ANTIBODY MOLECULES TO TIM-3 AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/934,469, filed January 31, 2014, and U.S. Provisional Application No. 62/094,912, filed December 19, 2014, the contents of the aforementioned applications are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on January 26, 2015, is named C2160-7002WO_SL.txt and is 208,625 bytes in size.

BACKGROUND

Activation of naive CD4+ T helper cells results in the development of at least two distinct effector populations, Th1 cells and Th2 cells. See US 7,470,428, Mosmann T R et al. (1986) *J Immunol* 136:2348-57; Mosmann T R et al. (1996) *Immunol Today* 17:138-46; Abbas A K et al. (1996) *Nature* 383:787-793. Th1 cells produce cytokines (*e.g.,* interferon gamma, interleukin-2, tumor necrosis factor alpha, and lymphotoxin) which are commonly associated with cell-mediated immune responses against intracellular pathogens, delayed-type hypersensitivity reactions (Sher A et al. (1992) *Annu Rev Immunol* 10:385-409), and induction of organ-specific autoimmune diseases. Liblau R S et al. (1995) *Immunol Today* 16:34-38. Th2 cells produce cytokines (*e.g.,* IL-4, IL-10, and IL-13) that are crucial for control of extracellular helminthic infections and promote atopic and allergic diseases. Sher A et al. (1992) *Annu Rev Immunol* 10:385-409. In addition to their distinct roles in disease, the Th1 and Th2 cells cross-regulate each other's expansion and functions. Thus, preferential induction of Th2 cells inhibits autoimmune diseases (Kuchroo V K et al. (1995) *Cell* 80:707-18; Nicholson L B et al. (1995) *Immunity* 3:397-405), and predominant induction of Th1 cells can regulate induction of asthma, atopy and allergies. Lack G et al. (1994) *J Immunol* 152:2546-54; Hofstra C L et al. (1998) *J Immunol* 161:5054-60.

TIM-3 is a transmembrane receptor protein that is expressed, *e.g.,* on Th1 (T helper 1) CD4+ cells and cytotoxic CD8+ T cells that secrete IFN-γ. TIM-3 is generally not expressed on naïve T cells but rather upregulated on activated, effector T cells. TIM-3 has a role in regulating immunity and tolerance *in vivo* (see Hastings et al., *Eur J Immunol.* 2009 Sep; 39(9):2492-501). There is a need in the art for new molecules that regulate TIM-3 function and the function of TIM-3 expressing cells.

SUMMARY

Disclosed herein are antibody molecules that bind to TIM-3 (T-cell immunoglobulin domain and mucin domain 3) with high affinity and specificity. Nucleic acid molecules encoding the antibody molecules, expression vectors, host cells and methods for making the antibody molecules are also provided. Immunoconjugates, multi- or bispecific antibody molecules and pharmaceutical compositions comprising the antibody molecules are also provided. The anti-TIM-3 antibody molecules disclosed herein can be used (alone or in combination with other agents or therapeutic modalities) to treat, prevent and/or diagnose immune disorders, cancer, infectious disease, Crohn's disease, sepsis, SIRS (Systemic Inflammatory Response Syndrome), and glomerulonephritis. Thus, compositions and methods for detecting TIM-3, as well as methods for treating various disorders, including cancer and immune disorders using the anti-TIM-3 antibody molecules are disclosed herein.

Accordingly, in certain aspects, this disclosure provides an antibody molecule (*e.g.*, an isolated or recombinant antibody molecule) having one or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or all) of the following properties (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o), (p) or (q):

(a) binds to TIM-3, *e.g.*, human TIM-3, with high affinity, *e.g.*, with a dissociation constant (K_D) of less than about 100 nM, typically about 10 nM, and more typically, about 1-0.1 nM or stronger, *e.g.*, less than about 0.2, 0.16, 0.15, 0.1, 0.075, 0.05, or 0.042 nM,

(b) binds substantially to a non-human primate TIM-3, *e.g.*, cynomolgus TIM-3, with a dissociation constant (K_D) of less than about 100 nM, typically about 10 nM, and more typically, about 3-0.3 nM or stronger, *e.g.*, 1-0.1 nM or stronger, *e.g.*, less than about 1 nM, 0.75 nM, or 0.68 nM,

(c) inhibits binding of TIM-3 to a TIM-3 ligand, *e.g.*, phosphatidylserine (PtdSer), HMGB1, or CEACAM-1,

(d) enhances IFN-gamma and/or TNF-alpha secretion and/or proliferation in T cells, *e.g.*, CD4+ or CD8+ T cells, *e.g.*, in CD4+ T cells that were stimulated with anti-CD3/CD28 in the presence of IL-12 or in T cell-DC autologous culture assays with anti-CD3/CD28 stimulation,

(e) enhances cytotoxic NK (natural killer) cell activity against a target cell (*e.g.*, K562 cells), *e.g.*, in an *in vitro* assay,

(f) enhances capacity of macrophages or antigen presenting cells to stimulate a T cell response, *e.g.*, increasing IL-12 secretion of antigen presenting cells,

(g) binds specifically to an epitope on TIM-3, *e.g.*, the same or similar epitope as the epitope recognized by an antibody molecule described herein, *e.g.*, a murine or humanized anti-TIM-3 antibody molecule as described herein, *e.g.*, an antibody molecule of Tables 1-4,

(h) shows the same or similar binding affinity or specificity, or both, as an antibody molecule of Tables 1-4,

(i) shows the same or similar binding affinity or specificity, or both, as an antibody molecule (*e.g.*, an heavy chain variable region and light chain variable region) described in Tables 1-4,

(j) shows the same or similar binding affinity or specificity, or both, as an antibody molecule (*e.g.*, an heavy chain variable region and light chain variable region) comprising an amino acid sequence shown in Tables 1-4,

(k) inhibits, *e.g.*, competitively inhibits, the binding of a second antibody molecule to TIM-3 wherein the second antibody molecule is an antibody molecule described herein, *e.g.*, an antibody molecule chosen from Tables 1-4,

(l) binds the same (or substantially the same) or an overlapping (or substantially overlapping) epitope with a second antibody molecule to TIM-3, wherein the second antibody molecule is an antibody molecule described herein, *e.g.*, an antibody molecule chosen from Tables 1-4,

(m) competes for binding, and/or binds the same (or substantially the same) or overlapping (or substantially overlapping) epitope, with a second antibody molecule

to TIM-3, wherein the second antibody molecule is an antibody molecule described herein, *e.g.*, an antibody molecule chosen from Tables 1-4, *e.g.,* as determined by the methods described in Example 11,

(n) has one or more biological properties of an antibody molecule described herein, *e.g.*, an antibody molecule chosen from Tables 1-4,

(o) has one or more pharmacokinetic properties of an antibody molecule described herein, *e.g.*, an antibody molecule chosen from Tables 1-4,

(p) modulates (*e.g.*, enhances or inhibits) one or more activities of TIM-3, *e.g.*, results in one or more of: enhancing IFN-gamma and/or TNF-alpha secretion in T cells; enhancing proliferation in T cells, *e.g.*, CD4+ or CD8+ T cells; enhancing NK cell cytotoxic activity; reducing suppressor activity of regulatory T cells (Tregs); or increasing immune stimulation properties of macrophages and/or antigen presenting cells, *e.g.*, increasing cytokine secretion, *e.g.*, IL-12 secretion; or

(q) binds to one or more residues within: the two residues adjacent to the N-terminus of the A strand (residues Val24 and Glu25 in human TIM-3), the BC loop, the CC' loop, the F strand, the FG loop, and the G strand of TIM-3, or one or more residues within a combination of two, three, four, five or all of: the two residues adjacent to the N-terminus of the A strand (residues Val24 and Glu25 in human TIM-3), the BC loop, the CC' loop, the F strand, the FG loop, and the G strand of TIM-3, *e.g.*, wherein the binding is assayed using ELISA or Biacore.

In some embodiments, the antibody molecule binds to TIM-3 with high affinity, *e.g.*, with a K_D that is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% lower than the K_D of a murine anti-TIM-3 antibody molecule, *e.g.*, a murine anti-TIM-3 antibody molecule described herein.

In some embodiments, the expression level of the anti-TIM-3 antibody molecule is higher, *e.g.*, at least about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10-fold higher, than the expression level of a murine antibody molecule, *e.g.*, a murine or chimeric anti-TIM-3 antibody molecule described herein. In some embodiments, the antibody molecule is expressed in mammalian cells, *e.g.*, rodent cells.

In some embodiments, the anti-TIM-3 antibody molecule reduces one or more activities of TIM-3 with an IC50 (concentration at 50% inhibition) that is lower, *e.g.*, at least about 10%,

20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% lower, than the IC50 of a murine anti-TIM-3 antibody molecule, *e.g.*, a murine anti-TIM-3 antibody molecule described herein. In some embodiments, the TIM-3 activity is the binding of TIM-3 to one or more (*e.g.,* one, two, three, four or all) of the TIM-3 ligands described herein, *e.g.,* one, two or more (all) of PtdSer, CEACAM-1, or HMGB1.

In some embodiments, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a TIM-3 surface (*e.g.*, one, two, three, five, eight, ten, fifteen, or more continuous or discontinuous (*e.g.,* noncontiguous) amino acid residues chosen from Val24, Glu25, Thr41, Gly56, Ala57, Cys58, Pro59, Val60, Phe61, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, and/or Leu127.

In some embodiments, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a TIM-3 surface (*e.g.*, one, two, three, five, eight, ten, fifteen, twenty, twenty-one, twenty-five, or more continuous or discontinuous (*e.g.,* noncontiguous) amino acid residues chosen from Val24, Glu25, Tyr26, Phe39, Tyr40, Thr41, Gly56, Ala57, Cys58, Pro59, Val60, Phe61, Ser105, Gly106, Ile107, Asn119, Asp120, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, Leu127, and/or Val128, *e.g.*, as detailed in Table 13.

In some embodiments, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a TIM-3 surface (*e.g.*, one, two, three, five, eight, ten, fifteen, twenty, twenty-one, twenty-five, or more continuous or discontinuous (*e.g.,* noncontiguous) amino acid residues chosen from Glu23, Val24, Glu25, Tyr26, Thr41, Pro42, Ala43, Ala44, Pro45, Gly46, Asn47, Leu48, Val49, Pro50, Val51, Cys52, Trp53, Gly54, Lys55, Gly56, Ala57, Cys58, Pro59, Val60, Phe61, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126 and/or Leu127.

In some embodiments, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a TIM-3 surface (*e.g.*, one, two, three, five, eight, ten, fifteen, twenty, twenty-one, twenty-five, or more continuous or discontinuous (*e.g.,* noncontiguous) amino acid residues chosen from Val24, Glu25, Tyr26, Phe39, Tyr40, Thr41, Pro42, Ala43, Ala44, Pro45, Gly46, Asn47, Leu48, Val49, Pro50, Val51, Cys52, Trp53, Gly54, Lys55, Gly56, Ala57, Cys58, Pro59, Val60, Phe61, Ser105, Gly106, Ile107, Asn119, Asp120, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, Leu127, and/or Val128.

In other embodiments, the anti-TIM-3 antibody molecule competes with CEACAM-1 for binding to TIM-3. In one embodiment, the anti-TIM-3 antibody molecule interacts, *e.g.*, binds

to, one, two, or more (all) of Cys58, Asn119 and Lys122 of TIM-3, *e.g.*, displaces or competes CEACAM-1 for binding to these residues. In one embodiment, the anti-TIM-3 antibody molecule reduces or blocks the formation of a hydrogen bond between Lys122 of TIM-3 and Asn42 of CEACAM-1, *e.g.*, by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90%, compared to the formation of a hydrogen bond between between Lys122 of TIM-3 and Asn42 of CEACAM-1 in the absence of the anti-TIM-3 antibody molecule.

In another embodiment, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a PtdSer-binding loop of TIM-3. In one embodiment, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, at least two PtdSer-binding loops of TIM-3, *e.g.*, the FG loop and CC' loop of TIM-3 (*e.g.*, a metal ion-dependent ligand binding site (MILIBS)). For example, the carboxyl group of PtdSer can bind to the CC' loop of TIM-3 and the amino group of PtdSer can bind to the FG loop of TIM-3. In one embodiment, the anti-TIM-3 antibody molecule reduces or prevents PtdSer-mediated membrane penetration of TIM-3.

In another embodiment, the anti-TIM-3 antibody molecule competes with HMGB1 for binding to TIM-3. *E.g.*, it reduces binding of HMGB1 to residue 62 of TIM-3 (Q in mouse, E in human TIM-3), *e.g.*, by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90%, compared to the binding of HMGB1 to residue 62 of TIM-3 in the absence of the anti-TIM-3 antibody molecule.

In yet another embodiment, the anti-TIM-3 antibody molecule does not compete with a Galectin-9 (Gal-9) ligand for binding to TIM-3.

In some embodiments, the anti-TIM-3 antibody molecule has improved stability, *e.g.*, at least about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10-fold more stable *in vivo* or *in vitro*, than a murine or humanized anti-TIM-3 antibody molecule, *e.g.*, a murine or humanized anti-TIM-3 antibody molecule described herein.

In some embodiments, the anti-TIM-3 antibody molecule comprises at least one antigen-binding region, *e.g.*, a variable region or an antigen-binding fragment thereof, from an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-

hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In certain embodiments, the anti-TIM-3 antibody molecule comprises at least one, two, three, or four variable regions from an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TIM-3 antibody molecule comprises at least one or two heavy chain variable regions from an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In certain embodiments, the anti-TIM-3 antibody molecule comprises at least one or two light chain variable regions from an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.*, at

least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In one embodiment, the anti-TIM-3 antibody molecule includes a heavy chain constant region for an IgG4, *e.g.*, a human IgG4. In another embodiment, the human IgG4 includes a substitution (*e.g.*, a Ser to Pro substitution) at position 228 according to EU numbering or at position 108 of SEQ ID NO: 108 or 110. In still another embodiment, the anti-TIM-3 antibody molecule includes a heavy chain constant region for an IgG1, *e.g.,* a human IgG1. In one embodiment, the human IgG1 includes a substitution (*e.g.*, an Asn to Ala substitution) at position 297 according to EU numbering or at position 180 of SEQ ID NO: 112. In one embodiment, the human IgG1 includes a substitution (*e.g.*, an Asp to Ala substitution) at position 265 according to EU numbering or at position 148 of SEQ ID NO: 113, a substitution (*e.g.,* a Pro to Ala substitution) at position 329 according to EU numbering or at position 212 of SEQ ID NO: 113, or both . In one embodiment, the human IgG1 includes a substitution (*e.g.*, a Leu to Ala substitution) at position 234 according to EU numbering or at position 117 of SEQ ID NO: 114, a substitution (*e.g.*, a Leu to Ala substitution) at position 235 according to EU numbering or at position 118 of SEQ ID NO: 114, or both. In one embodiment, the heavy chain constant region comprises an amino sequence set forth in Table 1-5, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In yet another embodiment, the anti-TIM-3 antibody molecule includes a kappa light chain constant region, *e.g.*, a human kappa light chain constant region. In one embodiment, the light chain constant region comprises an amino sequence set forth in Table 1-5, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In another embodiment, the anti-TIM-3 antibody molecule includes a heavy chain constant region for an IgG4, *e.g.*, a human IgG4, and a kappa light chain constant region, *e.g.*, a human kappa light chain constant region, *e.g.,* a heavy and light chain constant region comprising an amino sequence set forth in Table 1-5, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto. In yet another embodiment, the anti-TIM-3 antibody molecule includes a heavy chain constant region for an IgG1, *e.g.*, a human IgG1, and a kappa light chain constant region, *e.g.*, a human kappa light chain constant region, *e.g.,* a heavy and light chain constant region comprising an amino

sequence set forth in Table 1-5, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto. In one embodiment, the human IgG1 includes a substitution at position 297 according to EU numbering (*e.g.*, an Asn to Ala substitution). In one embodiment, the human IgG1 includes a substitution at position 265 according to EU numbering, a substitution at position 329 according to EU numbering, or both (*e.g.*, an Asp to Ala substitution at position 265 and/or a Pro to Ala substitution at position 329). In one embodiment, the human IgG1 includes a substitution at position 234 according to EU numbering, a substitution at position 235 according to EU numbering, or both (*e.g.*, a Leu to Ala substitution at position 234 and/or a Leu to Ala substitution at position 235).

In another embodiment, the anti-TIM-3 antibody molecule includes a heavy chain variable domain and a constant region, a light chain variable domain and a constant region, or both, comprising the amino acid sequence of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three complementarity determining regions (CDRs) from a heavy chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4, or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TIM-3 antibody molecule comprises at least one, two, or three complementarity determining regions (CDRs) from a heavy chain variable region

comprising an amino acid sequence shown in Tables 1-4, or encoded by the nucleotide sequence in Tables 1-4. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the amino acid sequence shown in Tables 1-4, or encoded by a nucleotide sequence shown in Tables 1-4. In certain embodiments, the anti-TIM-3 antibody molecule includes a substitution in a heavy chain CDR, *e.g.*, one or more substitutions in a CDR1, CDR2 and/or CDR3 of the heavy chain. In one embodiment, the anti-TIM-3 antibody molecule includes a substitution in the heavy chain CDR2 at position 55 of the heavy chain region, *e.g.*, a substitution of an asparagine to serine, or an asparagine to glutamine, at position 55 of the heavy chain region according to Tables 1-4 (*e.g.*, any of SEQ ID NOs: 1 or 18 for murine or humanized, unmodified; or any of SEQ ID NOs: 26, or 32 for a modified sequence).

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three complementarity determining regions (CDRs) from a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4, or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.,* at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In certain embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three CDRs (or collectively all of the CDRs) from a light chain variable region comprising an amino acid sequence shown in Tables 1-4, or encoded by a nucleotide sequence shown in Tables 1-4. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the CDRs shown in Tables 1-4, or encoded by a nucleotide sequence shown in Tables 1-4. In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three CDRs (or collectively all of the CDRs) from a light chain variable region comprising an amino acid sequence shown in Tables 1-4, or encoded by a nucleotide sequence shown in Tables 1-4. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two,

three, four, five, six or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the CDRs shown in Tables 1-4, or encoded by a nucleotide sequence shown in Tables 1-4.

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, three, four, five or six CDRs (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Tables 1-4, or encoded by a nucleotide sequence shown in Tables 1-4. In some embodiments, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions, insertions, or deletions, relative to the CDRs shown in Tables 1-4, or encoded by a nucleotide sequence shown in Tables 1-4.

In certain embodiments, the anti-TIM-3 antibody molecule includes all six CDRs from an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4, or closely related CDRs, *e.g.*, CDRs which are identical or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions). In certain embodiments, the anti-TIM-3 antibody molecule may include any CDR described herein. In certain embodiments, the anti-TIM-3 antibody molecule includes a substitution in a heavy chain CDR, *e.g.*, one or more substitutions in a CDR1, CDR2 and/or CDR3 of the heavy chain. In one embodiment, the anti-TIM-3 antibody molecule includes a substitution in the heavy chain CDR2 at position 55 of the heavy chain region, *e.g.*, a substitution of an asparagine to serine, or an asparagine to glutamine, at position 55 of the heavy chain region according to Tables 1-4 (*e.g.*, any of SEQ ID NOs: 1 or 18 for murine or humanized, unmodified; or any of SEQ ID NOs: 26, or 32 for a modified sequence).

