (SEQ ID NO: 11), wherein X₁ is Q or E; an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12); an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and an FR-H4 comprising the amino acid sequence of WGQGTLLTVSS (SEQ ID NO: 14). In some examples, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of EVQLQQSGPGLVKPSQTLSTLCAISGDSVS (SEQ ID NO: 15); an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12); an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and an FR-H4 comprising the amino acid sequence of WGQGTLLTVSS (SEQ ID NO: 14). In some examples, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of QVQLQQSGPGLVKPSQTLSTLCAISGDSVS (SEQ ID NO: 16); an FR-H2 comprising the amino acid sequence of WIRQSPSRGLEWLG (SEQ ID NO: 12); an FR-H3 comprising the amino acid sequence of RITINPDTSKNQFSLQLNSVTPEDTAVFYCTR (SEQ ID NO: 13); and an FR-H4 comprising the amino acid sequence of WGQGTLLTVSS (SEQ ID NO: 14). In some examples, the antibody is capable of binding to rabbit TIGIT.

In one aspect, the present disclosure refers to an antibody that specifically binds to human T-cell immunoreceptor with Ig and ITIM domains (TIGIT), wherein the antibody comprises the following six hypervariable regions (HVRs): an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17); an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18); an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19); an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20); an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and an HVR-L3 comprising the amino acid sequence of QHLHGYPX₁N (SEQ ID NO: 22), wherein X₁ is C or S. In one example, the disclosure features an antibody that specifically binds to human TIGIT, wherein the antibody comprises the following six HVRs: an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17); an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18); an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19); an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20); an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and an HVR-L3 comprising the amino acid sequence of QHLHGYPX₁N (SEQ ID NO: 22), wherein X₁ is C or S. In some examples, the antibody comprises the following six HVRs: an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17); an HVR-H2 comprising the amino acid sequence of WINTNTGNPTYVQGFTG (SEQ ID NO: 18); an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19); an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20); an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and an HVR-L3 comprising the amino acid sequence of QHLHGYPN (SEQ ID NO: 23). In some examples, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of EVQLVQSGSDLKKPGASVRVSCASGYTFT (SEQ ID NO: 24); an FR-H2 comprising the amino acid sequence of WVRQAPGHGLEWLG (SEQ ID NO: 25); an FR-H3 comprising the amino acid sequence of RFVFSLDTSVNTAYLQISSSLKAEDTAVYFCAR (SEQ ID NO: 26); and an FR-H4 comprising the amino acid sequence of WGQGTMTVTVSS (SEQ ID NO: 27). In some examples, antibody comprises the following six HVRs: an HVR-H1 comprising the amino acid sequence of SYPMN (SEQ ID NO: 17); an HVR-H2 comprising the amino acid sequence of

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WINTNTGNPTYVQGFTG (SEQ ID NO: 18); an HVR-H3 comprising the amino acid sequence of TGGHTYDSYAFDV (SEQ ID NO: 19); an HVR-L1 comprising the amino acid sequence of RASQVISSSLA (SEQ ID NO: 20); an HVR-L2 comprising the amino acid sequence of AASTLQS (SEQ ID NO: 21); and an HVR-L3 comprising the amino acid sequence of QHLHGYPNCN (SEQ ID NO: 28). In some examples, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of QVQLVQSGSDLKKPGASVRVSCASGYTFT (SEQ ID NO: 29); an FR-H2 comprising the amino acid sequence of WVRQAPGHGLEWMG (SEQ ID NO: 25); an FR-H3 comprising the amino acid sequence of RFVFSLDTSVNTAYLQISSSLKAEDTAVYFCAR (SEQ ID NO: 26); and an FR-H4 comprising the amino acid sequence of WGQGTMTVTSS (SEQ ID NO: 27). In some examples, the antibody further comprises the following light chain variable region FRs: an FR-L1 comprising the amino acid sequence of DIQLTQSPTFLSASVGDRVTITC (SEQ ID NO: 30); an FR-L2 comprising the amino acid sequence of WYQQNPGKAPKLLIY (SEQ ID NO: 31); an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTEFTLTISSLQPEDFVITYC (SEQ ID NO: 32); and an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 33).

In another example, the disclosure features an antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 34 or 35; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b). In some examples, antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 34; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b). In some examples, the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 35; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b). In some examples, the antibody is capable of binding to rabbit TIGIT.

In another example, the disclosure features an antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 37; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 38; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b). In one aspect, the present disclosure refers to an antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a VH having the amino acid sequence of SEQ ID NO: 37 and (b) a VL having the amino acid sequence of SEQ ID NO: 38.

