

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.

SUMMARY OF THE INVENTION

The present inventiondisclosure 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 inventiondisclosure
25 provides anti-TIGIT 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 aspectexample, the inventiondisclosure features an antibody that specifically binds to
30 human TIGIT, 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 embodimentexample, the epitope comprises amino acid residues Ser80 and Lys82 of human TIGIT. In another embodimentexample, the epitope comprises amino acid residues Ser78, Ser80, and Lys82 of human TIGIT. In another
35 embodimentexample, the epitope further comprises amino acid residue Ala67 of human TIGIT. In another embodimentexample, the epitope further comprises one or more additional amino acid residues selected from the group consisting of Glu60, Leu65, and Ile68 of human TIGIT. In another
40 embodimentexample, 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 embodimentexample, 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 embodimentexample, the 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 [aspectexample](#), the [inventiondisclosure](#) 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 Thr55, Ser80, and Lys82 of human TIGIT. In one [embodimentexample](#), the epitope comprises amino acid residue Lys82 of human TIGIT. In another [embodimentexample](#), the epitope comprises amino acid residues Thr55, Ser80, and Lys82 of human TIGIT. In another [embodimentexample](#), the epitope further comprises amino acid residue Gln56 of human TIGIT. In another [embodimentexample](#), the epitope further comprises amino acid residue Ile77 or Pro79 of human TIGIT. In another [embodimentexample](#), the epitope further comprises amino acid residues Ile77 and Pro79 of human TIGIT. In another [embodimentexample](#), the epitope further comprises amino acid residue Asn58 or Glu60 of human TIGIT. In another [embodimentexample](#), the epitope further comprises amino acid residues Asn58 and Glu60 of human TIGIT. In another [embodimentexample](#), 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 [embodimentexample](#), the epitope further comprises amino acid residues Leu65, Ile68, Leu73, His76, Ser78, and His111 of human TIGIT. In yet another [embodimentexample](#), the epitope consists of Thr55, Gln56, Asn58, Glu60, Leu65, Ile68, Leu73, His76, Ile77, Ser78, Pro79, Ser80, Lys82, and His111 of human TIGIT.

In another [aspectexample](#), the [inventiondisclosure](#) features an antibody that specifically binds to human TIGIT, wherein the antibody comprises a paratope comprising one or more amino acid residues selected from 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 [embodimentexample](#), 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 Tyr27d, Tyr92, Ser93, Thr94, and Phe96. In any of the above [aspectexamples](#), the antibody may be capable of binding to rabbit TIGIT.

In another [aspectexample](#), the [inventiondisclosure](#) 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 [embodimentexamples](#), the epitope further comprises Gln56 of human TIGIT. In some [embodimentexamples](#), the epitope further comprises Glu60, Leu65, Ile68, Asn70, Leu73, and His76 of human TIGIT.

In another [aspectexample](#), the [inventiondisclosure](#) 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 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 [embodimentexamples](#), the antibody further comprises the following light chain variable region 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 WYQQKPGQPPNLLIY (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 embodimentexamples, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of X₁VQLQQSGPGLVKPSQTLSTCAISGDSVS (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 WGQGTLTVSS (SEQ ID NO: 14). In some embodimentexamples, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of EVQLQQSGPGLVKPSQTLSTCAISGDSVS (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 WGQGTLTVSS (SEQ ID NO: 14). In some embodimentexample, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of QVQLQQSGPGLVKPSQTLSTCAISGDSVS (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 WGQGTLTVSS (SEQ ID NO: 14). In some embodimentexamples, 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 another aspect one example, the inventiondisclosure 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 embodimentexamples, 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 embodimentexamples, 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 WVRQAPGHGLEWMG (SEQ ID NO: 25); an FR-H3 comprising the amino acid sequence of RFVFSLDTSVNTAYLQISSLKAEDTAVFYCAR (SEQ ID NO: 26); and an FR-H4 comprising the amino acid sequence of WGQGTMTVTVSS (SEQ ID NO: 27). In some embodimentexamples, 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 QHLHGYP CN (SEQ ID NO: 28). In some embodiment examples, the antibody further comprises the following heavy chain variable region FRs: an FR-H1 comprising the amino acid sequence of QVQLVQSGSDLKKPGASVRV SCKASGYTFT (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 RFVFSLDTSVNTAYLQISSLKAEDTAVYFCAR (SEQ ID NO: 26); and an FR-H4 comprising the amino acid sequence of WGQGTMTVTVSS (SEQ ID NO: 27). In some embodiment 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 GVPSRFSGSGSGTEFTLTISSLQPEDFVITYYC (SEQ ID NO: 32); and an FR-L4 comprising the amino acid sequence of FGQGTKVEIK (SEQ ID NO: 33).