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three CDRs according to Kabat *et al.* (*e.g.,* at least one, two, or three CDRs according to the Kabat definition as set out in Tables 1-4) from a heavy chain variable region of an antibody

described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.,* at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three CDRs according to Kabat *et al.* shown in Tables 1-4.

In certain embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three CDRs according to Kabat *et al.* (*e.g.,* at least one, two, or three CDRs according to the Kabat definition as set out in Tables 1-4) from a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.,* at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three CDRs according to Kabat *et al.* shown in Tables 1-4.

In certain embodiments, the anti-TIM-3 antibody molecule includes at least one, two, three, four, five, or six CDRs according to Kabat *et al.* (*e.g.,* at least one, two, three, four, five, or six CDRs according to the Kabat definition as set out in Tables 1-4) from the heavy and light chain variable regions of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-

hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.,* at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, three, four, five, or six CDRs according to Kabat *et al.* shown in Tables 1-4.

In some embodiments, the anti-TIM-3 antibody molecule includes all six CDRs according to Kabat *et al.* (*e.g.,* all six CDRs according to the Kabat definition as set out in Tables 1-4) from the heavy and light chain variable regions of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.,* at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to all six CDRs according to Kabat *et al.* shown in Tables 1-4. In one embodiment, the anti-TIM-3 antibody molecule may include any CDR described herein.

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three Chothia hypervariable loops (*e.g.*, at least one, two, or three hypervariable loops according to the Chothia definition as set out in Tables 1-4) from a heavy chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21,

ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or at least the amino acids from those hypervariable loops that contact TIM-3; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three hypervariable loops according to Chothia et al. shown in Tables 1-4.

In certain embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three Chothia hypervariable loops (*e.g.*, at least one, two, or three hypervariable loops according to the Chothia definition as set out in Tables 1-4) of a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or at least the amino acids from those hypervariable loops that contact TIM-3; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three hypervariable loops according to Chothia et al. shown in Tables 1-4.

In certain embodiments, the anti-TIM-3 antibody molecule includes at least one, two, three, four, five, or six hypervariable loops (*e.g.*, at least one, two, three, four, five, or six hypervariable loops according to the Chothia definition as set out in Tables 1-4) from the heavy and light chain variable regions of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or at least the amino acids from those hypervariable loops that contact TIM-3; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*,

conservative substitutions) relative to one, two, three, four, five or six hypervariable loops according to Chothia et al. shown in Tables 1-4.

In some embodiments, the anti-TIM-3 antibody molecule includes all six hypervariable loops (*e.g.*, all six hypervariable loops according to the Chothia definition as set out in Tables 1-4) of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or closely related hypervariable loops, *e.g.*, hypervariable loops which are identical or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions); or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to all six hypervariable loops according to Chothia et al. shown in Tables 1-4. In one embodiment, the anti-TIM-3 antibody molecule may include any hypervariable loop described herein.

In still another embodiment, the anti-TIM-3 antibody molecule includes at least one, two, or three hypervariable loops that have the same canonical structures as the corresponding hypervariable loop of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23, *e.g.*, the same canonical structures as at least loop 1 and/or loop 2 of the heavy and/or light chain variable domains of an antibody described herein. See, *e.g.*, Chothia et al., (1992) *J. Mol. Biol.* 227:799-817; Tomlinson et al., (1992) *J. Mol. Biol.* 227:776-798 for descriptions of hypervariable loop canonical structures. These structures can be determined by inspection of the tables described in these references.

In certain embodiments, the anti-TIM-3 antibody molecule includes a combination of CDRs or hypervariable loops defined according to the Kabat et al. and Chothia et al.

In one embodiment, the anti-TIM-3 antibody molecule includes at least one, two or three CDRs or hypervariable loops from a heavy chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23, according to the Kabat and Chothia definition (*e.g.*, at least one, two, or three CDRs or hypervariable loops according to the Kabat and Chothia definition as set out in Tables 1-4); or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three CDRs or hypervariable loops according to Kabat and/or Chothia shown in Tables 1-4.

In nother embodiment, the anti-TIM-3 antibody molecule includes at least one, two or three CDRs or hypervariable loops from a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23, according to the Kabat and Chothia definition (*e.g.*, at least one, two, or three CDRs or hypervariable loops according to the Kabat and Chothia definition as set out in Tables 1-4); or encoded by the nucleotide sequence in Tables 1-4; or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three CDRs or hypervariable loops according to Kabat and/or Chothia shown in Tables 1-4.

The anti-TIM-3 antibody molecule can contain any combination of CDRs or hypervariable loops according to the Kabat and Chothia definitions.

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three Chothia hypervariable loops from a heavy chain variable region of an antibody described herein, *e.g.*, an antibody of Tables 1-4, or at least the amino acids from those hypervariable loops that contact TIM-3.

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three Chothia hypervariable loops from a light chain variable region of an antibody described herein, *e.g.*, an antibody of Tables 1-4, or at least the amino acids from those hypervariable loops that contact TIM-3.

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three Kabat hypervariable loops from a heavy chain variable region of an antibody described herein, *e.g.*, an antibody of Tables 1-4, or at least the amino acids from those hypervariable loops that contact TIM-3.

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three Kabat hypervariable loops from a light chain variable region of an antibody described herein, *e.g.*, an antibody of Tables 1-4, or at least the amino acids from those hypervariable loops that contact TIM-3.

In certain embodiments, the anti-TIM-3 antibody molecule includes at least one, two, three, four, five, or six hypervariable loops from the heavy and light chain variable regions of an antibody described herein, *e.g.*, an antibody of Tables 1-4, or at least the amino acids from those hypervariable loops that contact TIM-3.

In certain embodiments, the anti-TIM-3 antibody molecule includes all six hypervariable loops from the heavy and light chain variable regions of an antibody described herein, *e.g.*, an antibody of Tables 1-4, or at least the amino acids from those hypervariable loops that contact TIM-3, or at least the amino acids from those hypervariable loops that contact TIM-3, or closely related hypervariable loops, *e.g.*, hypervariable loops which are identical or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, *e.g.*, conservative substitutions, deletions, or insertions).

In some embodiments, the anti-TIM-3 antibody molecule includes at least one, two, or three hypervariable loops that have the same canonical structures as the corresponding

hypervariable loop of an antibody described herein, *e.g.*, an antibody of Tables 1-4, *e.g.*, the same canonical structures as at least loop 1 and/or loop 2 of the heavy and/or light chain variable domains of an antibody described herein. See, *e.g.*, Chothia et al., (1992) J. Mol. Biol. 227:799-817; Tomlinson et al., (1992) J. Mol. Biol. 227:776-798 for descriptions of hypervariable loop canonical structures. These structures can be determined by inspection of the tables described in these references. In an embodiment, *e.g.*, an embodiment comprising a variable region, CDR (*e.g.*, Chothia CDR or Kabat CDR), or other sequence referred to herein, *e.g.*, in Tables 1-4, the antibody molecule is a monospecific antibody molecule, a bispecific antibody molecule, or is an antibody molecule that comprises an antigen binding fragment of an antibody, *e.g.*, a half antibody or antigen binding fragment of a half antibody. In certain embodiments the antibody molecule is a bispecific antibody molecule having a first binding specificity for TIM-3 and a second binding specificity for PD-1, LAG-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), PD-L1 or PD-L2.

In certain embodiments, the light or the heavy chain variable framework (*e.g.*, the region encompassing at least FR1, FR2, FR3, or FR4) of the anti-TIM-3 antibody molecule can be chosen from: (a) a light or heavy chain variable framework including at least 80%, 85%, 87% 90%, 92%, 93%, 95%, 97%, 98%, or preferably 100% of the amino acid residues from a human light or heavy chain variable framework, *e.g.*, a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (b) a light or heavy chain variable framework including from 20% to 80%, 40% to 60%, 60% to 90%, or 70% to 95% of the amino acid residues from a human light or heavy chain variable framework, *e.g.*, a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (c) a non-human framework (*e.g.*, a rodent framework); or (d) a non-human framework that has been modified, *e.g.*, to remove antigenic or cytotoxic determinants, *e.g.*, deimmunized, or partially humanized. In some embodiments, the light or heavy chain variable framework region includes a light or heavy chain variable framework sequence at least 70, 75, 80, 85, 87, 88, 90, 92, 94, 95, 96, 97, 98, 99% identical or identical to the frameworks of a VL or VH segment of a human germline gene.

In certain embodiments, the anti-TIM-3 antibody molecule comprises a heavy chain variable domain having at least one, two, three, four, five, six, seven, ten, fifteen, twenty or more

changes, *e.g.*, amino acid substitutions, insertions, or deletions, from an amino acid sequence of, *e.g.*, the amino acid sequence of the FR region in the entire variable region, *e.g.*, shown in Figure 1A. In some embodiments, the anti-TIM-3 antibody molecule comprises a heavy chain variable domain having one or more (*e.g.*, all) of: A at position 2, Y at position 3, S at position 7, R at position 13, V at position 37, R at position 42, V at position 72, A at position 79, or F at position 95, *e.g.*, the amino acid sequence of the FR in the entire variable region, *e.g.*, as shown in Figure. 1A. In some embodiments, the anti-TIM-3 antibody molecule comprises a heavy chain variable domain having 2, 3, 4, 5, 6, 7, 8, or 9 positions selected from: A at position 2, Y at position 3, S at position 7, R at position 13, V at position 37, R at position 42, V at position 72, A at position 79, or F at position 95 of the amino acid sequence of an antibody of Tables 1-4, *e.g.*,

In certain embodiments (and optionally in combination with the heavy chain substitutions described herein, *e.g.*, in the previous paragraph), the anti-TM-3 antibody molecule comprises a light chain variable domain having at least one, two, three, four, five, six, seven, ten, fifteen, twenty or more amino acid changes, *e.g.*, amino acid substitutions, insertions, or deletions, from an amino acid sequence of Tables 1-4, *e.g.*, the amino acid sequence of the FR region in the entire variable region, *e.g.*, shown in Figure 1B. In certain embodiments, the anti-TIM-3 antibody comprises a light chain variable domain having M at position 89 of the amino acid sequence of an antibody of Tables 1-4.

In some embodiments, the heavy or light chain variable domain, or both, of the of the anti-TIM-3 antibody molecule includes an amino acid sequence, which is substantially identical to an amino acid disclosed herein, *e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical to a variable region of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; or as described in Tables 1-4; or encoded by the nucleotide sequence in Tables 1-4; or which differs at least 1 or 5 residues, but less than 40, 30, 20, or 10 residues, from a variable region of an antibody described herein.

In certain embodiments, the heavy or light chain variable region, or both, of the anti-TIM-3 antibody molecule includes an amino acid sequence encoded by a nucleic acid sequence

described herein or a nucleic acid that hybridizes to a nucleic acid sequence described herein (*e.g.*, a nucleic acid sequence as shown in Tables 1-4) or its complement, *e.g.*, under low stringency, medium stringency, or high stringency, or other hybridization condition described herein.

In certain embodiments, the anti-TIM-3 antibody molecule comprises at least one, two, three, or four antigen-binding regions, *e.g.*, variable regions, having an amino acid sequence as set forth in Tables 1-4, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the sequences shown in Tables 1-4. In certain embodiments, the anti-TIM-3 antibody molecule includes a VH and/or VL domain encoded by a nucleic acid having a nucleotide sequence that encodes an antibody of Tables 1-4, or a sequence substantially identical to any one of the nucleotide sequences (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in Tables 1-4).

In certain embodiments, the anti-TIM-3 antibody molecule comprises at least one, two, or three (*e.g.*, all) CDRs from a heavy chain variable region having an amino acid sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions). In some embodiments, the anti-TIM-3 antibody molecule comprises at least one, two, or three (*e.g.*, all) CDRs from a light chain variable region having an amino acid sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions). In certain embodiments, the anti-TIM-3 antibody molecule comprises at least one, two, three, four, five or six (*e.g.*, all) CDRs from heavy and light chain variable regions having an amino acid sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-TIM-3 antibody molecule comprises at least one, two, or three (*e.g.*, all) CDRs and/or hypervariable loops from a heavy chain variable region having an

amino acid sequence of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23, as summarized in Tables 1-4, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions). In certain embodiments, the anti-TIM-3 antibody molecule comprises at least one, two, or three (*e.g.*, all) CDRs and/or hypervariable loops from a light chain variable region having an amino acid sequence of an antibody described herein, *e.g.*, an antibody chosen from any of ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23, as summarized in Tables 1-4, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions). In some embodiments, the anti-TIM-3 antibody molecule comprises all six CDRs and/or hypervariable loops described herein, *e.g.*, described in Tables 1-4.

In some embodiments, the antibody molecule has a variable region that is identical in sequence, or which differs by 1, 2, 3, or 4 amino acids from a variable region described herein (*e.g.*, an FR region disclosed herein).

In some embodiments, the anti-TIM-3 antibody molecule is a full antibody or fragment thereof (*e.g.*, a Fab, F(ab')2, Fv, or a single chain Fv fragment (scFv)). In certain embodiments, the anti-TIM-3 antibody molecule is a monoclonal antibody or an antibody with single specificity. The anti-TIM-3 antibody molecule can also be a humanized, chimeric, camelid, shark, or *in vitro*-generated antibody molecule. In some embodiments, the anti-TIM-3 antibody molecule thereof is a humanized antibody molecule. The heavy and light chains of the anti-TIM-3 antibody molecule can be full-length (*e.g.*, an antibody can include at least one or at least two

complete heavy chains, and at least one or at least two complete light chains) or can include an antigen-binding fragment (*e.g.*, a Fab, F(ab')2, Fv, a single chain Fv fragment, a single domain antibody, a diabody (dAb), a bivalent or bispecific antibody or fragment thereof, a single domain variant thereof, or a camelid antibody).

In certain embodiments, the anti-TIM-3 antibody molecule is in the form of a bispecific or multispecific antibody molecule. In one embodiment, the bispecific antibody molecule has a first binding specificity to TIM-3 and a second binding specifity, *e.g.*, a second binding specificity to PD-1, LAG-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), PD-L1 or PD-L2. In one embodiment, the bispecific antibody molecule binds to TIM-3 and PD-1. In another embodiment, the bispecific antibody molecule binds to TIM-3 and LAG-3. In another embodiment, the bispecific antibody molecule binds to TIM-3 and CEACAM (*e.g.*, CEACAM-1, -3 and/or -5). In another embodiment, the bispecific antibody molecule binds to TIM-3 and CEACAM-1. In another embodiment, the bispecific antibody molecule binds to TIM-3 and CEACAM-3. In yet another embodiment, the bispecific antibody molecule binds to TIM-3 and CEACAM-5. In another embodiment, the bispecific antibody molecule binds to TIM-3 and PD-L1. In yet another embodiment, the bispecific antibody molecule binds to TIM-3 and PD-L2. Any combination of the aforesaid molecules can be made in a multispecific antibody molecule, *e.g.*, a trispecific antibody that includes a first binding specificity to TIM-3, and a second and third binding specifities to one or more of: PD-1, LAG-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), PD-L1 or PD-L2.

In other embodiments, the anti-TIM-3 antibody molecule is used in combination with a bispecific molecule comprising one or more of: PD-1, LAG-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), PD-L1 or PD-L2. In one embodiment, the bispecific antibody molecule used in combination binds to CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) and LAG-3. In another embodiment, the bispecific antibody molecule used in combination binds to CEACAM (*e.g.*, CEACAM-1, -3 and/or -5) and PD-1. In another embodiment, the bispecific antibody molecule used in combination binds to LAG-3 and PD-1.

In certain embodiments, the anti-TIM-3 antibody molecule has a heavy chain constant region (Fc) chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE; particularly, chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4, more particularly, the heavy chain constant region of IgG1 or IgG2

(*e.g.*, human IgG1 or IgG2). In some embodiments, the heavy chain constant region is human IgG1. In some embodiments, the anti-TIM-3 antibody molecule has a light chain constant region chosen from, *e.g.*, the light chain constant regions of kappa or lambda, in some embodiments kappa (*e.g.*, human kappa). In some embodiments, the constant region is altered, *e.g.*, mutated, to modify the properties of the anti-TIM-3 antibody molecule (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function). For example, the constant region may be mutated at positions 296 (M to Y), 298 (S to T), 300 (T to E), 477 (H to K) and 478 (N to F) to alter Fc receptor binding (*e.g.*, the mutated positions correspond to positions 132 (M to Y), 134 (S to T), 136 (T to E), 313 (H to K) and 314 (N to F) of SEQ ID NOs: 108 or 110; or positions 135 (M to Y), 137 (S to T), 139 (T to E), 316 (H to K) and 317 (N to F) of SEQ ID NOs: 111, 112, 113 or 114). In another embodiment, the heavy chain constant region of an IgG4, *e.g.*, a human IgG4, is mutated at position 228 according to EU numbering (*e.g.,* S to P), *e.g.*, as shown in Table 5. In certain embodiments, the anti-TIM-3 antibody molecules comprises a human IgG4 mutated at position 228 according to EU numbering (*e.g.,* S to P), *e.g.*, as shown in Table 5; and a kappa light chain constant region, *e.g.*, as shown in Table 5. In still another embodiment, the heavy chain constant region of an IgG1, *e.g.*, a human IgG1, is mutated at one or more of position 297 (*e.g.,* N to A), position 265 (*e.g.,* D to A), position 329 (*e.g.,* P to A), position 234 (*e.g.,* L to A), or position 235 (*e.g.,* L to A), all according to EU numbering, *e.g.*, as shown in Table 5. In certain embodiments, the anti-TIM-3 antibody molecules comprises a human IgG1 mutated at one or more of the aforesaid positions, *e.g.*, as shown in Table 5; and a kappa light chain constant region, *e.g.*, as shown in Table 5. In some embodiments, the anti-TIM-3 antibody molecule is a humanized antibody molecule.

In some embodiments, the anti-TIM-3 antibody molecules comprise combinations of human or humanized framework regions with CDRs (complementarity determining regions).

The invention also features an antibody molecule that competes with a monoclonal antibody, *e.g.,* an antibody molecule described herein, for binding to human TIM-3.

In certain embodiments, the monoclonal antibody comprises:

(a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 10; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a light chain variable region (VL)

comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(b) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 4; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(c) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 25; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(d) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 24; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(e) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 31; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14; or

(f) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 30; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8.

The invention also features an antibody molecule that binds to the same (or substantially the same) or an overlapping (or substantially overlapping) epitope as a monoclonal antibody, *e.g.,* an antibody molecule described herein, to human TIM-3.

In certain embodiments, the monoclonal antibody comprises:

(a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 10; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(b) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 4; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(c) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 25; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(d) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 24; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(e) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 31; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14; or

(f) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 30; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8.