In yet another example, the disclosure features an antibody that specifically binds to human TIGIT, wherein the antibody comprises (a) a heavy chain variable region (VH) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 39; (b) a light chain variable region (VL) having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 40; or (c) a heavy chain variable region as in (a) and a light chain variable region as in (b).

In any one of the examples described above, the antibody may be capable of binding to both human TIGIT and cynomolgus monkey (cyno) TIGIT, but not murine TIGIT. In some examples, the antibody binds human TIGIT with a K_d of about 10 nM or lower and cyno TIGIT with a K_d of about 10 nM

or lower. In some examples, the antibody binds human TIGIT with a K_d of about 0.1 nM to about 1 nM and cyno TIGIT with a K_d of about 0.5 nM to about 1 nM. In some examples, the antibody binds human TIGIT with a K_d of about 0.1 nM or lower and cyno TIGIT with a K_d of about 0.5 nM or lower.

In any one of the examples described above, the antibody may be an antagonist antibody or an agonist antibody.

In some examples, the antagonist antibody specifically binds TIGIT and inhibits or blocks TIGIT interaction with poliovirus receptor (PVR). In some examples, the antagonist antibody inhibits intracellular signaling mediated by TIGIT binding to PVR. In some examples, the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC_{50} value of 10 nM or lower. In some examples, the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC_{50} value of 1 nM to about 10 nM. In some examples, the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC_{50} value of 50 nM or lower. In some examples, the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC_{50} value of 1 nM to about 50 nM. In some examples, the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC_{50} value of 1 nM to about 5 nM.

In some examples, the agonist antibody specifically binds TIGIT and stimulates the interaction of PVR with CD226 or CD96. In some examples, the agonist antibody specifically binds TIGIT and stimulates the interaction of PVR with CD226 and CD96. In some examples, the agonist antibody specifically binds TIGIT and stimulates the interaction of human PVR with human CD226 and human CD96. In some examples, the agonist antibody specifically binds TIGIT and stimulates the interaction of cyno PVR with cyno CD226 and cyno CD96.

In another example, the disclosure features an isolated antibody that competes for binding to TIGIT with an antibody of any one of the above examples.

In another example, the disclosure features an isolated antibody that binds to the same epitope as an antibody of any one of the above examples.

In some examples of any one of the examples described above, the antibody is monoclonal. In some examples, the antibody is human, humanized, or chimeric. In some examples, the antibody is a full-length antibody. In some examples, the antibody has a clearance following administration (e.g., injection, e.g., intravenous injection) of less than about 10 ml/kg/day (e.g., about 3 ml/kg/day to about 10 ml/kg/day). In some examples, the antibody has a clearance of about 3 ml/kg/day to about 8 ml/kg/day. In some examples, administration of the antibody is to a mammal (e.g., a monkey, such as a cynomolgus monkey, or a human). In some examples, the antibody is an antibody fragment that binds TIGIT. In some examples, the antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, Fv, single chain variable fragment (scFv), and (Fab')₂ fragments. In some examples, the antibody is an IgG class antibody. In some examples, the IgG class antibody is an IgG1 subclass antibody. In some examples, an antibody described herein can be for use as a medicament. In one aspect, the present disclosure refers to any one of the antibodies described herein for use as a medicament. In some examples, an antibody described herein may be for use in treating or delaying progression of a cancer in a subject in need thereof. In one aspect, the present disclosure refers to any one of the antibodies described herein for use in treating or delaying progression of a cancer in a subject in need thereof. In some examples, the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma,

a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy. In some examples, an antibody described herein may be for use in treating or delaying progression of multiple myeloma (MM). In some examples, an antibody described herein may be for use in treating or delaying progression of an immune-related disease in a subject in need thereof. In some examples, the immune-related disease is associated with a T cell dysfunctional disorder. In some examples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some examples, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some examples, an antibody described herein may be for use in increasing, enhancing, or stimulating an immune response or function in a subject in need thereof.