In another aspect example, the invention 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 embodiment 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 embodiment 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 embodiment examples, the antibody is capable of binding to rabbit TIGIT.

In another aspect example, the invention 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 aspect example, the invention 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 aspect 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 embodiment 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 [embodimentexamples](#), the antibody binds human TIGIT with a Kd of about 0.1 nM to about 1 nM and cyno TIGIT with a Kd of about 0.5 nM to about 1 nM. In some [embodimentexamples](#), the antibody binds human TIGIT with a Kd of about 0.1 nM or lower and cyno TIGIT with a Kd of about 0.5 nM or lower.

5 In any one of the [aspectexamples](#) described above, the antibody may be an antagonist antibody or an agonist antibody.

In some [embodimentexamples](#), the antagonist antibody specifically binds TIGIT and inhibits or blocks TIGIT interaction with poliovirus receptor (PVR). In some [embodimentexamples](#), the antagonist antibody inhibits intracellular signaling mediated by TIGIT binding to PVR. In some
10 [embodimentexamples](#), the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC50 value of 10 nM or lower. In some [embodimentexamples](#), the antagonist antibody inhibits or blocks binding of human TIGIT to human PVR with an IC50 value of 1 nM to about 10 nM. In some [embodimentexamples](#), the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 50 nM or lower. In some [embodimentexamples](#), the antagonist antibody inhibits or
15 blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 50 nM. In some [embodimentexamples](#), the antagonist antibody inhibits or blocks binding of cyno TIGIT to cyno PVR with an IC50 value of 1 nM to about 5 nM.

In some [embodimentexamples](#), the agonist antibody specifically binds TIGIT and stimulates the interaction of PVR with CD226 or CD96. In some [embodimentexamples](#), the agonist antibody specifically
20 binds TIGIT and stimulates the interaction of PVR with CD226 and CD96. In some [embodimentexamples](#), the agonist antibody specifically binds TIGIT and stimulates the interaction of human PVR with human CD226 and human CD96. In some [embodimentexamples](#), the agonist antibody specifically binds TIGIT and stimulates the interaction of cyno PVR with cyno CD226 and cyno CD96.

In another [aspectexample](#), the [inventiondisclosure](#) features an isolated antibody that competes
25 for binding to TIGIT with an antibody of any one of the above [aspectexamples](#).

In another [aspectexample](#), the [inventiondisclosure](#) features an isolated antibody that binds to the same epitope as an antibody of any one of the above [aspectexamples](#).