The invention also features a nucleic acid molecule that comprise one or both nucleotide sequences that encode heavy and light chain variable regions, CDRs, hypervariable loops,

framework regions of the anti-TIM-3 antibody molecules, as described herein. In certain embodiments, the nucleotide sequence that encodes the anti-TIM-3 antibody molecule is codon optimized. For example, the invention features a first and second nucleic acid encoding heavy and light chain variable regions, respectively, of an anti-TIM-3 antibody molecule chosen from one or more of, *e.g.*, any of ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23, as summarized in Tables 1-4, or a sequence substantially identical thereto. For example, the nucleic acid can comprise a nucleotide sequence as set forth in Tables 1-4, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in Tables 1-4).

In some embodiments, nucleic acids comprising nucleotide sequences that encode heavy and light chain variable regions and CDRs of the anti-TIM-3 antibody molecules, as described herein, are disclosed. For example, the disclosure provides a first and second nucleic acid encoding heavy and light chain variable regions, respectively, of an anti-TIM-3 antibody molecule according to Tables 1-4 or a sequence substantially identical thereto. For example, the nucleic acid can comprise a nucleotide sequence encoding an an anti-TIM-3 antibody molecule according to Table 1-4, or a sequence substantially identical to that nucleotide sequence (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the aforementioned nucleotide sequence.

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs, or hypervariable loops, from a heavy chain variable region having an amino acid sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs, or hypervariable loops, from a light chain variable region having

an amino acid sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs, or hypervariable loops, from heavy and light chain variable regions having an amino acid sequence as set forth in Table 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, *e.g.*, conserved substitutions).

In some embodiments, the anti-TIM-3 antibody molecule is isolated or recombinant.

In certain aspects, this disclosure features host cells and vectors containing the nucleic acids described herein. The nucleic acids may be present in a single vector or separate vectors present in the same host cell or separate host cell. The host cell can be a eukaryotic cell, *e.g.*, a mammalian cell, an insect cell, a yeast cell, or a prokaryotic cell, *e.g.*, *E. coli*. For example, the mammalian cell can be a cultured cell or a cell line. Exemplary mammalian cells include lymphocytic cell lines (*e.g.*, NS0), Chinese hamster ovary cells (CHO), COS cells, oocyte cells, and cells from a transgenic animal, *e.g.*, mammary epithelial cell.

In some aspects, the present disclosure provides a method of providing an antibody molecule described herein. The method may include: providing a TIM-3 antigen (*e.g.*, an antigen comprising at least a portion of a TIM-3 epitope, *e.g.*, the IgV domain of TIM-3); obtaining an antibody molecule that specifically binds to the TIM-3 antigen; and evaluating if the antibody molecule specifically binds to the TIM-3 antigen, or evaluating efficacy of the antibody molecule in modulating, *e.g.*, stimulating or inhibiting, the activity of TIM-3. The method can further include administering the antibody molecule to a subject, *e.g.*, a human or non-human animal.

In certain aspects, the disclosure provides, compositions, *e.g.*, pharmaceutical compositions, which include a pharmaceutically acceptable carrier, excipient or stabilizer, and at least one of the anti-TIM-3 antibody molecules described herein. In one embodiment, the composition, *e.g.*, the pharmaceutical composition, includes a combination of the antibody molecule and one or more agents, *e.g.*, a therapeutic agent or other antibody molecule, as

described herein. In some embodiments, the antibody molecule is conjugated to a label or a therapeutic agent. In some embodiments, the compositions, *e.g.*, the pharmaceutical compositions, comprise a combination of the antibody molecule and a second agent, *e.g.*, a therapeutic agent, or two or more of the aforesaid antibody molecules, as further described herein.

The anti-TIM-3 antibody molecules disclosed herein can inhibit, reduce or neutralize one or more activities of TIM-3, *e.g.,* resulting in blockade or reduction of an immune checkpoint on T cells or NK cells, or reinvigoration of an immune response by modulating antigen-presenting cells. In one embodiment, the antibody molecule results in one or more of: enhancing IFN-gamma and/or TNF alpha section in T cells; enhancing proliferation in T cells, *e.g.*, CD4+ or CD8+ T cells; enhancing NK cell cytotoxic activity; or reducing suppressor activity of regulatory T cells (Tregs) or macrophages; or increasing capacity of macrophages or dendritic cells to stimulate an immune response. Thus, such antibody molecules can be used to treat or prevent disorders where enhancing an immune response in a subject is desired.

Uses of the Anti-TIM-3 Antibody Molecules

The antibody molecules disclosed herein can modulate (*e.g.*, enhance, stimulate, increase, inhibit, reduce or neutralize) one or more activities of TIM-3. In some embodiments, the antibody molecule results in one or more of: enhancing IFN-gamma secretion and/or proliferation in T cells or enhancing NK cell cytotoxic activity. For instance, in some embodiments, the anti-TIM-3 antibody molecule increases IFN-gamma secretion by at least 16%, 18%, 20%, 22%, 24%, 26%, 28%, or 30%, *e.g.*, in an assay of Example 4. In certain embodiments, the anti-TIM-3 antibody molecule increases NK cell cytotoxic activity by at least about 10%, 20%, 30%, 40%, 60%, 80%, or 100%, *e.g.*, in an assay of Example 5. For example, the anti-TIM-3 antibody molecule could increase NK cell cytotoxic activity to at least about 60% or 70% of target cells killed when E/T = 5, to at least about 75% or 85% of target cells killed when E/T = 12, or to at least about 85% or 95% of target cells killed when E/T = 25, *e.g.*, in an assay of Example 5.

In certain aspects, a method of modulating (*e.g.*, stimulating or inhibiting) an immune response in a subject is provided. The method comprises administering to the subject an anti-TIM-3 antibody molecule disclosed herein, (*e.g.,* a therapeutically effective amount of an anti-

TIM-3 antibody molecule), alone or in combination with one or more agents or procedures (*e.g.*, in combination with other immunomodulatory agents), such that the immune response in the subject is modulated. In some embodiments, the antibody molecule enhances, stimulates or increases an immune response in the subject. In some embodiments, the antibody molecule inhibits, reduces, or neutralizes an immune response in a subject.

The subject can be a mammal, *e.g.*, a monkey, a primate, preferably a higher primate, *e.g.*, a human (*e.g.*, a patient having, or at risk of having, a disorder described herein). In some embodiments, the subject is in need of enhancing an immune response, and in some embodiments, the subject is in need of inhibiting an immune response. In one embodiment, the subject has, or is at risk of, having a disorder described herein, *e.g.*, a cancer or an infectious disorder as described herein. In certain embodiments, the subject is, or is at risk of being, immunocompromised. For example, the subject is undergoing or has undergone a chemotherapeutic treatment and/or radiation therapy. Alternatively, or in combination, the subject is, or is at risk of being, immunocompromised as a result of an infection.

In one aspect, a method of treating (*e.g.*, one or more of reducing, inhibiting, or delaying progression) a cancer or a tumor in a subject is provided. The method comprises administering to the subject an anti-TIM-3 antibody molecule described herein, *e.g.*, a therapeutically effective amount of an anti-TIM-3 antibody molecule, alone or in combination with one or more agents or procedures. In certain embodiments, the anti-TIM-3 antibody molecule is administered in combination with a modulator of a costimulatory molecule (*e.g.,* an agonist of a costimulatory molecule) or a modulator of an inhibitory molecule (*e.g.,* an inhibitor of an immune checkpoint inhibitor), *e.g.,* as described herein.

This disclosure also provides a method of reducing or inhibiting growth of a cancer or tumor cells (*e.g.*, treating a cancer) in a subject, comprising administering to the subject an anti-TIM-3 antibody molecule described herein, *e.g.*, a therapeutically effective amount of an anti-TIM-3 antibody molecule, alone or in combination with a second agent, *e.g.*, an immunomodulator (*e.g.*, an anti-PD-1, PD-L1, LAG-3 or CEACAM-1 inhibitor (*e.g.*, antibody), or a combination thereof.

In certain embodiments, the cancer treated with the anti-TIM-3 antibody molecule, alone or in combination with one or more immunomodulatos, includes but is not limited to, a solid tumor, a hematological cancer (*e.g.*, leukemia, lymphoma, myeloma, *e.g.*, multiple myeloma),

and a metastatic lesion. In one embodiment, the cancer is a solid tumor. Examples of solid tumors include malignancies, *e.g.*, sarcomas and carcinomas, *e.g.*, adenocarcinomas of the various organ systems, such as those affecting the lung, breast, ovarian, lymphoid, gastrointestinal (*e.g.*, colon), anal, genitals and genitourinary tract (*e.g.*, renal, urothelial, bladder cells, prostate), pharynx, CNS (*e.g.*, brain, neural or glial cells), head and neck, skin (*e.g.*, melanoma), and pancreas, as well as adenocarcinomas which include malignancies such as colon cancers, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell lung cancer, cancer of the small intestine and cancer of the esophagus. The cancer may be at an early, intermediate, late stage or metastatic cancer.

In one embodiment, the cancer is chosen from a lung cancer (*e.g.*, lung adenocarcinoma or a non-small cell lung cancer (NSCLC) (*e.g.*, a NSCLC with squamous and/or non-squamous histology, or a NSCLC adenocarcinoma)), a melanoma (*e.g.*, an advanced melanoma), a renal cancer (*e.g.*, a renal cell carcinoma), a liver cancer (*e.g.*, hepatocellular carcinoma), a myeloma (*e.g.*, a multiple myeloma), a prostate cancer, a breast cancer (*e.g.*, a breast cancer that does not express one, two or all of estrogen receptor, progesterone receptor, or Her2/neu, *e.g.*, a triple negative breast cancer), an ovarian cancer, a colorectal cancer, a pancreatic cancer, a head and neck cancer (*e.g.*, head and neck squamous cell carcinoma (HNSCC), anal cancer, gastro-esophageal cancer (*e.g.*, esophageal squamous cell carcinoma), mesothelioma, nasopharyngeal cancer, thyroid cancer, cervical cancer, a lymphoproliferative disease (*e.g.*, a post-transplant lymphoproliferative disease) or a hematological cancer, (*e.g.*, diffuse large B cell lymphoma, T-cell lymphoma, B-cell lymphoma, or a non-Hogdkin lymphoma), or a leukemia (*e.g.*, a myeloid leukemia or a lymphoid leukemia).

In another embodiment, the cancer is chosen form a carcinoma (*e.g.*, advanced or metastatic carcinoma), melanoma or a lung carcinoma, *e.g.*, a non-small cell lung carcinoma.

In one embodiment, the cancer is a lung cancer, *e.g.*, a lung adenocarcinoma, non-small cell lung cancer or small cell lung cancer.

In one embodiment, the cancer is a melanoma, *e.g.*, an advanced melanoma. In one embodiment, the cancer is an advanced or unresectable melanoma that does not respond to other therapies. In other embodiments, the cancer is a melanoma with a BRAF mutation (*e.g.*, a BRAF V600 mutation). In yet other embodiments, the anti-TIM-3 antibody molecule is administered

after treatment with an anti-CTLA-4 antibody (*e.g.*, ipilimumab) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib).

In another embodiment, the cancer is a hepatocarcinoma, *e.g.*, an advanced hepatocarcinoma, with or without a viral infection, *e.g.*, a chronic viral hepatitis.

In another embodiment, the cancer is a prostate cancer, *e.g.*, an advanced prostate cancer.

In yet another embodiment, the cancer is a myeloma, *e.g.*, multiple myeloma.

In yet another embodiment, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic RCC, clear cell renal cell carcinoma (CCRCC) or kidney papillary cell carcinoma).

In one embodiment, the cancer microenvironment has an elevated level of PD-L1 expression. Alternatively, or in combination, the cancer microenvironment can have increased IFNγ and/or CD8 expression.

In some embodiments, the subject has, or is identified as having, a tumor that has one or more of high PD-L1 level or expression, or as being Tumor Infiltrating Lymphocyte (TIL)+ (*e.g.*, as having an increased number of TILs), or both. In certain embodiments, the subject has, or is identified as having, a tumor that has high PD-L1 level or expression and that is TIL+. In some embodiments, the methods described herein further include identifying a subject based on having a tumor that has one or more of high PD-L1 level or expression or as being TIL+, or both. In certain embodiments, the methods described herein further include identifying a subject based on having a tumor that has high PD-L1 level or expression and as being TIL+. In some embodiments, tumors that are TIL+ are positive for CD8 and IFNγ. In some embodiments, the subject has, or is identified as having, a high percentage of cells that are positive for one, two or more of PD-L1, CD8, and/or IFNγ. In certain embodiments, the subject has or is identified as having a high percentage of cells that are positive for all of PD-L1, CD8, and IFNγ.

In some embodiments, the methods described herein further include identifying a subject based on having a high percentage of cells that are positive for one, two or more of PD-L1, CD8, and/or IFNγ. In certain embodiments, the methods described herein further include identifying a subject based on having a high percentage of cells that are positive for all of PD-L1, CD8, and IFNγ. In some embodiments, the subject has, or is identified as having, one, two or more of PD-L1, CD8, and/or IFNγ, and one or more of a lung cancer, *e.g.*, squamous cell lung cancer or lung adenocarcinoma; a head and neck cancer; a squamous cell cervical cancer; a stomach cancer; an

esophageal cancer; a thyroid cancer; a melanoma, and/or a nasopharyngeal cancer (NPC). In certain embodiments, the methods described herein further describe identifying a subject based on having one, two or more of PD-L1, CD8, and/or IFNγ, and one or more of a lung cancer, *e.g.*, squamous cell lung cancer or lung adenocarcinoma; a head and neck cancer; a squamous cell cervical cancer; a stomach cancer; a thyroid cancer; a melanoma, and/or a nasopharyngeal cancer.

In some embodiments, subject has, or is identified as having, a tumor that has one, two, or more of high PD-1 level or expression, high TIM-3 level or expression, and/or high level of infiltration of regulatory T cells in the tumor, *e.g.*, an increased number or percentage of Tregs present in the tumor. In certain embodiments, the subject has, or is identified as having, a tumor that has a high level or expression of PD-1 and TIM-3, and a high level, *e.g.*, number, or regulatory T cells in the tumor. In some embodiments, the methods described herein further include identifying a subject based on one, two or more of a high percentage of cells that are positive for PD-1, a high percentage of cells that are positive for TIM-3, and/or a high level of infiltration of regulatory T cells in the tumor, *e.g.*, an increased number or percentage of Tregs present in the tumor. In some embodiments, the methods described herein further include identifying a subject based on one, two or more of a high percentage of cells that are positive for PD-1, a high percentage of cells that are positive for TIM-3, and/or a high level of infiltration of regulatory T cells in the tumor, *e.g.*, an increased number or percentage of Tregs present in the tumor, and one or more of a lung cancer, *e.g.*,non-small cell lung cancer (NSCLC); a hepatocellular cancer, *e.g.*, hepatocellular carcinoma; or an ovarian cancer, *e.g.*, ovarian carcinoma.

Methods and compositions disclosed herein are useful for treating metastatic lesions associated with the aforementioned cancers.

In further aspects, this disclosure provides a method of treating an infectious disease in a subject, comprising administering to a subject a therapeutically effective amount of an anti-TIM-3 antibody described herein, or antigen-binding portion thereof, alone or in combination with one or more agents or procedures (*e.g.,* one or more immunomodulatory agents).

Still further, this disclosure provides methods of enhancing an immune response to an antigen in a subject, comprising administering to the subject: (i) the antigen; and (ii) an anti-TIM-3 antibody, or antigen-binding portion thereof, such that an immune response to the antigen

in the subject is enhanced. The antigen can be, for example, a tumor antigen, a viral antigen, a bacterial antigen or an antigen from a pathogen.

The anti-TIM-3 antibody molecule can be administered to the subject systemically (*e.g.*, orally, parenterally, subcutaneously, intravenously, rectally, intramuscularly, intraperitoneally, intranasally, transdermally, or by inhalation or intracavitary installation), topically, or by application to mucous membranes, such as the nose, throat and bronchial tubes.

The anti-TIM-3 antibody molecule can be used alone in unconjugated form, or can be bound to a substance, *e.g.*, a cytotoxic agent or moiety (*e.g.*, a therapeutic drug; a compound emitting radiation; molecules of plant, fungal, or bacterial origin; or a biological protein (*e.g.*, a protein toxin) or particle (*e.g.*, a recombinant viral particle, *e.g.*, via a viral coat protein). For example, the anti-TIM-3 antibody can be coupled to a radioactive isotope such as an α-, β-, or γ-emitter, or a β-and γ-emitter.

Dosages and therapeutic regimens of the anti-TIM-3 antibody molecule can be determined by a skilled artisan. In certain embodiments, the anti-TIM-3 antibody molecule is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose of about 1 to 30 mg/kg, *e.g.*, about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, or about 3 mg/kg. The dosing schedule can vary from *e.g.*, once a week to once every 2, 3, or 4 weeks. In one embodiment, the anti-TIM-3 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week.

The antibody molecules described herein are preferred for use in the methods described herein, although other anti-TIM-3 antibodies can be used instead, or in combination with an anti-TIM-3 antibody molecule of the invention.

Combination Therapies

The methods and compositions described herein can be used in combination with other therapeutic modalities. In some embodiments, the methods of described herein include administering to the subject an anti-TIM-3 antibody molecule as described herein, in combination with a cytotoxic agent, in an amount effective to treat or prevent said disorder. The antibody molecule and the cytotoxic agent can be administered simultaneously or sequentially.

Any combination and sequence of the anti-TIM-3 antibody molecules and other therapeutic modalities can be used. The anti-TIM-3 antibody molecule and/or other therapeutic

modalities can be administered during periods of active disorder, or during a period of remission or less active disease. The anti-TIM-3 antibody molecule and other therapeutic modalities can be administered before treatment, concurrently with treatment, post-treatment, or during remission of the disorder.

In certain embodiments, the methods and compositions described herein are administered in combination with one or more of other antibody molecules, chemotherapy, other anti-cancer therapy (*e.g.*, targeted anti-cancer therapies, gene therapy, viral therapy, RNA therapy bone marrow transplantation, nanotherapy, or oncolytic drugs), cytotoxic agents, immune-based therapies (*e.g.*, cytokines or cell-based immune therapies), surgical procedures (*e.g.*, lumpectomy or mastectomy) or radiation procedures, or a combination of any of the foregoing. The additional therapy may be in the form of adjuvant or neoadjuvant therapy. In some embodiments, the additional therapy is an enzymatic inhibitor (*e.g.*, a small molecule enzymatic inhibitor) or a metastatic inhibitor. Exemplary cytotoxic agents that can be administered in combination with include antimicrotubule agents, topoisomerase inhibitors, anti-metabolites, mitotic inhibitors, alkylating agents, anthracyclines, vinca alkaloids, intercalating agents, agents capable of interfering with a signal transduction pathway, agents that promote apoptosis, proteosome inhibitors, and radiation (*e.g.*, local or whole body irradiation (*e.g.*, gamma irradiation). In other embodiments, the additional therapy is surgery or radiation, or a combination thereof. In other embodiments, the additional therapy is a therapy targeting one or more of PI3K/AKT/mTOR pathway, an HSP90 inhibitor, or a tubulin inhibitor.