In another example, the disclosure features a polynucleotide (e.g., an isolated polynucleotide) encoding any of the antibodies described herein. In one aspect, the present disclosure refers to a polynucleotide encoding any one of the antibodies described herein. In another example, the disclosure features a vector (e.g., an expression vector) comprising the polynucleotide for expressing the antibody. In one aspect, the present disclosure refers to a vector comprising the polynucleotide described herein. In another example, the disclosure features host cells comprising the preceding polynucleotides and/or vectors. In one aspect, the present disclosure refers to a host cell comprising the vector described herein. In some examples, the host cell is a eukaryotic (e.g., a mammalian cell). In some examples, the eukaryotic cell is a 293 cell, a Chinese hamster ovary (CHO) cell, a yeast cell, or a plant cell. In some examples, the host cell is a prokaryotic cell. In some examples, the prokaryotic cell is *E. coli*.

In another example, the disclosure features a method of producing any of the antibodies described herein, the method comprising culturing a host cell that comprises any of the preceding vectors (e.g., expression vectors) in a culture medium. In one aspect, the present disclosure refers to a method of producing any one of the antibodies described herein, the method comprising culturing the host cell described herein in a culture medium. In some examples, the method further comprises recovering the antibody from the host cell or the culture medium. In some examples, the host cell is a eukaryotic cell, for example, a mammalian cell, for example, a 293 cell, a Chinese hamster ovary (CHO) cell, a yeast cell, or a plant cell. In some examples, the host cell is a prokaryotic cell. In some examples, the prokaryotic cell is *E. coli*.

In another example, the disclosure features an immunoconjugate comprising any one of the antibodies described herein and an agent (e.g., a therapeutic agent, e.g., a cytotoxic agent).

In another example, the disclosure features a composition comprising an antibody described herein. In one aspect, the present disclosure refers to a composition comprising any one of the antibodies described herein. In some examples, the composition further comprises a pharmaceutically acceptable carrier, excipient, or diluent. In some examples, the composition is for diagnostic use (e.g., to detect TIGIT expression levels, e.g., TIGIT protein expression levels). In some examples, the composition is a pharmaceutical composition. In some examples, the composition further comprises a PD-1 axis binding antagonist or an additional therapeutic agent.

In another example, the disclosure features the use of an antibody described herein in the manufacture of a medicament for treating or delaying progression of a cancer in a subject in need thereof. In one aspect, the present disclosure refers to use of any one of the antibodies described herein in the manufacture of a medicament for treating or delaying progression of a cancer. In some examples, the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a

cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy. In some examples, the myeloma is MM. In some examples, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the subject is a human.

In another example, the disclosure features the use of an antibody described herein in the manufacture of a medicament for treating or delaying progression of an immune-related disease in a subject in need thereof. In some examples, the immune-related disease is associated with a T cell dysfunctional disorder. In some examples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some examples, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some examples, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the subject is a human.

In another example, the disclosure features the use of an antibody described herein in the manufacture of a medicament for increasing, enhancing, or stimulating an immune response or function in a subject in need thereof. In some examples, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the subject is a human.

In another example, the disclosure features a method for treating or delaying progression of a cancer in a subject, the method comprising administering to the subject an effective amount of any one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein, thereby treating or delaying the progression of the cancer in the subject. In some examples, the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy. In some examples, the myeloma is MM.

In another example, the disclosure features a method for treating or delaying progression of an immune-related disease in a subject, the method comprising administering to the subject an effective amount of one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein, thereby treating or delaying the progression of the immune-related disease in the subject. In some examples, the immune-related disease is associated with a T cell dysfunctional disorder. In some examples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some examples, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.

In another example, the disclosure features a method of increasing, enhancing, or stimulating an immune response or function in a subject, the comprising administering to the subject an effective amount

of one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein, thereby increasing, enhancing, or stimulating an immune response or function in the subject. In some examples, the method further comprises administering to the subject a PD-1 axis binding antagonist. In some examples, the PD-1 axis binding antagonist is administered prior to or subsequent to the administration of the antibody.

5 In some examples, the PD-1 axis binding antagonist is administered concurrently with the antibody. In some examples, the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist, and a PD-L2 binding antagonist. In some examples, the PD-1 axis binding antagonist is a PD-1 binding antagonist. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In some examples, the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In some examples, the PD-1 binding antagonist is an anti-PD-1 antibody. In some examples, the PD-1 binding antagonist is selected from the group consisting of MDX 1106 (nivolumab), MK-3475 (pembrolizumab), CT-011 (pidilizumab), MEDI-0680 (AMP-514), PDR001, REGN2810, and BGB-108. In some examples, the PD-1 axis binding antagonist is a PD-L1 binding antagonist. In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1. In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1. In some examples, the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1. In some examples, the PD-L1 binding antagonist is an anti-PD-L1 antibody. In some examples, the anti-PD-L1 antibody is selected from the group consisting of: MPDL3280A (atezolizumab), YW243.55.S70, MDX-1105, MEDI4736 (durvalumab), and MSB0010718C (avelumab). In some examples, the antibody is MPDL3280A. In some examples, the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In some examples, the PD-L2 binding antagonist is an anti-PD-L2 antibody. In some examples, the PD-L2 binding antagonist is an immunoadhesin.