In some [embodimentexamples](#) of any one of the [aspectexamples](#) described above, the antibody is monoclonal. In some [embodimentexamples](#), the antibody is human, humanized, or chimeric. In some
30 [embodimentexamples](#), the antibody is a full-length antibody. In some [embodimentexamples](#), 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 [embodimentexamples](#), the antibody has a clearance of about 3 ml/kg/day to about 8 ml/kg/day. In some [embodimentexamples](#), administration of the antibody is to a mammal (e.g., a monkey, such as a cynomolgus monkey, or a human). In some [embodimentexamples](#), the antibody is an antibody fragment that binds TIGIT. In some
35 [embodimentexamples](#), 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 [embodimentexamples](#), the antibody is an IgG class antibody. In some [embodimentexamples](#), the IgG class antibody is an IgG1 subclass antibody. In some [embodimentexamples](#), an antibody described herein can be for use as a
40 medicament. In one aspect, the present disclosure refers to any one of the antibodies described herein for use as a medicament. In some [embodimentexamples](#), 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 [embodimentexamples](#), the cancer is selected from the
45 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 [embodimentexamples](#), an antibody described herein may be for use in treating or delaying progression of multiple myeloma (MM). In some [embodimentexamples](#), 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 [embodimentexamples](#), the immune-related disease is associated with a T cell dysfunctional disorder. In some [embodimentexamples](#), the T cell dysfunctional disorder is characterized by T cell exhaustion. In some [embodimentexamples](#), the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some [embodimentexamples](#), 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 [aspectexample](#), the [inventiondisclosure](#) 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 [aspectexample](#), the [inventiondisclosure](#) 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 [aspectexample](#), the [inventiondisclosure](#) 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 [embodimentexamples](#), the host cell is a eukaryotic (e.g., a mammalian cell). In some [embodimentexamples](#), the eukaryotic cell is a 293 cell, a Chinese hamster ovary (CHO) cell, a yeast cell, or a plant cell. In some [embodimentexamples](#), the host cell is a prokaryotic cell. In some [embodimentexamples](#), the prokaryotic cell is *E. coli*.

In another [aspectexample](#), the [inventiondisclosure](#) 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 [embodimentexamples](#), the method further comprises recovering the antibody from the host cell or the culture medium. In some [embodimentexamples](#), 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 [embodimentexamples](#), the host cell is a prokaryotic cell. In some [embodimentexamples](#), the prokaryotic cell is *E. coli*.

In another [aspectexample](#), the [inventiondisclosure](#) 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 [aspectexample](#), the [inventiondisclosure](#) 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 [embodimentexamples](#), the composition further comprises a pharmaceutically acceptable carrier, excipient, or diluent. In some [embodimentexamples](#), the composition is for diagnostic use (e.g., to detect TIGIT expression levels, e.g., TIGIT protein expression levels). In some [embodimentexamples](#), the composition is a pharmaceutical composition. In some [embodimentexamples](#), the composition further comprises a PD-1 axis binding antagonist or an additional therapeutic agent.

In another [aspectexample](#), the [inventiondisclosure](#) 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 [embodimentexamples](#), 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 embodimentexamples, the myeloma is MM. In some embodimentexamples, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodimentexamples, the subject is a human.

In another aspectexample, the inventiondisclosure 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 embodimentexamples, the immune-related disease is associated with a T cell dysfunctional disorder. In some embodimentexamples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodimentexamples, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some embodimentexamples, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodimentexamples, the subject is a human.

In another aspectexample, the inventiondisclosure 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 embodimentexamples, the medicament is formulated for administration subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodimentexamples, the subject is a human.

In another aspectexample, the inventiondisclosure 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 embodimentexamples, 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 embodimentexamples, the myeloma is MM.

In another aspectexample, the inventiondisclosure 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 embodimentexamples, the immune-related disease is associated with a T cell dysfunctional disorder. In some embodimentexamples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodimentexamples, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity.

In another aspectexample, the inventiondisclosure 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 [embodimentexamples](#), the method further comprises administering to the subject a PD-1 axis binding antagonist. In some [embodimentexamples](#), the PD-1 axis binding antagonist is administered prior to or subsequent to the administration of the antibody. In some [embodimentexamples](#), the PD-1 axis binding antagonist is administered concurrently with the antibody. In some [embodimentexamples](#), 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 [embodimentexamples](#), the PD-1 axis binding antagonist is a PD-1 binding antagonist. In some [embodimentexamples](#), the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners. In some [embodimentexamples](#), the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1. In some [embodimentexamples](#), the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2. In some [embodimentexamples](#), the PD-1 binding antagonist is an anti-PD-1 antibody. In some [embodimentexamples](#), 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 [embodimentexamples](#), the PD-1 axis binding antagonist is a PD-L1 binding antagonist. In some [embodimentexamples](#), the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1. In some [embodimentexamples](#), the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1. In some [embodimentexamples](#), the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1. In some [embodimentexamples](#), the PD-L1 binding antagonist is an anti-PD-L1 antibody. In some [embodimentexamples](#), 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 [embodimentexamples](#), the antibody is MPDL3280A. In some [embodimentexamples](#), the PD-1 axis binding antagonist is a PD-L2 binding antagonist. In some [embodimentexamples](#), the PD-L2 binding antagonist is an anti-PD-L2 antibody. In some [embodimentexamples](#), the PD-L2 binding antagonist is an immunoadhesin.