Alternatively, or in combination with the aforesaid combinations, the methods and compositions described herein can be administered in combination with one or more of: an immunomodulator (*e.g.*, an activator of a costimulatory molecule or an inhibitor of an inhibitory molecule, *e.g.,* an immune checkpoint molecule); a vaccine, *e.g.*, a therapeutic cancer vaccine; or other forms of cellular immunotherapy.

Exemplary non-limiting combinations and uses of the anti-TIM-3 antibody molecules include the following.

In certain embodiments, the anti-TIM-3 antibody molecule is administered in combination with a modulator of a costimulatory molecule or an inhibitory molecule, *e.g.*, a co-inhibitory ligand or receptor.

In one embodiment, the anti-TIM-3 antibody molecule is administered in combination with a modulator, *e.g.*, agonist, of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (*e.g.*, an agonistic antibody or antigen-binding fragment thereof, or a soluble fusion) of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand.

In one embodiment, the anti-TIM-3 antibody molecule is administered in combination with an inhibitor of an inhibitory (or immune checkpoint) molecule chosen from PD-1, PD-L1, PD-L2, CTLA-4, LAG-3, CEACAM (*e.g.*, CEACAM-1, -3 and/or -5), VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and/or TGFR beta. Inhibition of an inhibitory molecule can be performed by inhibition at the DNA, RNA or protein level. In embodiments, an inhibitory nucleic acid (*e.g.*, a dsRNA, siRNA or shRNA), can be used to inhibit expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is, a polypeptide *e.g.*, a soluble ligand, or an antibody or antigen-binding fragment thereof, that binds to the inhibitory molecule. In one embodiment, the inhibitor is a soluble ligand (*e.g.*, a CTLA-4-Ig), or an antibody or antibody fragment that binds to PD-L1, PD-L2 or CTLA-4. For example, the anti-TIM-3 antibody molecule can be administered in combination with an anti-CTLA-4 antibody, *e.g.*, ipilimumab, for example, to treat a cancer (*e.g.*, a cancer chosen from: a melanoma, *e.g.*, a metastatic melanoma; a lung cancer, *e.g.*, a non-small cell lung carcinoma; or a prostate cancer). In one embodiment, the anti-TIM-3 antibody molecule is administered after treatment with an anti-CTLA-4 antibody (*e.g.*, ipilimumab) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib).

In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with an anti-TIM-3 antibody or antigen-binding fragment thereof.

In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with an anti-PD-1 antibody or antigen-binding fragment thereof.

In yet other embodiments, the anti-TIM-3 antibody molecule is administered in combination with an anti-TIM-3 antibody and an anti-TIM-3 antibody (or antigen-binding fragments thereof).

In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with a CEACAM inhibitor (*e.g.*, CEACAM-1, -3 and/or -5 inhibitor), *e.g.*, an anti-

CEACAM antibody molecule. In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with a CEACAM-1 inhibitor, *e.g.*, an anti- CEACAM-1 antibody molecule. In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with a CEACAM-3 inhibitor, *e.g.*, an anti- CEACAM-3 antibody molecule. In another embodiment, the anti-TIM-31 antibody molecule is administered in combination with a CEACAM-5 inhibitor, *e.g.*, an anti- CEACAM-5 antibody molecule.

The combination of antibodies recited herein can be administered separately, *e.g.*, as separate antibodies or antigen-binding fragments thereof, or linked, *e.g.*, as a bispecific or trispecific antibody molecule. In one embodiment, a bispecific antibody that includes an anti-TIM-3 antibody molecule and an anti-PD-1, anti-CEACAM (*e.g.*, anti- CEACAM-1, -3 and/or -5), or anti-TIM-3 antibody, or an antigen-binding fragment thereof, is administered. In certain embodiments, the combination of antibodies recited herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor or a hematologic malignancy).

In other embodiments, the anti-TIM-3 antibody molecule is administered in combination with a cytokine. The cytokine can be administered as a fusion molecule to the anti-TIM-3 antibody molecule, or as separate compositions. In one embodiment, the anti-TIM-3 antibody is administered in combination with one, two, three or more cytokines, *e.g.*, as a fusion molecule or as separate compositions. In one embodiment, the cytokine is an interleukin (IL) chosen from one, two, three or more of IL-1, IL-2, IL-12, IL-15 or IL-21. In one embodiment, a bispecific antibody molecule has a first binding specificity to a first target (*e.g.*, to TIM-3), a second binding specificity to a second target (*e.g.*, LAG-3 or PD-1), and is optionally linked to an interleukin (*e.g.*, IL-12) domain *e.g.*, full length IL-12 or a portion thereof. In certain embodiments, the combination of anti-TIM-3 antibody molecule and the cytokine described herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor).

In certain embodiments, the anti-TIM-3 antibody molecule is administered in combination with an antibody specific against an HLA C, *e.g.*, an antibody specific to Killer-cell Immunoglobulin-like Receptors (also referred to herein as an "anti-KIR antibody"). In certain embodiments, the combination of anti-TIM-3 antibody molecule and anti-KIR antibody is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor, *e.g.*, an advanced solid tumor).

In one embodiment, the anti-TIM-3 antibody molecule is administered in combination with a cellular immunotherapy (*e.g.*, Provenge® (*e.g.*, Sipuleucel-T)), and optionally in combination with cyclophosphamide. In certain embodiments, the combination of anti-TIM-3 antibody molecule, Provenge® and/or cyclophosphamide is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a prostate cancer, *e.g.*, an advanced prostate cancer).

In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with a vaccine, *e.g.*, a cancer vaccine, (*e.g.*, a dendritic cell renal carcinoma (DC-RCC) vaccine). In one embodiment, the vaccine is peptide-based, DNA-based, RNA-based, or antigen-based, or a combination thereof. In embodiments, the vaccine comprises one or more peptides, nucleic acids (*e.g.*, DNA or RNA), antigens, or a combination thereof. In certain embodiments, the combination of anti-TIM-3 antibody molecule and the DC-RCC vaccine is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a renal carcinoma, *e.g.*, metastatic renal cell carcinoma (RCC) or clear cell renal cell carcinoma (CCRCC)).

In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with an adjuvant.

In yet another embodiment, the anti-TIM-3 antibody molecule is administered in combination with chemotherapy, and/or immunotherapy. For example, the anti-TIM-3 antibody molecule can be used to treat a myeloma, alone or in combination with one or more of: chemotherapy or other anti-cancer agents (*e.g.*, thalidomide analogs, *e.g.*, lenalidomide), an anti-PD-1 antibody, tumor antigen-pulsed dendritic cells, fusions (*e.g.*, electrofusions) of tumor cells and dendritic cells, or vaccination with immunoglobulin idiotype produced by malignant plasma cells. In one embodiment, the anti-TIM-3 antibody molecule is used in combination with an anti-TIM-3 antibody to treat a myeloma, *e.g.*, a multiple myeloma.

In one embodiment, the anti-TIM-3 antibody molecule is used in combination with chemotherapy to treat a lung cancer, *e.g.*, non-small cell lung cancer. In one embodiment, the anti-TIM-3 antibody molecule is used with standard lung, *e.g.*, NSCLC, chemotherapy, *e.g.*, platinum doublet therapy, to treat lung cancer. In yet other embodiments, the anti-TIM-3 antibody molecule is used in combination with an indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor (*e.g.*, INCB24360) in a subject with advanced or metastatic cancer (*e.g.*, a patient with metastic and recurrent NSCLC cancer).

In yet other embodiments, the anti-TIM-3 antibody molecule is used in combination with one or more of: an immune-based strategy (*e.g.*, interleukin-2 or interferon-α), a targeting agent (*e.g.*, a VEGF inhibitor such as a monoclonal antibody to VEGF); a VEGF tyrosine kinase inhibitor such as sunitinib, sorafenib, axitinib and pazopanib; an RNAi inhibitor; or an inhibitor of a downstream mediator of VEGF signaling, *e.g.*, an inhibitor of the mammalian target of rapamycin (mTOR), *e.g.*, everolimus and temsirolimus. Any of such combinations can be used to treat a renal cancer, *e.g.*, renal cell carcinoma (RCC) (*e.g.,* clear cell renal cell carcinoma (CCRCC)) or metastatic RCC.

In some embodiments, the anti-TIM-3 antibody molecule, *e.g.*, the anti-TIM-3 antibody molecule described herein, is used in combination with a MEK inhibitor (*e.g.*, a MEK inhibitor as described herein). In some embodiments, the combination of the anti-TIM-3 antibody and the MEK inhibitor is used to treat a cancer (*e.g.,* a cancer described herein). In some embodiments, the cancer treated with the combination is chosen from a melanoma, a colorectal cancer, a non-small cell lung cancer, an ovarian cancer, a breast cancer, a prostate cancer, a pancreatic cancer, a hematological malignancy or a renal cell carcinoma. In certain embodiments, the cancer includes a BRAF mutation (*e.g.*, a BRAF V600E mutation), a BRAF wildtype, a KRAS wildtype or an activating KRAS mutation. The cancer may be at an early, intermediate or late stage.

In another embodiment, the anti-TIM-3 antibody molecule is used in combination with one, two or all of oxaliplatin, leucovorin or 5-FU (*e.g.*, a FOLFOX co-treatment). Alternatively or in combination, combination further includes a VEGF inhibitor (*e.g.*, a VEGF inhibitor as disclosed herein). In some embodiments, the combination of the anti-TIM-3 antibody, the FOLFOX co-treatment, and the VEGF inhibitor is used to treat a cancer (*e.g.*, a cancer described herein). In some embodiments, the cancer treated with the combination is chosen from a melanoma, a colorectal cancer, a non-small cell lung cancer, an ovarian cancer, a breast cancer, a prostate cancer, a pancreatic cancer, a hematological malignancy or a renal cell carcinoma. The cancer may be at an early, intermediate or late stage.

In other embodiments, the anti-TIM-3 antibody molecule is administered with a tyrosine kinase inhibitor (*e.g.*, axitinib) to treat renal cell carcinoma and other solid tumors.

In other embodiments, the anti-TIM-3 antibody molecule is administered with a 4-1BB receptor targeting agent (*e.g.*, an antibody that stimulates signaling through 4-1BB (CD-137),

e.g., PF-2566). In one embodiment, the anti-TIM-3 antibody molecule is administered in combination with a tyrosine kinase inhibitor (*e.g.*, axitinib) and a 4-1BB receptor targeting agent.

The anti-TIM-3 antibody molecule can be bound to a substance, *e.g.*, a cytotoxic agent or moiety (*e.g.*, a therapeutic drug; a compound emitting radiation; molecules of plant, fungal, or bacterial origin; or a biological protein (*e.g.*, a protein toxin) or particle (*e.g.*, a recombinant viral particle, *e.g.*, via a viral coat protein). For example, the antibody can be coupled to a radioactive isotope such as an α-, β-, or γ-emitter, or a β-and γ-emitter.

Additional Combination Therapies

The methods and compositions described herein (*e.g.*, anti-TIM-3 antibodies and methods of using them) can be used in combination with other agents or therapeutic modalities, *e.g.*, a second therapeutic agent chosen from one or more of the agents listed in Table 6. In one embodiment, the methods described herein include administering to the subject an anti-TIM-3 antibody molecule as described herein (optionally in combination with one or more inhibitors of PD-1, PD-L1, PD-L2, LAG-3, CEACAM (*e.g.*, CEACAM-1 and/or CEACAM-5), or CTLA-4)), further include administration of a second therapeutic agent chosen from one or more of the agents listed in Table 6, in an amount effective to treat or prevent a disorder, *e.g.*, a disorder as described herein, *e.g.*, a cancer. When administered in combination, the anti-TIM-3 antibody molecule, the additional agent (*e.g.*, second or third agent), or all, can be administered in an amount or dose that is higher, lower or the same than the amount or dosage of each agent used individually, *e.g.*, as a monotherapy. In certain embodiments, the administered amount or dosage of the anti-TIM-3 antibody, the additional agent (*e.g.*, second or third agent), or all, is lower (*e.g.*, at least 20%, at least 30%, at least 40%, or at least 50%) than the amount or dosage of each agent used individually, *e.g.*, as a monotherapy. In other embodiments, the amount or dosage of the anti-TIM-3 antibody, the additional agent (*e.g.*, second or third agent), or all, that results in a desired effect (*e.g.*, treatment of cancer) is lower (*e.g.*, at least 20%, at least 30%, at least 40%, or at least 50% lower).

In other embodiments, the second therapeutic agent is chosen from one or more of the agents listed in Table 6. In one embodiment, the cancer is chosen from a lung cancer (*e.g.*, a non-small cell lung cancer (NSCLC) (*e.g.*, a NSCLC with squamous and/or non-squamous histology, or a NSCLC adenocarcinoma), or disclosed in a publication listed in Table 6. In some

embodiments, the second therapeutic agent is chosen from one or more of: 1) a protein kinase C (PKC) inhibitor; 2) a heat shock protein 90 (HSP90) inhibitor; 3) an inhibitor of a phosphoinositide 3-kinase (PI3K) and/or target of rapamycin (mTOR); 4) an inhibitor of cytochrome P450 (*e.g.*, a CYP17 inhibitor or a 17alpha-Hydroxylase/C17-20 Lyase inhibitor); 5) an iron chelating agent; 6) an aromatase inhibitor; 7) an inhibitor of p53, *e.g.*, an inhibitor of a p53/Mdm2 interaction; 8) an apoptosis inducer; 9) an angiogenesis inhibitor; 10) an aldosterone synthase inhibitor; 11) a smoothened (SMO) receptor inhibitor; 12) a prolactin receptor (PRLR) inhibitor; 13) a Wnt signaling inhibitor; 14) a CDK4/6 inhibitor; 15) a fibroblast growth factor receptor 2 (FGFR2)/fibroblast growth factor receptor 4 (FGFR4) inhibitor; 16) an inhibitor of macrophage colony-stimulating factor (M-CSF); 17) an inhibitor of one or more of c-KIT, histamine release, Flt3 (*e.g.*, FLK2/STK1) or PKC; 18) an inhibitor of one or more of VEGFR-2 (*e.g.*, FLK-1/KDR), PDGFRbeta, c-KIT or Raf kinase C; 19) a somatostatin agonist and/or a growth hormone release inhibitor; 20) an anaplastic lymphoma kinase (ALK) inhibitor; 21) an insulin-like growth factor 1 receptor (IGF-1R) inhibitor; 22) a P-Glycoprotein 1 inhibitor; 23) a vascular endothelial growth factor receptor (VEGFR) inhibitor; 24) a BCR-ABL kinase inhibitor; 25) an FGFR inhibitor; 26) an inhibitor of CYP11B2; 27) a HDM2 inhibitor, *e.g.*, an inhibitor of the HDM2-p53 interaction; 28) an inhibitor of a tyrosine kinase; 29) an inhibitor of c-MET; 30) an inhibitor of JAK; 31) an inhibitor of DAC; 32) an inhibitor of 11β-hydroxylase; 33) an inhibitor of IAP; 34) an inhibitor of PIM kinase; 35) an inhibitor of Porcupine; 36) an inhibitor of BRAF, *e.g.*, BRAF V600E or wild-type BRAF; 37) an inhibitor of HER3; 38) an inhibitor of MEK; or 39) an inhibitor of a lipid kinase, *e.g.*, as described herein and in Table 6.

In one embodiment, the second therapeutic agent is chosen from one or more of: Compound A8, Compound A17, Compound A23, Compound A24, Compound A27, Compound A29, Compound A33, and Compound A13.

In other embodiments, the second therapeutic agent is chosen from one or more of: Compound A5, Compound A8, Compound A17, Compound A23, Compound A24, Compound A29, and Compound A40.

In other embodiments, the second therapeutic agent is chosen from one or more of: Compound A9, Compound A16, Compound A17, Compound A21, Compound A22, Compound A25, Compound 28, Compound A48, and Compound 49.

In other embodiments, the second therapeutic agent is chosen from a modulator of an apoptotic pathway, *e.g.*, an IDH1 inhibitor, or a Bcl-2 or Bcl-XL inhibitor. In one embodiment, the second therapeutic agent is chosen from Compound A21, A14 or a combination thereof. Without being bound by theory, TIM-3 is known to interact with PtdSer, which tends to be exposed on the surface of apoptotic cells, and can cause immunosuppression. Blockade of a PtdSer-TIM-3 interaction, *e.g.*, using an anti-TIM-3 antibody molecule as described herein may ameliorate or overcome the immunosuppression.

In other embodiments, the second therapeutic agent is an inhibitor of CSF-1R, *e.g.*, an anti-CSF-1R antibody or small molecule inhibitor (such as Compound A15 or A33). These second therapeutic agents may inhibit macrophages (*e.g.*, M2 macrophages). In certain embodiments, such second therapeutic agents can facilitate the conversion to M1 macrophages.

In embodiments, the second therapeutic agent is administered at a therapeutic or lower-than therapeutic dose. In certain embodiments, the concentration of the second therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the second therapeutic agent is administered in combination with the anti-TIM-3 antibody molecule than when the second therapeutic agent is administered individually. In certain embodiments, the concentration of the anti-TIM-3 antibody molecule that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the anti-TIM-3 antibody molecule is administered in combination with the second therapeutic agent than when the anti-TIM-3 antibody molecule is administered individually. In certain embodiments, in a combination therapy, the concentration of the second therapeutic agent that is required to achieve inhibition, *e.g.*, growth inhibition, is lower than the therapeutic dose of the second therapeutic agent as a monotherapy, *e.g.*, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower. In certain embodiments, in a combination therapy, the concentration of the anti-TIM-3 antibody molecule that is required to achieve inhibition, *e.g.*, growth inhibition, is lower than the therapeutic dose of the anti-TIM-3 antibody molecule as a monotherapy, *e.g.*, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower.

Detection

In some aspects, the present disclosure provides methods for detecting the presence of TIM-3 in a sample, *e.g.*, *in vitro* or *in vivo* (*e.g.*, a biological sample, *e.g.*, blood, serum, semen or

urine, or a tissue biopsy, *e.g.*, from a hyperproliferative or cancerous lesion). The methods herein can be used to evaluate (*e.g.*, monitor treatment or progression of, diagnose and/or stage a disorder described herein, *e.g.*, an immune disorder, a cancer, or an infectious disease, in a subject). The method may include: (i) contacting the sample with (and optionally, a reference, *e.g.*, a control sample), or administering to the subject, an anti-TIM-3 antibody molecule as described herein, under conditions that allow interaction to occur, and (ii) detecting whether there is formation of a complex between the antibody molecule and the sample (and optionally, the reference, *e.g.*, control, sample). Formation of the complex is indicative of the presence of TIM-3, and can indicate the suitability or need for a treatment described herein. The method can involve, *e.g.*, an immunohistochemistry, immunocytochemistry, flow cytometry, antibody molecule complexed magnetic beads, ELISA assays, PCR-techniques (*e.g.*, RT-PCR).