In some examples, any one of the methods of treatment described above may further comprise administering to the subject an OX40 binding agonist. In some examples, the OX40 binding agonist is administered prior to or subsequent to the administration of the antibody and/or the PD-1 axis binding antagonist. In some examples, the OX40 binding agonist is administered concurrently with the antibody and/or the PD-1 axis binding antagonist. In some examples, the OX40 binding agonist is selected from the group consisting of an OX40 agonist antibody, an OX40L agonist fragment, an OX40 oligomeric receptor, and an OX40 immunoadhesin. In some examples, the OX40 agonist antibody depletes cells that express human OX40. In some examples, the cells that express human OX40 are CD4+ effector T cells. In some examples, the cells that express human OX40 are regulatory T (Treg) cells. In some examples, the depleting is by ADCC and/or phagocytosis. In some examples, the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 1 nM. In some examples, the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM. In some examples, the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM. In some examples, the OX40 agonist antibody binds human OX40 with an EC50 of less than or equal to 0.3 µg/ml. In some examples, the OX40 agonist antibody binds human OX40 with an EC50 of less than or equal to 0.2 µg/ml. In some examples, the OX40

agonist antibody increases CD4+ effector T cell proliferation and/or increases cytokine production by the CD4+ effector T cell as compared to proliferation and/or cytokine production prior to treatment with the OX40 agonist antibody. In some examples, the OX40 agonist antibody increases memory T cell proliferation and/or cytokine production by a memory T cell. In some examples, the cytokine production is IFN- γ production. In some examples, the OX40 agonist antibody inhibits Treg function. In some examples, the OX40 agonist antibody inhibits Treg suppression of effector T cell function (e.g., effector T cell proliferation and/or cytokine production). In some examples, the effector T cell is a CD4+ effector T cell. In some examples, the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40. In some examples, the OX40 signal transduction is detected by monitoring NFkB downstream signaling. In some examples, the the OX40 agonist antibody comprises a variant IgG1 Fc polypeptide comprising a mutation that eliminates binding to human effector cells and has diminished activity relative to the OX40 agonist antibody comprising a native sequence IgG1 Fc portion. In some examples, the OX40 agonist antibody comprises a variant IgG1 Fc polypeptide comprising a DANA mutation. In some examples, the OX40 agonist antibody comprises (a) a VH domain comprising (i) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278, 279, or 280, (ii) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281, 282, 283, 284, 285, or 286, and (iii) a HVR-H3 comprising an amino acid sequence selected from SEQ ID NO: 287, 288, or 289; and (b) a VL domain comprising (i) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290, (ii) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291, and (iii) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 292, 293, 294, 295, 296, 297, 298, or 299. In some examples, the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 287; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO: 292. In some examples, the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 287; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO: 297. In some examples, the OX40 agonist antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 287; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NO: 298. In some examples, the OX40 agonist antibody comprises a VH sequence having at least 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 300-325. In some examples, the OX40 agonist antibody comprises a VH sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 300. In some examples, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in SEQ ID NO: 300. In some examples, the OX40 agonist antibody comprises a VH comprising one, two, or

three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 278, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 281, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 287. In some examples, the OX40 agonist antibody comprises a VL sequence having at least 90% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 326-351. In some examples, the OX40 agonist antibody comprises a VL having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 326. In some examples, a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in SEQ ID NO: 326. In some examples, the OX40 agonist antibody comprises a VL comprising one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 290; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 291; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 292. In some examples, the OX40 agonist antibody comprises (a) a VH sequence of SEQ ID NO: 300; (b) a VL sequence of SEQ ID NO: 326; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some examples, the OX40 agonist antibody comprises (a) a VH sequence of SEQ ID NO: 319; (b) a VL sequence of SEQ ID NO: 345; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some examples, the OX40 agonist antibody comprises (a) a VH sequence of SEQ ID NO: 320; (b) a VL sequence of SEQ ID NO: 346; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some examples, the OX40 agonist antibody is antibody L106, antibody ACT35, MEDI6469, or MEDI0562. In some examples, the OX40 agonist antibody is a full-length IgG1 antibody. In some examples, the OX40 immunoadhesin is a trimeric OX40-Fc protein.