In some [embodimentexamples](#), any one of the methods of treatment described above may further comprise administering to the subject an OX40 binding agonist. In some [embodimentexamples](#), 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 [embodimentexamples](#), the OX40 binding agonist is administered concurrently with the antibody and/or the PD-1 axis binding antagonist. In some [embodimentexamples](#), 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 [embodimentexamples](#), the OX40 agonist antibody depletes cells that express human OX40. In some [embodimentexamples](#), the cells that express human OX40 are CD4+ effector T cells. In some [embodimentexamples](#), the cells that express human OX40 are regulatory T (Treg) cells. In some [embodimentexamples](#), the depleting is by ADCC and/or phagocytosis. In some [embodimentexamples](#), the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 1 nM. In some [embodimentexamples](#), the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.45 nM. In some [embodimentexamples](#), the OX40 agonist antibody binds human OX40 with an affinity of less than or equal to about 0.4 nM. In some [embodimentexamples](#), the OX40 agonist antibody binds human OX40 with an EC50 of less than or equal to 0.3 µg/ml. In some [embodimentexamples](#), the OX40 agonist antibody binds human OX40 with an EC50 of less than or equal to 0.2 µg/ml. In some [embodimentexamples](#), 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 [embodimentexamples](#), the OX40 agonist antibody increases memory T cell proliferation and/or cytokine production by a memory T cell. In some [embodimentexamples](#), the cytokine production is IFN- γ production. In some [embodimentexamples](#), the OX40 agonist antibody inhibits Treg function. In some [embodimentexamples](#), the OX40 agonist antibody inhibits Treg suppression of effector T cell function (e.g., effector T cell proliferation and/or cytokine production). In some [embodimentexamples](#), the effector T cell is a CD4+ effector T cell. In some [embodimentexamples](#), the OX40 agonist antibody increases OX40 signal transduction in a target cell that expresses OX40. In some [embodimentexamples](#), the OX40 signal transduction is detected by monitoring NFkB downstream signaling. In some [embodimentexamples](#), 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 [embodimentexamples](#), the OX40 agonist antibody comprises a variant IgG1 Fc polypeptide comprising a DANA mutation. In some [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in SEQ ID NO: 300. In some [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexample](#), 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 [embodimentexamples](#), a total of 1 to 10 amino acids have been substituted, inserted, and/or deleted in SEQ ID NO: 326. In some [embodimentexamples](#), 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 [embodimentexample](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), the OX40 agonist antibody is antibody L106, antibody ACT35, MEDI6469, or MEDI0562. In some [embodimentexamples](#), the OX40 agonist antibody is a full-length IgG1 antibody. In some [embodimentexamples](#), the OX40 immunoadhesin is a trimeric OX40-Fc protein.

In some [embodimentexamples](#), 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 [embodimentexamples](#), 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 [embodimentexamples](#), any one of the methods of treatment described above may further comprise administering to the subject an additional therapeutic agent. In some [embodimentexamples](#), the additional therapeutic agent is a chemotherapeutic agent. In some [embodimentexamples](#), antibody is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some [embodimentexamples](#), the subject is a human.

In another [aspectexample](#), the [inventiendisclosure](#) 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 [embodimentexamples](#), 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 [embodimentexamples](#), the subject is a human. In some [embodimentexamples](#), the myeloma is MM.

In another [aspectexample](#), the [inventiendisclosure](#) 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 embodimentexamples, the immune-related disease is associated with a T cell dysfunctional disorder. In some embodimentexamples, the T cell dysfunctional disorder is characterized by T cell exhaustion. In some embodimentexample, the immune-related disease is selected from the group consisting of unresolved acute infection, chronic infection, and tumor immunity. In some embodimentexamples, the subject is a human.

In another aspectexample, the inventiondisclosure 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 embodimentexamples, 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.