Typically, the anti-TIM-3 antibody molecule used in the *in vivo* and *in vitro* diagnostic methods is directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound binding agent. Suitable detectable substances include various biologically active enzymes, prosthetic groups, fluorescent materials, luminescent materials, paramagnetic (*e.g.*, nuclear magnetic resonance active) materials, and radioactive materials.

Additional embodiments provide a method of treating a cancer, comprising: identifying in a sample (*e.g.*, a subject's sample comprising cancer cells and optionally immune cells such as TILs) the presence of one, two or all of PD-L1, CD8, or IFN-γ, thereby providing a value for one, two or all of PD-L1, CD8, and IFN-γ. The method can further include comparing the PD-L1, CD8, and/or IFN-γ values to a reference value, *e.g.*, a control value. If the PD-L1, CD8, and/or IFN-γ values are greater than the reference value, *e.g.*, the control values, administering a therapeutically effective amount of an anti-TIM-3 antibody (*e.g.*, an anti-TIM-3 antibody described herein) to the subject, optionally in combination with one or more other agents, thereby treating the cancer. The cancer may be, *e.g.*, a cancer described herein, such as lung cancer (squamous), lung cancer (adenocarcinoma), head and neck cancer, cervical cancer (squamous), stomach cancer, thyroid cancer, melanoma, nasopharyngeal cancer, or breast cancer, *e.g.*, TN breast cancer, *e.g.*, IM-TN breast cancer. In some embodiments, the cancer is ER+ breast cancer or pancreatic cancer.

Also provided is a method of treating a cancer, comprising: testing a sample (*e.g.*, a subject's sample comprising cancer cells) for the presence of PD-L1, thereby identifying a PD-

L1 value, comparing the PD-L1 value to a control value, and if the PD-L1 value is greater than the control value, administering a therapeutically effective amount of an anti-TIM-3 antibody (*e.g.*, an anti-TIM-3 antibody described herein) to the subject, optionally in combination with one or more other agents, *e.g.,* an anti-PD-1 antibody molecule, thereby treating the cancer. The cancer may be, *e.g.*, a cancer as described herein, such as cancer is non-small cell lung (NSCLC) adenocarcinoma (ACA), NSCLC squamous cell carcinoma (SCC), or hepatocellular carcinoma (HCC).

In some aspects, the present disclosure provides diagnostic or therapeutic kits that include the anti-TIM-3 antibody molecules described herein and instructions for use.

The disclosure contemplates all combinations of any one or more of the foregoing aspects and/or embodiments, as well as combinations with any one or more of the embodiments set forth in the detailed description and examples.

Other features, objects, and advantages of the compositions and methods herein will be apparent from the description and drawings, and from the claims.

Figures and Tables are provided herewith.

BRIEF DESCRIPTION OF DRAWINGS

Each of the Figures is described herein in more detail.

Figures 1A-1B depict exemplary anti-TIM-3 antibodies. Figure 1A provides the heavy chain and light chain variable regions of ABTIM3 (SEQ ID NOS: 1 and 2, respectively, in order of appearance). Figure 1B provides a sequence alignment between the variable regions of ABTIM3 and murine (mouse) germline antibodies (SEQ ID NOS: 134 and 135, respectively, in order of appearance). The CDRs are boxed (depicted in white text on a black background in the priority documents).

Figures 2A-2E illustrate the binding and activity of various anti-TIM-3 antibodies. Figure 2A summarizes affinity data for the murine antibody ABTIM3 and another TIM-3 binding antibody. Figure 2B shows a binding curve of one panel of antibodies for human TIM-3 in transfected cells. Figure 2C shows a binding curve of a second panel of antibodies, including ABTIM3 (triangles) for human TIM-3 in transfected cells. Figure 2D shows a binding curve of ABTIM3 and other anti-TIM-3 antibodies for cynomolgus monkey TIM-3. Figure 2E shows the affinity of several anti-TIM-3 antibodies for cynomolgus monkey TIM-3. Monoclonal antibody

ABTIM3 has the highest affinity of the antibodies tested in these experiments, indicating it has good cross-reactivity with human and monkey targets.

Figures 3A-3B show that anti-TIM-3 monoclonal antibodies, includingand ABTIM3, bind to the IgV domain, while 4A4 binds to the mucin domain. Figure 3A illustrates the recombinant construct used for epitope analysis. Figure 3B shows that the anti-TIM-3 monoclonal antibody (anti-TIM-3 #3), and anti-PD-L1 control monoclonal antibodies (anti-PD-L1 #1 and #2), bind to the chimeric protein of Figure 3A, while anti-TIM-3 #2 and ABTIM3 do not substantially bind.

Figure 4 illustrates that anti-TIM-3 antibodies anti-TIM-3 #2 and ABTIM3 block binding of TIM-3 to PtdSer (phosphatidylserine).

Figures 5A-5B illustrate that the anti-TIM-3 antibody ABTIM3 enhances IFN-gamma secretion and proliferation in IL-12 Stimulated CD4+ T Cells. Figure 5A shows the results of a representative experiment where cells were exposed to antibodies ABTIM3, anti-TIM-3 #2, mIgG1, and anti-PD-L1 control antibody (from left to right). IFN-gamma levels were measured by flow cytometry. Figure 5B quantifies IFN-gamma expression in cells exposed to these four antibodies.

Figure 6 shows that a ABTIM3 blockade enhances *in vitro* cytotoxic activity of purified NK cells.

Figure 7 shows that humanized anti-TIM-3 antibodies competed for binding with the parent murine ABTIM3 antibody in a FACS assay.

Figures 8A-8B illustrate that humanized anti-TIM-3 antibodies bind to cells expressing human TIM-3. Figure 8A shows that humanized anti-TIM-3 antibodies bound to cells expressing huTIM-3 in a FACs assay. Figure 8B shows that the humanized anti-TIM-3 antibodies competed with the parental murine ABTIM3 for cells expressing huTIM-3 in a FACS assay.

Figures 9A-9B illustrate the structure of ABTIM3-hum21 Fab binding to TIM-3. Figure 9A shows the overall structure of ABTIM3-hum21 Fab binding to TIM-3. Labeled in the figure are 1) the deduced PtdSer, Ca^{2+} and Galectin-9 binding sites on human TIM-3 and 2) names of the β strands and BC, FG and CC' loops. Figure 9B shows a detailed view of ABTIM3-hum21 epitope residues on TIM-3 (shown as sticks and labeled). Figure 9B discloses residues 56-61 ("GACPVF") as SEQ ID NO: 136 and residues 119-127 ("NDEKFNLKL") as SEQ ID NO: 137.

Figures 10A-10C shows the comparison of ABTIM3-hum21 epitope with CEACAM-1-binding site on human TIM-3. Figure 10A shows the comparison of the crucial CEACAM-1-binding residues of TIM-3 (residues 117-120 ("IMND") disclosed as SEQ ID NO: 138) (left panel, grey surface, residues are labeled) and the ABTIM3-hum21 epitope (right panel, grey surface, residues that overlap with CECAM1-binding site are labeled). Since TIM-3 is oriented the same way in both panels, it is obvious that ABTIM3-hum21 epitope overlaps with CEACAM-1 binding site. Figure 10B shows the K122 of TIM-3 forms hydrogen bond with CEACAM-1 (left panel), and is completed blocked by ABTIM3-hum21 (right panel). Figure 10C shows two-angle views of the superimposition of TIM-3/ ABTIM3-hum21 Fab and TIM-3/CEACAM-1 structures, which shows significant clash between ABTIM3-hum21 and TIM-3, indicating ABTIM3-hum21 will disrupt CEACAM-1 binding to TIM-3.

Figure 11 illustrates the comparison of PtdSer-mediated membrane penetration of moue TIM-3 (left panel) and binding of ABTIM3-hum21 to human TIM-3 (right panel). The two TIM-3 structures are oriented the same way. The attacking angle of ABTIM3-hum21 is similar to the orientation of the membrane penetrated by TIM-3, which suggests that ABTIM3-hum21 will prevent PtdSer-mediated penetration of TIM-3.

Figure 12 shows the cancer indications with the highest expression of TIM-3 (HAVCR2) from the TCGA database.

Figure 13 shows the cancer indications with the highest expression of a macrophage expression signature from the TCGA database.

Figure 14 shows exemplary cancers having relatively high proportions of patients that are triple-positive for PD-L1/CD8/IFN-γ.

Figure 15 shows exemplary ER+ breast cancer and pancreatic cancer having relatively low proportions for patients that are triple positive for PD-L1/CD8/IFN-γ.

Figure 16 shows the proportion of exemplary breast cancer patients that are triple positive for PD-L1/CD8/IFN-γ.

Figure 17 shows the proportion of exemplary colon cancer patients that are triple positive for PD-L1/CD8/IFN-γ.

Figure 18 shows the peptides that are monitored in HDx-MS experiments on the human TIM-3 (residues 23 to 135 ("SEVEYRAEVGQNAYLPCFYTPAAPGNLVPVCWGKGACPVFECGNVVLRTDERDVNY

WTSRYWLNGDFRKGDVSLTIENVTLADSGIYCCRIQIPGIMNDEKFNLKLVIKPAKVT") as SEQ ID NO: 139). Each bar represents a peptide.

Figure 19 illustrates the difference in deuterium uptake for the TIM-3 ABTIM3-hum03 complex (grey bars) and the TIM-3 ABTIM3-hum11 complex (black bars) for amino acids 22 through 127. All differences are relative to the deuterium uptake of unbound TIM-3 (control).

Figure 20 shows the competition between ABTIM3-hum21 and ABTIM3-hum03 and ABTIM3-hum11 for binding to human TIM3, as determined by flow cytometry assay.

Figure 21 shows a representative sensogram from a Biacore competition assay testing the competition between a 1st antibody and a 2nd antibody for immobilized human TIM-3.

Figure 22 shows that ABTIM3 increases proliferation in a co-culture containing dendritic cells and T cells (DC-T co-culture). DC-T co-cultures were incubated with no antibody or a titrated dilution series (0.01-25 μg/mL) of the following antibodies mouse IgG1 (control), ABTIM3 or anti-TIM3 #3 antibody.

Figures 23A-23B show the concentration of ABTIM3-hum11 detected in the serum over time in rodents. The indicated dosages were injected into mice or rats, and the concentration of antibody in the blood was calculated at the indicated time points. Figure 23A shows the mean serum concentration of BTIM3-hum11 in mice after antibody administration. Figure 23B shows the mean serum concentration of ABTIM3-hum11 in rats after antibody administration.

BRIEF DESCRIPTION OF THE TABLES

Each of the Tables is described herein in more detail.

Table 1 summarizes the sequences of the murine anti-TIM-3 antibody, ABTIM3.

Table 2 depicts the amino acid sequences of ABTIM3heavy chain variable domain and light chain variable domain.

Table 3 depicts the amino acid sequences of ABTIM3 heavy chain CDRs and light chain CDRs.

Table 4 is a summary of the amino acid and nucleotide sequences for the murine and humanized anti-TIM-3 antibody molecules. The antibody molecules include murine ABTIM3 and humanized anti-TIM-3 antibodies: ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13,

ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, and ABTIM3-hum23. The amino acid and nucleotide sequences of the heavy and light chain CDRs, the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the amino acid and nucleotide sequences of the heavy and light chains are shown in this Table.

Table 5 depicts the constant region amino acid sequences of human IgG heavy chains and human kappa light chain.

Table 6 is a summary of selected therapeutic agents that can be administered in combination with the anti-TIM-3 antibody molecules and other immunomodulators (*e.g.*, one or more of: an activator of a costimulatory molecule and/or an inhibitor of an immune checkpoint molecule) described herein. **Table 6** provides from left to right the following: the Compound Designation of the second therapeutic agent, the Compound structure, and Patent publication(s) disclosing the Compound.

Table 7 summarizes the K_D values for anti-TIM-3 antibody binding to activated PBMCs.

Table 8 summarizes the K_D values for anti-TIM-3 antibody binding to PD-L1 IgV/TIM-3 mucin construct.

Table 9 summarizes the K_D values for a panel of humanized anti-TIM-3 antibodies as measured by Biacore assay.

Table 10 summarizes the K_D values for anti-TIM-3 antibody binding to cells expressing human TIM-3.

Table 11 summarizes the K_D values for anti-TIM-3 antibody binding to TIM-3-Ig.

Table 12 summarizes the amino acid sequences used for crystal structure determination.

Table 13 summarizes the amino acids in TIM-3 and anti-TIM-3 antibody that participate in the binding interaction.

Table 14 summerizes the Biacore competition assay cycles.

Table 15 summerizes the results from Biacore competition assay.

Table 16 summerizes the pharmacokinetic properties of ABTIM3-hum11.

DETAILED DESCRIPTION

T-cell immunoglobulin domain and mucin domain 3 (TIM-3, also known as Hepatitis A virus cellular receptor 2, and HAVCR2) is a cell surface protein expressed, *e.g.*, on activated

CD4+ and CD8+ T cells, natural regulatory T cells (nTregs), NK cells, and innate cells, *e.g.,* macrophages, monocytes and dendritic cells (DCs). TIM-3 is generally not expressed on naïve T cells, but rather upregulated on activated, effector T cells, *e.g.,* on a PD-1+ subset of cells. TIM-3 is also expressed on tissue site natural regulatory cells and in murine models. TIM-3+ Tregs have been shown to have a more suppressive phenotype while TIM-3+ Tregs have also been shown to correlate with disease severity in NSCLC, hepatocellular and ovarian carcinoma. TIM-3 is constitutively expressed on DCs, monocytes/macrophages and NK cells, and blockade of TIM-3 has been shown to correlate with increased cytotoxicity in NK cells; increased secretion of IL-12/TNF-α by monocytes/macrophages; and increased NF-κB expression in DCs. Blockade of TIM-3 (partially alone and additively or synergistically in combination with PD-1 pathway blockade) has shown anti-tumor efficacy in several preclinical cancer models, including CT26 colon carcinoma (Sakuishi et al., *J Exp Med.* 2010; 207(10):2187-94), WT3 sarcoma and TRAMP-C1 prostate carcinoma (Ngiow et al., *Cancer Res.* 2011; 71(10):3540-3551). Recent studies have highlighted TIM-3 as an important player in the T effector cell exhaustion and suppression that takes place in chronic immune conditions such as infection, *e.g.*, bacterial or viral, and cancer in both humans and experimental models. TIM-3 has been described as an inhibitory receptor in the immunological synapse, and blocking of TIM-3 may enhance immune response against infection and cancer.

Blockade of TIM-3 has been shown to restore activity in effector cells, such as cytokine secretion and proliferation. In virally exhausted cell populations, *e.g.*, cells infected with HCV, TIM-3-expressing cells (TIM3+ cells) express less TNF-alpha and IFN-gamma cytokines than TIM-3 negative cells in both effector cell populations, CD4+ and CD8+ T cells (Golden-Mason et al., 2009, *J. Virol*, 83:9122). Blockade of TIM-3 restores proliferation in CD8+ T cells from an HIV patient, or in cells that recapitulate viral exhaustion (Jones et al., 2008, *J. Exp. Med.*, 205:2763), or proliferation and IFN-γ and/or TNF-α secretion in NY-ESO-1 specific T cells from PBMCs from metastatic patients (Fourcade et al., 2010, *J. Exp. Med.*, 207:2175). TIM-3 blockade may also diminish the suppressor activity of regulatory T cells. TIM-3+ T cells have been found to be concentrated in tumors, and contribute to the immunosuppressive tumor environment (Sakuishi et al., 2013, *Oncoimmunology*, 2:e23849; Gao et al., 2012, *Plos One*; and Yan et al., 2013, *Plos One*.). Thus, blockade of TIM-3, *e.g.*, by antibodies that inhibit TIM-3 function, can improve the immune response against infection and anti-tumor immunity.

TIM-3 has also been implicated in regulating immune response through macrophage activity. Blockade of TIM-3 leads to an increase in TLR-mediated IL-12 production (Zhang et al., 2010, *J Leukoc Biol*, 91:189). Thus, TIM-3 blockade may increase immune stimulation properties of macrophages to enhance immune response against infection and anti-tumor activity.

TIM-3 has five reported ligands: Galectin-9 (Gal-9), phosphatidylserine (PtdSer), HMGB1, Semaphorin-4A, and CEACAM-1. S-type lectin galectin-9 can inhibit TIM-3-associated Th1 effector function and induce apoptosis on TIM-3-expressing T cells in murine models. PtdSer usually resides on the intracellular side of the plasma membrane, but is flipped to the extracellular side during apoptosis. PtdSer binds a preserved cleft in all three human TIM family members (TIM-1, 3, 4). Inhibition of PtdSer binding to TIM-3 may activate T-cell response. Galectin-9 is secreted by tumor cells and can contribute to evasion from anti-tumor immunity. DNA alarmin HMGB1, for which TIM-3 may act as a "sink," can prevent the HMGB1/RAGE interactions that stimulate innate immunity. Semaphorin-4A and CEACAM-1 (another immune checkpoint molecule whose inhibition can enhance immune response) can interact with TIM-3 both in *cis* as a heterodimer on T cells and in *trans* as a ligand. Interaction between CEACAM-1 and TIM-3 may help mediate block immune response signaling. Co-blockade of TIM-3 and CEACAM-1 in CT26 colon carcinoma showed similar efficacy to that seen for co-blockade of PD-L1 and TIM-3.

The TIM-3 cytoplasmic tail has seven sites for tyrosine phosphorylation and no known inhibitory (*i.e.,* ITIM) motifs, which suggests that TIM-3 could co-stimulate with the T cell receptor, leading to functional exhaustion through increased T cell signaling. TIM-3 can interact with Fyn and facilitate accumulation of receptor phosphatases CD148 and CD45 at the immunologic synapse. The presence of CEACAM-1 as a co-receptor in the TIM-3/CEACAM-1 heterodimer suggests that this co-expression may lead to inhibitory signaling in T cells via the ITIM motif in the CEACAM-1 cytoplasmic tail which has been shown to interact with both SHP1 and SHP2.

Disclosed herein are antibody molecules that bind to TIM-3 with high affinity and specificity. In one embodiment, humanized antibodies against TIM-3 are disclosed. Additional aspects of the invention include nucleic acid molecules encoding the antibody molecules, expression vectors, host cells and methods for making the antibody molecules are also provided. Immunoconjugates, multi- or bispecific antibody molecules and pharmaceutical compositions

comprising the antibody molecules are also provided. The anti-TIM-3 antibody molecules disclosed herein can be used (alone or in combination with other agents or therapeutic modalities) to treat, prevent and/or diagnose immune disorders, cancer, infectious disease, Crohn's disease, sepsis, SIRS (Systemic Inflammatory Response Syndrome), and glomerulonephritis. Thus, compositions and methods for detecting TIM-3, as well as methods for treating various disorders, including cancer and immune disorders using the anti-TIM-3 antibody molecules are disclosed herein.

The term "TIM-3" include isoforms, mammalian, *e.g.*, human TIM-3, species homologs of human TIM-3, and analogs comprising at least one common epitope with TIM-3. The amino acid sequence of TIM-3, e.g, human TIM-3, is known in the art, *e.g.*, Sabatos et al., 2003. *Nat Immunol*, 4(11):1102.