In some examples, any one of the methods of treatment described above may further comprise administering to the subject an agent that decreases or inhibits one or more additional immune co-inhibitory receptors. In some examples, the one or more additional immune co-inhibitory receptor is selected from the group consisting of PD-1, CTLA-4, LAG3, TIM3, BTLA, VISTA, B7H4, and CD96. In some examples, any one of the methods of treatment described above may further comprise administering to the subject an additional therapeutic agent. In some examples, the additional therapeutic agent is a chemotherapeutic agent. In some examples, antibody is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some examples, the subject is a human.

In another example, the disclosure features a kit comprising any one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein and package insert comprising instructions for using the antibody for treating or delaying progression of a cancer in a subject. In one aspect, the present disclosure refers to a kit comprising any one of the antibodies described herein and a package insert comprising instructions for using the antibody for treating or delaying progression of a cancer in a subject. In some examples, the cancer is selected from the group consisting of a non-small cell lung cancer, a small cell lung cancer, a renal cell cancer, a colorectal cancer, an ovarian cancer, a breast cancer, a pancreatic cancer, a gastric carcinoma, a bladder cancer, an esophageal cancer, a mesothelioma, a melanoma, a head and neck cancer, a thyroid cancer, a sarcoma, a prostate cancer, a glioblastoma, a cervical cancer, a thymic carcinoma, a leukemia, a lymphoma, a myeloma, mycoses fungoides, a merkel cell cancer, and a hematologic malignancy. In some examples, the subject is a human. In some examples, the myeloma is MM.

In another example, the disclosure features a kit comprising any one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein and a package insert comprising instructions for using the

antibody for treating or delaying progression of an immune-related disease in a subject. In some examples, the immune-related disease is associated with a T cell dysfunctional disorder. In some examples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some examples, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some examples, the subject is a human.

In another example, the disclosure features a kit comprising any one or more (e.g., 1, 2, 3, 4, 5, or 6 or more) of the antibodies described herein and a package insert comprising instructions for increasing, enhancing, or stimulating an immune response or function in a subject. In some examples, the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1A is a schematic diagram of a CHO-TIGIT binding assay.

FIGURE 1B is a graph showing the results of the CHO-TIGIT binding assay depicted in Figure 1A using human TIGIT-expressing CHO cells and the indicated OMT-derived anti-TIGIT antibodies at varying concentrations, as analyzed by FACS.

FIGURE 1C is a graph showing the results of the CHO-TIGIT binding assay depicted in Figure 1A using cynomolgus monkey (cyno) TIGIT-expressing CHO cells and the indicated OMT-derived anti-TIGIT antibodies at varying concentrations, as analyzed by FACS.

FIGURE 1D is a graph showing the results of the CHO-TIGIT binding assay depicted in Figure 1A using human TIGIT-expressing CHO cells and the indicated SD-derived anti-TIGIT antibodies at varying concentrations, as analyzed by FACS.

FIGURE 1E is a graph showing the results of the CHO-TIGIT binding assay depicted in Figure 1A using cyno TIGIT-expressing CHO cells and the indicated SD-derived anti-TIGIT antibodies at varying concentrations, as analyzed by FACS.

FIGURE 2A is a graph showing the binding of the indicated OMT-derived anti-TIGIT antibodies to human CD4 T cells as a function of antibody concentration.

FIGURE 2B is a graph showing the binding of the indicated OMT-derived anti-TIGIT antibodies to human CD8 T cells as a function of antibody concentration.

FIGURE 2C is a graph showing the binding of the indicated SD-derived anti-TIGIT antibodies to human CD4 T cells as a function of antibody concentration.

FIGURE 2D is a graph showing the binding of the indicated SD-derived anti-TIGIT antibodies to human CD8 T cells as a function of antibody concentration.

FIGURE 3A is a graph showing the results of a blocking ELISA assay using human PVR-Fc fusion protein coated-plates, human TIGIT, and the indicated anti-TIGIT antibodies (10A7 and 4.1D3.Q1E in Fab or IgG format) or anti-CSF1 Fab control, as a function of antibody/Fab concentration.

FIGURE 3B is a graph showing the results of a blocking ELISA assay using cyno PVR-Fc fusion protein coated-plates, cyno TIGIT, and the indicated anti-TIGIT antibodies (10A7 and 4.1D3.Q1E in Fab or IgG format) or anti-CSF1 Fab control, as a function of antibody/Fab concentration.