Definitions

As used herein, the articles "a" and "an" refer to one or to more than one (*e.g.*, to at least one) of the grammatical object of the article.

The term "or" is used herein to mean, and is used interchangeably with, the term "and/or", unless context clearly indicates otherwise.

"About" and "approximately" shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.

The compositions and methods disclosed herein encompass polypeptides and nucleic acids having the sequences specified, or sequences substantially identical or similar thereto, *e.g.*, sequences at least 85%, 90%, 95% identical or higher to the sequence specified. In the context of an amino acid sequence, the term "substantially identical" is used herein to refer to a first amino acid that contains a sufficient or minimum number of amino acid residues that are i) identical to, or ii) conservative substitutions of aligned amino acid residues in a second amino acid sequence such that the first and second amino acid sequences can have a common structural domain and/or common functional activity. For example, amino acid sequences that contain a common structural domain having at least about 85%, 90%. 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, *e.g.*, a sequence provided herein.

In the context of nucleotide sequence, the term "substantially identical" is used herein to refer to a first nucleic acid sequence that contains a sufficient or minimum number of nucleotides that are identical to aligned nucleotides in a second nucleic acid sequence such that the first and second nucleotide sequences encode a polypeptide having common functional activity, or encode a common structural polypeptide domain or a common functional polypeptide activity. For example, nucleotide sequences having at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, *e.g.*, a sequence provided herein.

The term "functional variant" refers polypeptides that have a substantially identical amino acid sequence to the naturally-occurring sequence, or are encoded by a substantially identical nucleotide sequence, and are capable of having one or more activities of the naturally-occurring sequence.

To determine the percent identity of two amino acid sequences, or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, *e.g.*, at least 40%, 50%, 60%, *e.g.*, at least 70%, 80%, 90%, 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position.

The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a some embodiments, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch ((1970) *J. Mol. Biol.* 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In certain embodiments, the percent identity between two

nucleotide sequences is determined using the GAP program in the GCG software package (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. One suitable set of parameters (and the one that should be used unless otherwise specified) are a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

The percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of E. Meyers and W. Miller ((1989) CABIOS, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences described herein can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid as described herein. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to protein molecules described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See www.ncbi.nlm.nih.gov.

As used herein, the term "hybridizes under low stringency, medium stringency, high stringency, or very high stringency conditions" describes conditions for hybridization and washing. Guidance for performing hybridization reactions can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6, which is incorporated by reference. Aqueous and nonaqueous methods are described in that reference and either can be used. Specific hybridization conditions referred to herein are as follows: 1) low stringency hybridization conditions in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by two washes in 0.2X SSC, 0.1% SDS at least at 50°C (the temperature of the washes can be increased to 55°C for low stringency conditions); 2) medium stringency hybridization conditions in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 60°C; 3)

high stringency hybridization conditions in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C; and preferably 4) very high stringency hybridization conditions are 0.5M sodium phosphate, 7% SDS at 65°C, followed by one or more washes at 0.2X SSC, 1% SDS at 65°C. Very high stringency conditions (4) are suitable conditions and the ones that should be used unless otherwise specified.

It is understood that the molecules described herein may have additional conservative or non-essential amino acid substitutions, which do not have a substantial effect on their functions.

A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine).

The terms "polypeptide", "peptide" and "protein" (if single chain) are used interchangeably herein.

The terms "nucleic acid," "nucleic acid sequence," "nucleotide sequence," or "polynucleotide sequence," and "polynucleotide" are used interchangeably.

The term "isolated," as used herein, refers to material that is removed from its original or native environment (*e.g.*, the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or polypeptide, separated by human intervention from some or all of the co-existing materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature.

Various aspects of the compositions and methods herein are described in further detail below. Additional definitions are set out throughout the specification.

Antibody Molecules

In some embodiments, the antibody molecule binds to a mammalian, *e.g.*, human, TIM-3. For example, the antibody molecule binds specifically to an epitope, *e.g.*, linear or conformational epitope, (*e.g.*, an epitope as described herein) on TIM-3. In some embodiments, the epitope is at least a portion of the IgV domain of human or cynomolgus TIM-3.

As used herein, the term "antibody molecule" refers to a protein, *e.g.*, an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. The term “antibody molecule” includes, for example, a monoclonal antibody (including a full length antibody which has an immunoglobulin Fc region). In an embodiment, an antibody molecule comprises a full length antibody, or a full length immunoglobulin chain. In an embodiment, an antibody molecule comprises an antigen bindng or functional fragment of a full length antibody, or a full length immunoglobulin chain.

In an embodiment, an antibody molecule is a monospecific antibody molecule and binds a single epitope. *E.g.*, a monospecific antibody molecule having a plurality of immunoglobulin variable domain sequences, each of which binds the same or substantially the same epitope.

In an embodiment, an antibody molecule is a multispecific antibody molecule, *e.g.*, it comprises a plurality of immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment, the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap or substantially overlap. In an embodiment, the first and second epitopes do not overlap or do not substantially overlop. In an embodiment, the first and second epitopes are on different antigens, *e.g.*, the different proteins (or different subunits of a multimeric protein). In an embodiment, a multispecific antibody molecule comprises a third, fourth or fifth immunoglobulin variable domain. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule, a trispecific antibody molecule, or tetraspecific antibody molecule,

In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has

binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In an embodiment, the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In an embodiment, the first and second epitopes overlap or substantially overlap. In an embodiment the first and second epitopes do not overlap or do not substantially overlap. In an embodiment the first and second epitopes are on different antigens, *e.g.*, the different proteins (or different subunits of a multimeric protein). In an embodiment a bispecific antibody molecule comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In an embodiment, a bispecific antibody molecule comprises a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In an embodiment, a bispecific antibody molecule comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a scFv, or fragment thereof, have binding specificity for a first epitope and a scFv, or fragment thereof, have binding specificity for a second epitope. In an embodiment the first epitope is located on TIM-3 and the second epitope is located on a PD-1, LAG-3, CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), PD-L1, or PD-L2.

In an embodiment, an antibody molecule comprises a diabody, and a single-chain molecule, as well as an antigen-binding fragment of an antibody (*e.g.*, Fab, F(ab')$_2$, and Fv). For example, an antibody molecule can include a heavy (H) chain variable domain sequence (abbreviated herein as VH), and a light (L) chain variable domain sequence (abbreviated herein as VL). In an embodiment an antibody molecule comprises or consists of a heavy chain and a light chain (referred to herein as a half antibody. In another example, an antibody molecule includes two heavy (H) chain variable domain sequences and two light (L) chain variable domain sequence, thereby forming two antigen binding sites, such as Fab, Fab', F(ab')$_2$, Fc, Fd, Fd', Fv, single chain antibodies (scFv for example), single variable domain antibodies, diabodies (Dab) (bivalent and bispecific), and chimeric (*e.g.*, humanized) antibodies, which may be produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. These functional antibody fragments retain the ability to selectively bind with their

respective antigen or receptor. Antibodies and antibody fragments can be from any class of antibodies including, but not limited to, IgG, IgA, IgM, IgD, and IgE, and from any subclass (*e.g.*, IgG1, IgG2, IgG3, and IgG4) of antibodies. The preparation of antibody molecules can be monoclonal or polyclonal. An antibodymolecule can also be a human, humanized, CDR-grafted, or *in vitro* generated antibody. The antibody can have a heavy chain constant region chosen from, *e.g.*, IgG1, IgG2, IgG3, or IgG4. The antibody can also have a light chain chosen from, *e.g.*, kappa or lambda. The term "immunoglobulin" (Ig) is used interchangeably with the term "antibody" herein.

Examples of antigen-binding fragments of an antibody molecule include: (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a diabody (dAb) fragment, which consists of a VH domain; (vi) a camelid or camelized variable domain; (vii) a single chain Fv (scFv), see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883); (viii) a single domain antibody. These antibody fragments may be obtained using any suitable method, including several conventional techniques known to those with skill in the art, and the fragments can be screened for utility in the same manner as are intact antibodies.

The term "antibody" includes intact molecules as well as functional fragments thereof. Constant regions of the antibodies can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function).

The antibodies disclosed herein can also be single domain antibodies. Single domain antibodies can include antibodies whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, fish, shark, goat, rabbit, and bovine. According to some aspects,

a single domain antibody is a naturally occurring single domain antibody known as heavy chain antibody devoid of light chains. Such single domain antibodies are disclosed in WO 9404678, for example. For clarity reasons, this variable domain derived from a heavy chain antibody naturally devoid of light chain is known herein as a VHH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VHH molecule can be derived from antibodies raised in *Camelidae* species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides *Camelidae* may produce heavy chain antibodies naturally devoid of light chain; such VHHs are also contemplated.

The VH and VL regions can be subdivided into regions of hypervariability, termed "complementarity determining regions" (CDR), interspersed with regions that are more conserved, termed "framework regions" (FR). The extent of the framework region and CDRs has been precisely defined by a number of methods (see, Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia, C. et al. (1987) *J. Mol. Biol.* 196:901-917; and the AbM definition used by Oxford Molecular's AbM antibody modeling software. See, generally, *e.g.*, Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Antibody Engineering Lab Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg). In some embodiments, the following definitions are used: AbM definition of CDR1 of the heavy chain variable domain and Kabat definitions for the other CDRs. In certain embodiments, Kabat definitions are used for all CDRs. In addition, embodiments described with respect to Kabat or AbM CDRs may also be implemented using Chothia hypervariable loops. Each VH and VL typically includes three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

As used herein, an "immunoglobulin variable domain sequence" refers to an amino acid sequence which can form the structure of an immunoglobulin variable domain. For example, the sequence may include all or part of the amino acid sequence of a naturally-occurring variable domain. For example, the sequence may or may not include one, two, or more N- or C-terminal amino acids, or may include other alterations that are compatible with formation of the protein structure.

The term "antigen-binding site" refers to the part of an antibody molecule that comprises determinants that form an interface that binds to a TIM-3 polypeptide, or an epitope thereof.

With respect to proteins (or protein mimetics), the antigen-binding site typically includes one or more loops (of at least, *e.g.*, four amino acids or amino acid mimics) that form an interface that binds to the TIM-3 polypeptide. Typically, the antigen-binding site of an antibody molecule includes at least one or two CDRs, or more typically at least three, four, five or six CDRs.

The terms "compete" or "cross-compete" are used interchangeably herein to refer to the ability of an antibody molecule to interfere with binding of an anti-TIM-3 antibody molecule, *e.g.,* an anti-TIM-3 antibody molecule provided herein, to a target, *e.g.,* human TIM-3. The interference with binding can be direct or indirect (*e.g.,* through an allosteric modulation of the antibody molecule or the target). The extent to which an antibody molecule is able to interfere with the binding of another antibody molecule to the target, and therefore whether it can be said to compete, can be determined using a competition binding assay, for example, a FACS assay, an ELISA or BIACORE assay. In some embodiments, a competition binding assay is a quantitative competition assay. In some embodiments, a first anti-TIM-3 antibody molecule is said to compete for binding to the target with a second anti-TIM-3 antibody molecule when the binding of the first antibody molecule to the target is reduced by 10% or more, *e.g.,* 20% or more, 30% or more, 40% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, 99% or more in a competition binding assay (*e.g.,* a competition assay described herein).

As used herein, the term "epitope" refers to the moieties of an antigen (*e.g.,* human TIM-3) that specifically interact with an antibody molecule. Such moieties, referred to herein as epitopic determinants, typically comprise, or are part of, elements such as amino acid side chains or sugar side chains. An epitopic determinate can be defined by methods known in the art or disclosed herein, *e.g.,* by crystallography or by hydrogen-deuterium exchange. At least one or some of the moieties on the antibody molecule, that specifically interact with an epitopic determinant, are typically located in a CDR(s). Typically an epitope has a specific three dimensional structural characteristics. Typically an epitope has specific charge characteristics. Some epitopes are linear epitopes while others are conformational epitopes.

In an embodiment, an epitopic determinant is a moiety on the antigen, *e.g.,* such as amino acid side chain or sugar side chain, or part thereof, which, when the antigen and antibody molecule are co-crystallized, is within a predetermined distance, *e.g.,* within 5 Angstroms, of a moiety on the antibody molecule, referred to herein as a "crystallographic epitopic determinant."

The crystallographic epitopic determinants of an epitope are collectively refered to as the "crystallographic epitope."

A first antibody molecule binds the same epitope as a second antibody molecule (*e.g.*, a reference antibody molecule, *e.g.*, an antibody molecule disclosed herein, *e.g.*, ABTIM3-hum21, ABTIM-hum11 or ABTIM3-hum03) if the first antibody specifically interacts with the same epitopic determinants on the antigen as does the second or reference antibody, *e.g.*, when interaction is measured in the same way for both the antibody and the second or reference antibody. Epitopes that overlap share at least one epitopic determinant. A first antibody molecule binds an overlapping epitope with a second antibody molecule (*e.g.*, a reference antibody molecule, *e.g.*, an antibody disclosed herein, *e.g.*, ABTIM3-hum21, ABTIM-hum11 or ABTIM3-hum03) when both antibody molecules specifically interact with a common epitopic determinant. A first and a second antibody molecule (*e.g.*, a reference antibody moleucle, *e.g.*, an antibody moluecule disclosed herein, *e.g.*, ABTIM3-hum21, ABTIM-hum11 or ABTIM3-hum03) bind substantially overlapping epitopes if at least half of the epitopic determinants of the second or reference antibody are found as epitopic determinants in the epitope of the first antibody. A first and a second antibody molecule (*e.g.*, a reference antibody molecule, *e.g.*, an antibody molecule disclosed herein, *e.g.*, ABTIM3-hum21, ABTIM-hum11 or ABTIM3-hum03) bind substantially the same epitope if the first antibody molecule binds at least half of the core epitopic determinants of the epitope of the second or reference antibody, wherein the core epitopic determinants are defined by crystallography and hydrogen-deuterium exchange, *e.g.*, including residues Val24, Glu25, Thr41, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, Leu127, Val128, Gly56, Ala57, Cys58, Pro59, Val60, and Phe61 of human TIM-3.

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. A monoclonal antibody can be made by hybridoma technology or by methods that do not use hybridoma technology (*e.g.*, recombinant methods).

An "effectively human" protein is a protein that does not evoke a neutralizing antibody response, *e.g.*, the human anti-murine antibody (HAMA) response. HAMA can be problematic in a number of circumstances, *e.g.*, if the antibody molecule is administered repeatedly, *e.g.*, in treatment of a chronic or recurrent disease condition. A HAMA response can make repeated

antibody administration potentially ineffective because of an increased antibody clearance from the serum (see, *e.g.*, Saleh et al., *Cancer Immunol. Immunother.*, 32:180-190 (1990)) and also because of potential allergic reactions (see, *e.g.*, LoBuglio et al., *Hybridoma*, 5:5117-5123 (1986)).

The antibody molecule can be a polyclonal or a monoclonal antibody. In other embodiments, the antibody can be recombinantly produced, *e.g.*, produced by any suitable phage display or combinatorial methods.

Various phage display and combinatorial methods for generating antibodies are known in the art (as described in, *e.g.*, Ladner et al. U.S. Patent No. 5,223,409; Kang et al. International Publication No. WO 92/18619; Dower et al. International Publication No. WO 91/17271; Winter et al. International Publication WO 92/20791; Markland et al. International Publication No. WO 92/15679; Breitling et al. International Publication WO 93/01288; McCafferty et al. International Publication No. WO 92/01047; Garrard et al. International Publication No. WO 92/09690; Ladner et al. International Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum Antibod Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; Griffths et al. (1993) *EMBO J* 12:725-734; Hawkins et al. (1992) *J Mol Biol* 226:889-896; Clackson et al. (1991) *Nature* 352:624-628; Gram et al. (1992) *PNAS* 89:3576-3580; Garrad et al. (1991) *Bio/Technology* 9:1373-1377; Hoogenboom et al. (1991) *Nuc Acid Res* 19:4133-4137; and Barbas et al. (1991) *PNAS* 88:7978-7982, the contents of all of which are incorporated by reference herein).

In some embodiments, the antibody is a fully human antibody (*e.g.*, an antibody made in a mouse which has been genetically engineered to produce an antibody from a human immunoglobulin sequence), or a non-human antibody, *e.g.*, a rodent (mouse or rat), goat, primate (*e.g.*, monkey), camel antibody. In certain embodiments, the non-human antibody is a rodent (mouse or rat antibody). Methods of producing rodent antibodies are known in the art.

Human monoclonal antibodies can be generated using transgenic mice carrying the human immunoglobulin genes rather than the mouse system. Splenocytes from these transgenic mice immunized with the antigen of interest are used to produce hybridomas that secrete human mAbs with specific affinities for epitopes from a human protein (see, *e.g.*, Wood et al. International Application WO 91/00906, Kucherlapati et al. PCT publication WO 91/10741; Lonberg et al. International Application WO 92/03918; Kay et al. International Application

92/03917; Lonberg, N. et al. 1994 *Nature* 368:856-859; Green, L.L. et al. 1994 *Nature Genet.* 7:13-21; Morrison, S.L. et al. 1994 *Proc. Natl. Acad. Sci. USA* 81:6851-6855; Bruggeman et al. 1993 *Year Immunol* 7:33-40; Tuaillon et al. 1993 *PNAS* 90:3720-3724; Bruggeman et al. 1991 *Eur J Immunol* 21:1323-1326).

An antibody can be one in which the variable region, or a portion thereof, *e.g.*, the CDRs, are generated in a non-human organism, *e.g.*, a rat or mouse. Chimeric, CDR-grafted, and humanized antibodies are also contemplated. Antibodies generated in a non-human organism, *e.g.*, a rat or mouse, and then modified, *e.g.*, in the variable framework or constant region, to decrease antigenicity in a human are also contemplated.

Chimeric antibodies can be produced by any suitable recombinant DNA technique. Several are known in the art (see Robinson et al., International Patent Publication PCT/US86/02269; Akira, et al., European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison et al., European Patent Application 173,494; Neuberger *et al.*, International Application WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567; Cabilly et al., European Patent Application 125,023; Better *et al.* (1988 *Science* 240:1041-1043); Liu et al. (1987) *PNAS* 84:3439-3443; Liu *et al.*, 1987, *J. Immunol.* 139:3521-3526; Sun et al. (1987) *PNAS* 84:214-218; Nishimura *et al.*, 1987, *Canc. Res.* 47:999-1005; Wood et al. (1985) *Nature* 314:446-449; and Shaw *et al.*, 1988, *J. Natl Cancer Inst.* 80:1553-1559).

A humanized or CDR-grafted antibody will have at least one or two but generally all three recipient CDRs (of heavy and or light immunoglobulin chains) replaced with a donor CDR. The antibody may be replaced with at least a portion of a non-human CDR or only some of the CDRs may be replaced with non-human CDRs. It is only necessary to replace the number of CDRs required for binding of the humanized antibody to TIM-3. In some embodiments, the donor will be a rodent antibody, *e.g.*, a rat or mouse antibody, and the recipient will be a human framework or a human consensus framework. Typically, the immunoglobulin providing the CDRs is called the "donor" and the immunoglobulin providing the framework is called the "acceptor." In some embodiments, the donor immunoglobulin is a non-human (*e.g.*, rodent). The acceptor framework is typically a naturally-occurring (*e.g.*, a human) framework or a consensus framework, or a sequence about 85% or higher, *e.g.*, 90%, 95%, 99% or higher identical thereto.

As used herein, the term "consensus sequence" refers to the sequence formed from the most frequently occurring amino acids (or nucleotides) in a family of related sequences (See *e.g.*, Winnaker, From Genes to Clones (Verlagsgesellschaft, Weinheim, Germany 1987). In a family of proteins, each position in the consensus sequence is occupied by the amino acid occurring most frequently at that position in the family. If two amino acids occur equally frequently, either can be included in the consensus sequence. A "consensus framework" refers to the framework region in the consensus immunoglobulin sequence.

An antibody can be humanized by any suitable method, and several such methods known in the art (see *e.g.*, Morrison, S. L., 1985, *Science* 229:1202-1207, by Oi et al., 1986, *BioTechniques* 4:214, and by Queen et al. US 5,585,089, US 5,693,761 and US 5,693,762, the contents of all of which are hereby incorporated by reference).

Humanized or CDR-grafted antibodies can be produced by CDR-grafting or CDR substitution, wherein one, two, or all CDRs of an immunoglobulin chain can be replaced. *See e.g.*, U.S. Patent 5,225,539; Jones et al. 1986 *Nature* 321:552-525; Verhoeyan et al. 1988 *Science* 239:1534; Beidler et al. 1988 *J. Immunol.* 141:4053-4060; Winter US 5,225,539, the contents of all of which are hereby expressly incorporated by reference. Winter describes a CDR-grafting method which may be used to prepare humanized antibodies (UK Patent Application GB 2188638A, filed on March 26, 1987; Winter US 5,225,539), the contents of which is expressly incorporated by reference.

Also provided are humanized antibodies in which specific amino acids have been substituted, deleted or added. Criteria for selecting amino acids from the donor are described in, *e.g.*, US 5,585,089, *e.g.*, columns 12-16 of US 5,585,089, the contents of which are hereby incorporated by reference. Other techniques for humanizing antibodies are described in Padlan et al. EP 519596 A1, published on December 23, 1992.

The antibody molecule can be a single chain antibody. A single-chain antibody (scFV) may be engineered (see, for example, Colcher, D. *et al.* (1999) *Ann N Y Acad Sci* 880:263-80; and Reiter, Y. (1996) *Clin Cancer Res* 2:245-52). The single chain antibody can be dimerized or multimerized to generate multivalent antibodies having specificities for different epitopes of the same target protein.

In some embodiments, the antibody molecule has a heavy chain constant region chosen from, *e.g.*, the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD,

and IgE; particularly, chosen from, *e.g.*, the (*e.g.*, human) heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4. In another embodiment, the antibody molecule has a light chain constant region chosen from, *e.g.*, the (*e.g.*, human) light chain constant regions of kappa or lambda. The constant region can be altered, *e.g.*, mutated, to modify the properties of the antibody (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, and/or complement function). In some embodiments the antibody has effector function and can fix complement. In other embodiments the antibody does not recruit effector cells or fix complement. In certain embodiments, the antibody has reduced or no ability to bind an Fc receptor. For example, it may be an isotype or subtype, fragment or other mutant, which does not support binding to an Fc receptor, *e.g.*, it has a mutagenized or deleted Fc receptor binding region.

The antibody constant region is altered in some embodiments. Methods for altering an antibody constant region are known in the art. Antibodies with altered function, *e.g.* altered affinity for an effector ligand, such as FcR on a cell, or the C1 component of complement can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (see *e.g.*, EP 388,151 A1, U.S. Pat. No. 5,624,821 and U.S. Pat. No. 5,648,260, the contents of all of which are hereby incorporated by reference). Amino acid mutations which stabilize antibody structure, such as S228P (EU nomenclature, S241P in Kabat nomenclature) in human IgG4 are also contemplated. Similar type of alterations could be described which if applied to the murine, or other species immunoglobulin would reduce or eliminate these functions.

In some embodiments, the only amino acids in the anti-TIM-3 antibody molecule are canonical amino acids. In some embodiments, the anti-TIM-3 antibody molecule comprises naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains; and/or all stereoisomers of any of any of the foregoing. The anti-TIM-3 antibody molecule may comprise the D- or L- optical isomers of amino acids and peptidomimetics.

A polypeptide of an anti-TIM-3 antibody molecule may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The antibody molecule may also be modified; for example, by disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a

labeling component. The polypeptide can be isolated from natural sources, can be a produced by recombinant techniques from a eukaryotic or prokaryotic host, or can be a product of synthetic procedures.

An antibody molecule can be derivatized or linked to another functional molecule (*e.g.*, another peptide or protein). As used herein, a "derivatized" antibody molecule is one that has been modified. Methods of derivatization include but are not limited to the addition of a fluorescent moiety, a radionucleotide, a toxin, an enzyme or an affinity ligand such as biotin. Accordingly, the antibody molecules are intended to include derivatized and otherwise modified forms of the antibodies described herein, including immunoadhesion molecules. For example, an antibody molecule can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (*e.g.*, a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

Some types of derivatized antibody molecule are produced by crosslinking two or more antibodies (of the same type or of different types, *e.g.*, to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (*e.g.*, m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (*e.g.*, disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

Useful detectable agents with which an anti-TIM-3 antibody molecule may be derivatized (or labeled) to include fluorescent compounds, various enzymes, prosthetic groups, luminescent materials, bioluminescent materials, fluorescent emitting metal atoms, *e.g.*, europium (Eu), and other anthanides, and radioactive materials (described below). Exemplary fluorescent detectable agents include fluorescein, fluorescein isothiocyanate, rhodamine, 5dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin and the like. An antibody may also be derivatized with detectable enzymes, such as alkaline phosphatase, horseradish peroxidase, β-galactosidase, acetylcholinesterase, glucose oxidase and the like. When an antibody is derivatized with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a detectable reaction product. For example, when the detectable agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction

product, which is detectable. An antibody molecule may also be derivatized with a prosthetic group (*e.g.*, streptavidin/biotin and avidin/biotin). For example, an antibody may be derivatized with biotin, and detected through indirect measurement of avidin or streptavidin binding. Examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; and examples of bioluminescent materials include luciferase, luciferin, and aequorin.

Labeled antibody molecule can be used, for example, diagnostically and/or experimentally in a number of contexts, including (i) to isolate a predetermined antigen by standard techniques, such as affinity chromatography or immunoprecipitation; (ii) to detect a predetermined antigen (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the protein; (iii) to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to determine the efficacy of a given treatment regimen.

An antibody molecule may be conjugated to another molecular entity, typically a label or a therapeutic (*e.g.*, immunomodulatory, immunostimularoty, cytotoxic, or cytostatic) agent or moiety. Radioactive isotopes can be used in diagnostic or therapeutic applications. Radioactive isotopes that can be coupled to the anti-TIM-3 antibodies include, but are not limited to α-, β-, or γ-emitters, or β-and γ-emitters. Such radioactive isotopes include, but are not limited to iodine (^{131}I or ^{125}I), yttrium (^{90} Y), lutetium (^{177}Lu), actinium (^{225}Ac), praseodymium, astatine (^{211}At), rhenium (^{186}Re), bismuth (^{212}Bi or ^{213}Bi), indium (^{111}In), technetium (^{99} mTc), phosphorus (^{32}P), rhodium (^{188}Rh), sulfur (^{35}S) , carbon (^{14}C), tritium (^{3}H), chromium (^{51}Cr), chlorine (^{36}Cl), cobalt (^{57}Co or ^{58}Co), iron (^{59}Fe), selenium (^{75}Se), or gallium (^{67}Ga). Radioisotopes useful as therapeutic agents include yttrium (^{90}Y), lutetium (^{177} Lu), actinium (^{225}Ac), praseodymium, astatine (^{211}At), rhenium (^{186}Re), bismuth (^{212} Bi or ^{213}Bi), and rhodium (^{188}Rh). Radioisotopes useful as labels, *e.g.*, for use in diagnostics, include iodine (^{131}I or ^{125}I), indium (^{111}In), technetium (^{99}mTc), phosphorus (^{32}P), carbon (^{14}C), and tritium (^{3} H), or one or more of the therapeutic isotopes listed above.

The present disclosure provides radiolabeled antibody molecules and methods of labeling the same. In some embodiments, a method of labeling an antibody molecule is disclosed. The method includes contacting an antibody molecule, with a chelating agent, to thereby produce a

conjugated antibody. The conjugated antibody is radiolabeled with a radioisotope, *e.g.*, ^{111}Indium, ^{90}Yttrium and ^{177}Lutetium, to thereby produce a labeled antibody molecule.

As is discussed above, the antibody molecule can be conjugated to a therapeutic agent. Therapeutically active radioisotopes have already been mentioned. Examples of other therapeutic agents include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, maytansinoids, *e.g.*, maytansinol (see U.S. Pat. No. 5,208,020), CC-1065 (see U.S. Pat. Nos. 5,475,092, 5,585,499, 5,846, 545) and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, CC-1065, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclinies (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine, vinblastine, taxol and maytansinoids).

In some aspects, this disclosure provides a method of providing a target binding molecule that specifically binds to a TIM-3 receptor. For example, the target binding molecule is an antibody molecule. The method includes: providing a target protein that comprises at least a portion of non-human protein, the portion being homologous to (at least 70, 75, 80, 85, 87, 90, 92, 94, 95, 96, 97, 98, or 99% identical to) a corresponding portion of a human target protein, but differing by at least one amino acid (*e.g.*, at least one, two, three, four, five, six, seven, eight, or nine amino acids); obtaining an antibody molecule that specifically binds to the antigen; and evaluating efficacy of the binding agent in modulating activity of the target protein. The method can further include administering the binding agent (*e.g.*, antibody molecule) or a derivative (*e.g.*, a humanized antibody molecule) to a human subject.

In certain embodiments, the antibody molecule is a multi-specific (*e.g.*, a bispecific or a trispecific) antibody molecule. Protocols for generating bispecific or heterodimeric antibody molecules are known in the art; including but not limited to, for example, the "knob in a hole"

approach described in, *e.g.*, US 5731168; the electrostatic steering Fc pairing as described in, *e.g.*, WO 09/089004, WO 06/106905 and WO 2010/129304; Strand Exchange Engineered Domains (SEED) heterodimer formation as described in, *e.g.*, WO 07/110205; Fab arm exchange as described in, *e.g.*, WO 08/119353, WO 2011/131746, and WO 2013/060867; double antibody conjugate, *e.g.*, by antibody cross-linking to generate a bi-specific structure using a heterobifunctional reagent having an amine-reactive group and a sulfhydryl reactive group as described in, *e.g.*, US 4433059; bispecific antibody determinants generated by recombining half antibodies (heavy-light chain pairs or Fabs) from different antibodies through cycle of reduction and oxidation of disulfide bonds between the two heavy chains, as described in, *e.g.*, US 4444878; trifunctional antibodies, *e.g.*, three Fab' fragments cross-linked through sulfhdryl reactive groups, as described in, *e.g.*, US5273743; biosynthetic binding proteins, *e.g.*, pair of scFvs cross-linked through C-terminal tails preferably through disulfide or amine-reactive chemical cross-linking, as described in, *e.g.*, US5534254; bifunctional antibodies, *e.g.*, Fab fragments with different binding specificities dimerized through leucine zippers (*e.g.*, c-fos and c-jun) that have replaced the constant domain, as described in, *e.g.*, US5582996; bispecific and oligospecific mono-and oligovalent receptors, *e.g.*, VH-CH1 regions of two antibodies (two Fab fragments) linked through a polypeptide spacer between the CH1 region of one antibody and the VH region of the other antibody typically with associated light chains, as described in, *e.g.*, US5591828; bispecific DNA-antibody conjugates, *e.g.*, crosslinking of antibodies or Fab fragments through a double stranded piece of DNA, as described in, *e.g.*, US5635602; bispecific fusion proteins, *e.g.*, an expression construct containing two scFvs with a hydrophilic helical peptide linker between them and a full constant region, as described in, *e.g.*, US5637481; multivalent and multispecific binding proteins, *e.g.*, dimer of polypeptides having first domain with binding region of Ig heavy chain variable region, and second domain with binding region of Ig light chain variable region, generally termed diabodies (higher order structures are also encompassed creating for bispecific, trispecific, or tetraspecific molecules, as described in, *e.g.*, US5837242; minibody constructs with linked VL and VH chains further connected with peptide spacers to an antibody hinge region and CH3 region, which can be dimerized to form bispecific/multivalent molecules, as described in, *e.g.*, US5837821; VH and VL domains linked with a short peptide linker (*e.g.*, 5 or 10 amino acids) or no linker at all in either orientation, which can form dimers to form bispecific diabodies; trimers and tetramers, as described in, *e.g.*,

US5844094; String of VH domains (or VL domains in family members) connected by peptide linkages with crosslinkable groups at the C-terminus further associated with VL domains to form a series of FVs (or scFvs), as described in, *e.g.*, US5864019; and single chain binding polypeptides with both a VH and a VL domain linked through a peptide linker are combined into multivalent structures through non-covalent or chemical crosslinking to form, *e.g.*, homobivalent, heterobivalent, trivalent, and tetravalent structures using both scFV or diabody type format, as described in, *e.g.*, US5869620. Additional exemplary multispecific and bispecific molecules and methods of making the same are found, for example, in US5910573, US5932448, US5959083, US5989830, US6005079, US6239259, US6294353, US6333396, US6476198, US6511663, US6670453, US6743896, US6809185, US6833441, US7129330, US7183076, US7521056, US7527787, US7534866, US7612181, US2002004587A1, US2002076406A1, US2002103345A1, US2003207346A1, US2003211078A1, US2004219643A1, US2004220388A1, US2004242847A1, US2005003403A1, US2005004352A1, US2005069552A1, US2005079170A1, US2005100543A1, US2005136049A1, US2005136051A1, US2005163782A1, US2005266425A1, US2006083747A1, US2006120960A1, US2006204493A1, US2006263367A1, US2007004909A1, US2007087381A1, US2007128150A1, US2007141049A1, US2007154901A1, US2007274985A1, US2008050370A1, US2008069820A1, US2008152645A1, US2008171855A1, US2008241884A1, US2008254512A1, US2008260738A1, US2009130106A1, US2009148905A1, US2009155275A1, US2009162359A1, US2009162360A1, US2009175851A1, US2009175867A1, US2009232811A1, US2009234105A1, US2009263392A1, US2009274649A1, EP346087A2, WO0006605A2, WO02072635A2, WO04081051A1, WO06020258A2, WO2007044887A2, WO2007095338A2, WO2007137760A2, WO2008119353A1, WO2009021754A2, WO2009068630A1, WO9103493A1, WO9323537A1, WO9409131A1, WO9412625A2, WO9509917A1, WO9637621A2, WO9964460A1. The contents of the above-referenced applications are incorporated herein by reference in their entireties.

In other embodiments, the anti-TIM-3 antibody molecule (*e.g.*, a monospecific, bispecific, or multispecific antibody molecule) is covalently linked, *e.g.*, fused, to another partner *e.g.*, a protein *e.g.*, one, two or more cytokines, *e.g.*, as a fusion molecule for example a fusion protein. In other embodiments, the fusion molecule comprises one or more proteins, *e.g.*, one,

two or more cytokines. In one embodiment, the cytokine is an interleukin (IL) chosen from one, two, three or more of IL-1, IL-2, IL-12, IL-15 or IL-21. In one embodiment, a bispecific antibody molecule has a first binding specificity to a first target (*e.g.*, to TIM-3), a second binding specificity to a second target (*e.g.*, LAG-3 or PD-1), and is optionally linked to an interleukin (*e.g.*, IL-12) domain *e.g.*, full length IL-12 or a portion thereof. In other embodiments, the anti-TIM-3 antibody molecule is fused to another protein *e.g.*, one, two or more cytokines, *e.g.*, as a fusion molecule. In other embodiments, the fusion molecule comprises one or more proteins, *e.g.*, one, two or more cytokines. In one embodiment, the cytokine is an interleukin (IL) chosen from one, two, three or more of IL-1, IL-2, IL-12, IL-15 or IL-21.

A "fusion protein" and a "fusion polypeptide" refer to a polypeptide having at least two portions covalently linked together, where each of the portions is a polypeptide having a different property. The property may be a biological property, such as activity *in vitro* or *in vivo*. The property can also be simple chemical or physical property, such as binding to a target molecule, catalysis of a reaction, etc. The two portions can be linked directly by a single peptide bond or through a peptide linker, but are in reading frame with each other.

Exemplary Anti-TIM-3 Antibody Molecules

In certain embodiments, the anti-TIM-3 antibody comprises:

(a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 10; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(b) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 4; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(c) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 25; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a

VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(d) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 24; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(e) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 31; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14; or

(f) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 30; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8.

In certain embodiments, the antibody molecule comprises a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 10; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14.

In certain embodiments, the antibody molecule comprises a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 4; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8.

In certain embodiments, the antibody molecule comprises a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 25; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a

VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14.

In certain embodiments, the antibody molecule comprises a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 24; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8.

In certain embodiments, the antibody molecule comprises a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 31; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14.

In certain embodiments, the antibody molecule comprises a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 30; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8.

In certain embodiments, the anti-TIM-3 antibody molecule comprises:

(i) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3 or SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 10; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and

(ii) a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6 or SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 7 or SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 8 or SEQ ID NO: 14.

In other embodiments, the anti-TIM-3 antibody molecule comprises:

(i) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3 or SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 24 or SEQ ID NO: 25; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and

(ii) a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6 or SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 7 or SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 8 or SEQ ID NO: 14.

In other embodiments, the anti-TIM-3 antibody molecule comprises:

(i) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3 or SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 30 or SEQ ID NO: 31; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and

(ii) a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6 or SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 7 or SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 8 or SEQ ID NO: 14.

In embodiments of the aforesaid antibody molecules, the VHCDR1 comprises the amino acid sequence of SEQ ID NO: 3. In other embodiments, the VHCDR1 comprises the amino acid sequence of SEQ ID NO: 9.

In embodiments of the aforesaid antibody molecules, the VHCDR2 comprises the amino acid sequence of SEQ ID NO: 4. In other embodiments, the VHCDR2 comprises the amino acid sequence of SEQ ID NO: 10. In other embodiments, the VHCDR2 comprises the amino acid sequence of SEQ ID NO: 24. In other embodiments, the VHCDR2 comprises the amino acid sequence of SEQ ID NO: 25. In other embodiments, the VHCDR2 comprises the amino acid sequence of SEQ ID NO: 30. In other embodiments, the VHCDR2 comprises the amino acid sequence of SEQ ID NO: 31.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising an amino acid sequence at least 85% identical to any of SEQ ID NOs: 1, 16, 26, 32, 36, 44, 48, 52, 60, 68, 72, 76, 80, 84, 92, or 100.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 1, 16, 26, 32, 36, 44, 48, 52, 60, 68, 72, 76, 80, 84, 92, or 100.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising an amino acid sequence at least 85% identical to any of SEQ ID NOs: 2, 20, 40, 56, 64, 88, 96, or 104.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 2, 20, 40, 56, 64, 88, 96, or 104.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 1.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 16.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 18.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 26.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 28.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 32.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 34.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 36.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 38.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 44.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 46.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 48.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 50.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 52.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 54.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 60.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 62.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 68.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 70.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 72.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 74.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 76.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 78.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 80.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 82.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 84.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 86.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 92.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 94.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 100.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 102.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 116.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 121.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 2.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 20.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 22.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 64.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 88.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 90.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 96.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 98.

In other embodiments, the aforesaid antibody molecules comprise a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 104.

In other embodiments, the aforesaid antibody molecules comprise a light chain comprising the amino acid sequence of SEQ ID NO: 106.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 2.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 16 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 20.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 26 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 20.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 20.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 36 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 44 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 48 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 36 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 20.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 16 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 40.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 52 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 60 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 52 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 64.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 60 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 64.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 68 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 64.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 72 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 64.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 76 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 80 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 68 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 72 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 56.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 76 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 64.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 80 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 64.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 84 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 88.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 92 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 96.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 100 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 104.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain comprising the amino acid sequence of SEQ ID NO: 22.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 28 and a light chain comprising the amino acid sequence of SEQ ID NO: 22.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 34 and a light chain comprising the amino acid sequence of SEQ ID NO: 22.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 46 and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 50 and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 116 and a light chain comprising the amino acid sequence of SEQ ID NO: 22.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 121 and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 54 and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 62 and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 54 and a light chain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 62 and a light chain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 70 and a light chain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 74 and a light chain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 70 and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 74 and a light chain comprising the amino acid sequence of SEQ ID NO: 58.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and a light chain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and a light chain comprising the amino acid sequence of SEQ ID NO: 66.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 86 and a light chain comprising the amino acid sequence of SEQ ID NO: 90.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 94 and a light chain comprising the amino acid sequence of SEQ ID NO: 98.

In other embodiments, the aforesaid antibody molecules comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 and a light chain comprising the amino acid sequence of SEQ ID NO: 106.

In other embodiments, the aforesaid antibody molecules are chosen from a Fab, F(ab')2, Fv, or a single chain Fv fragment (scFv).

In other embodiments, the aforesaid antibody molecules comprise a heavy chain constant region selected from IgG1, IgG2, IgG3, and IgG4.

In other embodiments, the aforesaid antibody molecules comprise a light chain constant region chosen from the light chain constant regions of kappa or lambda.

In some embodiments, the anti-TIM-3 antibody molecule comprises the CDR2 of the VH region of SEQ ID NO: 1, using the Kabat or Chothia definitions of CDRs. In some embodiments, the anti-TIM-3 antibody molecule comprises the CDR2 and one or both of CDR1 and CDR3 of the VH region of SEQ ID NO: 1, using the Kabat or Chothia definitions of CDRs. In some embodiments, the anti-TIM-3 antibody molecule comprises CDR2 of the VH region of SEQ ID NO: 1 in combination with another 1, 2, 3, 4, or 5 (*e.g.*, collectively all) CDRs found in SEQ ID NO: 1 or SEQ ID NO: 2, using the Kabat of Chothia definitions of CDRs. In some embodiments, the anti-TIM-3 antibody molecule comprises the VHCDR2 of SEQ ID NO: 4. For instance, the anti-TIM-3 antibody molecule may comprise the VHCDR2 of SEQ ID NO: 4 in combination with one or both of the VHCDR1 of SEQ ID NO: 3 and the VHCDR3 of SEQ ID NO: 5. As a further example, the anti-TIM-3 antibody molecule may comprise the VHCDR2 of SEQ ID NO: 4 in combination with another 1, 2, 3, 4, or 5 (*e.g.*, collectively all) CDRs selected from SEQ ID NOS: 3, 5, 6, 7, and 8.

In some embodiments, the anti-TIM-3 antibody molecule comprises the CDR3 of the VL region of SEQ ID NO: 2, using the Kabat or Chothia definitions of CDRs. In some embodiments, the anti-TIM-3 antibody molecule comprises the CDR3 and one or both of CDR1 and CDR2 of the VL region of SEQ ID NO: 2, using the Kabat or Chothia definitions of CDRs. In some embodiments, the anti-TIM-3 antibody molecule comprises CDR3 of the VL region of SEQ ID NO: 2 in combination with another 1, 2, 3, 4, or 5 (*e.g.*, collectively all) CDRs found in SEQ ID NO: 1 or SEQ ID NO: 2, using the Kabat of Chothia definitions of CDRs. In some embodiments, the anti-TIM-3 antibody molecule comprises the VLCDR3 of SEQ ID NO: 8. For instance, the anti-TIM-3 antibody molecule may comprise the VLCDR3 of SEQ ID NO: 8 in combination with one or both of the VHCDR1 of SEQ ID NO: 6 and the VHCDR2 of SEQ ID NO: 7. As a further example, the anti-TIM-3 antibody molecule may comprise the VLCDR3 of SEQ ID NO: 8 in combination with another 1, 2, 3, 4, or 5 (*e.g.*, collectively all) CDRs selected from SEQ ID NOs: 3-7.

In some embodiments, the anti-TIM-3 antibody molecule comprises the CDR2 of the VH region of SEQ ID NO: 1 and the CDR3 of the VL region of SEQ ID NO: 2, optionally in combination with an additional 1, 2, 3, or 4 (*e.g.*, collectively all) CDRs found in SEQ ID NO: 1 and SEQ ID NO: 2, using the Kabat or Chothia definitions of CDRs. In certain embodiments, the anti-TIM-3 antibody molecule comprises the VHCDR2 of SEQ ID NO: 4 and the VLCDR3

of SEQ ID NO: 8, optionally in combination with an additional 1, 2, 3, or 4 (*e.g.*, collectively all) CDRs selected from SEQ ID NOS: 3, 5, 6, or 7.

In some embodiments, the anti-TIM-3 antibody molecule comprises a heavy chain constant region, a light chain constant region, and heavy and light chain variable regions of Tables 1-4 (*e.g.*, SEQ ID NO: 1 and SEQ ID NO: 2). In certain embodiments, the anti-TIM-3 antibody molecule comprises a heavy chain constant region, a light chain constant region, and 1, 2, 3, 4, 5, or 6 (*e.g.*, all) CDRs of Tables 1-4.

In some embodiments, the anti-TIM-3 antibody molecule comprises the sequence of all or a portion of the heavy chain of SEQ ID NO: 1. For instance, in some embodiments, the anti-TIM-3 antibody molecule comprises amino acids 1-98, 1-107, or 1-118 of SEQ ID NO: 1. In some embodiments, the anti-TIM-3 antibody molecule comprises amino acids 1-98 of SEQ ID NO: 1, a hCDR3 region (*e.g.*, SEQ ID NO: 5 or a sequence substantially identical thereto), and a VHFW4 region (*e.g.*, a human VHFW4 region, a homologous region of human D or J sequences, amino acids 108-118 of SEQ ID NO: 1, or a sequence substantially identical thereto). In some embodiments, the VHFW4 region has no more than 1 or 2 positions of non-identity relative to amino acids 108-118 of SEQ ID NO: 1. In some embodiments, the VHFW4 region has no more than 3, 4, 5, 6, 7, 8, 9, or 10 positions of non-identity relative to amino acids 108-118 of SEQ ID NO: 1. In some embodiments the hCDR3 region has no more than 1 or 2 positions of non-identity relative to SEQ ID NO: 5.

In other embodiments, the aforesaid antibody molecules are capable of binding to human TIM-3 with a dissociation constant (K_D) of less than 0.5 nM.

In some embodiments, the anti-TIM-3 antibody molecule is capable of independently binding to human TIM-3 and cynomolgus monkey TIM-3 with high affinity. In some embodiments, high affinity refers to a K_D of less than 5, 2, 1, 0.5, 0.4, 0.3, 0.2, or 0.1 nM, *e.g.*, about 0.3 to 0.01 nM, *e.g.*, about 0.2 to 0.05 nM, *e.g.*, as measured by a Biacore method.

In other embodiments, the aforesaid antibody molecules bind to cynomolgus TIM-3 with a K_D of less than 10, 5, 4, 3, 2, or 1 nM, *e.g.*, as measured by a Biacore method, FACS analysis, or ELISA.

In other embodiments, the aforesaid antibody molecules bind to human TIM-3 with a KD of less than 5, 2, 1, 0.5, 0.4, 0.3, 0.2, or 0.1 nM, *e.g.*, as measured by a Biacore method, FACS analysis, or ELISA.

In embodiments, the aforesaid antibody molecules do not bind to mouse TIM-3.

In some embodiments, the antibody molecule binds to a mammalian, *e.g.*, human, TIM-3. For example, the antibody molecule binds specifically to an epitope, *e.g.*, linear or conformational epitope, (*e.g.*, an epitope as described herein) on TIM-3. In some embodiments, the epitope is at least a portion of the IgV domain of human or cynomolgus TIM-3. In certain aspects, it is advantageous to identify an antibody that binds with high affinity to the human and cynomolgus homologs of a protein of interest. This desirable cross-reactivity allows the same antibody (or two antibodies with the same CDRs or variable regions) to be tested in an animal model and then administered to human patients as a therapeutic.

In certain embodiments, the aforesaid antibody molecules are not cross-reactive with mouse TIM-3. In certain embodiments, the aforesaid antibody molecules are less cross-reactive with rat TIM-3. For example, the cross-reactivity can be measured by a Biacore method or a binding assay using cells that expresses TIM-3 (*e.g.,* human TIM-3-expressing 300.19 cells). In other embodiments, the aforesaid antibody molecules bind an extracellular Ig-like domain (*e.g.,* IgV domain) of TIM-3.

In some embodiments, the aforesaid anti-TIM-3 antibody molecules bind to one or more residues within: the two residues adjacent to the N-terminus of the A strand, the BC loop, the CC' loop, the F strand, the FG loop, and the G strand of TIM-3, or one or more (*e.g.,* two, five, ten, fifteen, twenty, twenty-five, thirty, thirty-five, or all) residues within two or more of the two residues adjacent to the N-terminus of the A strand, the BC loop, the CC' loop, the F strand, the FG loop, or the G strand of TIM-3. The F strand of TIM-3 comprises residues G106 to I112; the G strand of TIM-3 comprises residues E121 to K130; the FG loop of TIM-3 comprises the residues between the F strand and the G strand, *e.g.*, comprising residues Q113 to D120; the BC loop of TIM-3 comprises the residues between the B strand and the C strand, *e.g.*, comprising residues P37 to P50; the two residues adjacent to the N-terminus of the A strand comprises residues V24 and E25; the CC' loop comprises the residues between the C strand and the C' strand, *e.g.*, comprising residues G56 to N65. In other embodiments, the aforesaid anti-TIM-3 antibody molecules bind to one or more residues within: the A strand, the EF loop, the C strand, the C'C'' loop, or the C'' strand. The A strand comprises residues Y26 to E29; the EF loop comprises the residues between the E strand and the F strand, *e.g.,* comprising residues E98 to S105; the C strand comprises residues V51 to K55; the C'C'' loop comprises the residues

between the C' strand and the C'' strand, *e.g.,* comprising residues D71 to D74; and the C'' strand comprises residues V75 to W78. The numbering for the residues of TIM-3 is described, *e.g.,* in Figure 18. In an embodiment, the anti-TIM-3 antibody molecules bind to one or more (*e.g.,* two, five, ten, fifteen, twenty, twenty-five, thirty, thirty-five, or all) residues in the F strand, the G strand, and the CC' loop of TIM-3.

In some embodiments, the aforesaid anti-TIM-3 antibody molecules reduce or inhibit plasma membrane penetration or PtdSer-dependent membrane penetration of TIM-3. In some embodiments, the aforesaid anti-TIM-3 antibody molecules reduce or inhibit binding to TIM-3 ligand PtdSer. In some embodiments, the aforesaid anti-TIM-3 antibody molecules reduce or inhibit binding to TIM-3 ligand HMGB1. In some embodiments, the aforesaid anti-TIM-3 antibody molecules reduce or inhibit binding to TIM-3 ligand CEACAM-1. In some embodiments, the aforesaid anti-TIM-3 antibody molecules reduce or inhibit binding to TIM-3 ligand Semaphorin-4A. In some embodiments, the aforesaid anti-TIM-3 antibody molecules do not reduce or inhibit binding to TIM-3 ligand Galectin-9.

In some embodiments, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a TIM-3 surface (*e.g.*, one, two, three, five, eight, ten, fifteen, or more continuous or discontinuous (*e.g.,* noncontiguous) amino acid residues chosen from Val24, Glu25, Thr41, Gly56, Ala57, Cys58, Pro59, Val60, Phe61, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, and/or Leu127.

In some embodiments, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a TIM-3 surface (*e.g.*, one, two, three, five, eight, ten, fifteen, twenty, twenty-one, twenty-five, or more continuous and discontinuous (*e.g.,* noncontiguous) amino acid residues chosen from Val24, Glu25, Tyr26, Phe39, Tyr40, Thr41, Gly56, Ala57, Cys58, Pro59, Val60, Phe61, Ser105, Gly106, Ile107, Asn119, Asp120, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, Leu127, and/or Val128, *e.g.*, as detailed in Table 13.

In some embodiments, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a TIM-3 surface (*e.g.*, one, two, three, five, eight, ten, fifteen, twenty, twenty-one, twenty-five, or more continuous or discontinuous (*e.g.,* noncontiguous) amino acid residues chosen from Glu23, Val24, Glu25, Tyr26, Thr41, Pro42, Ala43, Ala44, Pro45, Gly46, Asn47, Leu48, Val49, Pro50, Val51, Cys52, Trp53, Gly54, Lys55, Gly56, Ala57, Cys58, Pro59, Val60, Phe61, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, and/or Leu127.

In some embodiments, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a TIM-3 surface (*e.g.*, one, two, three, five, eight, ten, fifteen, twenty, twenty-one, twenty-five, or more continuous or discontinuous (*e.g.,* noncontiguous) amino acid residues chosen from Val24, Glu25, Tyr26, Phe39, Tyr40, Thr41, Pro42, Ala43, Ala44, Pro45, Gly46, Asn47, Leu48, Val49, Pro50, Val51, Cys52, Trp53, Gly54, Lys55, Gly56, Ala57, Cys58, Pro59, Val60, Phe61, Ser105, Gly106, Ile107, Asn119, Asp120, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, Leu127, and/or Val128.

In other embodiments, the anti-TIM-3 antibody molecule competes with CEACAM-1 for binding to TIM-3. In one embodiment, the anti-TIM-3 antibody molecule interacts, *e.g.*, binds to, one, two, or more (all) of C58, N119 and K122 of TIM-3, *e.g.*, displaces or competes CEACAM-1 for binding to these residues. In one embodiment, the anti-TIM-3 antibody molecule reduces or blocks the formation of a hydrogen bond between K122 of TIM-3 and N42 of CEACAM-1. With respect to CEACAM-1, it has been shown that CEACAM-1 is a ligand for TIM-3and is required for its ability to mediate T-cell inhibition, which may have important role in regulating autoimmunity and anti-tumour immunity (Huang, *et al.* (2014) *Nature* doi:10.1038/nature13848). Inhibition of an interaction between TIM-3 and CEACAM-1 can be used with the other immunomodulators described herein (*e.g.*, anti-PD-1 inhibitor) to enhance an immune response against a cancer.

In another embodiment, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, a PtdSer-binding loop of TIM-3, *e.g.*, the human TIM-3 IgV domain. In one embodiment, the anti-TIM-3 antibody molecule interacts with, *e.g.*, binds to, at least two PtdSer-binding loops of TIM-3, *e.g.*, the FG loop and CC' loop of TIM-3 (*e.g.*, a metal ion-dependent ligand binding site (MILIBS)). For example, the carboxyl group of PtdSer can bind to the CC' loop of TIM-3 and the amino group of PtdSer can bind to the FG loop of TIM-3. In one embodiment, the anti-TIM-3 antibody molecule reduces or prevents PtdSer-mediated membrane penetration of TIM-3 Thus, the anti-TIM-3 antibody molecule may reduce engagement of TIM-3-expressing cells and/or penetration into the membrane of apoptotic cells (which can display PtdSer) for engulfment.

In another embodiment, the anti-TIM-3 antibody molecule competes with HMGB1 for bind to TIM-3. *E.g.*, it reduces binding of HMGB1 to residue 62 of TIM-3 (Q in mouse, E in human TIM-3). With respect to HMGB1, it has been reported to interact with TIM-3 to help

tumor-associated dendritic cells suppress nucleic acid-mediated innate immune response (Chiba *et al.*, (2012) Nat. Immunol. 13(9):832-842). Thus, the anti-TIM-3 antibody molecule may enhance nucleic acid-mediated innate immune response.

In yet another embodiment, the anti-TIM-3 antibody molecule does not compete with or reduce a Galectin-9 (Gal-9) ligand to binding to TIM-3.

In embodiments, the anti-TIM-3 antibody molecule is a monospecific antibody molecule or a bispecific antibody molecule. In embodiments, the antibody molecule has a first binding specificity for TIM-3 and a second binding specifity for PD-1, LAG-3, CEACAM (*e.g.*, CEACAM-1 and/or CEACAM-5), PD-L1 or PD-L2. In embodiments, the antibody molecule comprises an antigen binding fragment of an antibody, *e.g.*, a half antibody or antigen binding framgment of a half antibody.

In other embodiments, the aforesaid antibody molecules are capable of enhancing an antigen-specific T cell response.

Provided herein is an isolated nucleic acid molecule encoding the above antibody molecule, vectors and host cells thereof. The nucleic acid molecule includes but is not limited to RNA, genomic DNA and cDNA.

In embodiments, the isolated nucleic acid encodes the antibody heavy chain variable region or light chain variable region, or both, of any the aforesaid antibody molecules.

In other embodiments, the isolated nucleic acid comprises a nucleotide sequence encoding a heavy chain variable domain, wherein the nucleotide sequence is at least 85% identical to any of SEQ ID NOs: 11, 17, 29, 33, 37, 45, 49, 53, 61, 69, 73, 77, 81, 85, 93, 101, 115, or 120.

In other embodiments, the isolated nucleic acid comprises a nucleotide sequence encoding a heavy chain variable domain, wherein the nucleotide sequence comprises any of SEQ ID NOs: 11, 17, 27, 33, 37, 45, 49, 53, 61, 69, 73, 77, 81, 85, 93, 101, 115, or 120.

In other embodiments, the isolated nucleic acid comprises a nucleotide sequence encoding a heavy chain, wherein the nucleotide sequence is at least 85% identical to any of SEQ ID NOs: 19, 29, 35, 39, 47, 51, 55, 63, 71, 75, 79, 83, 87, 95, 103, 117, or 122.

In other embodiments, the isolated nucleic acid comprises a nucleotide sequence encoding a heavy chain, wherein the nucleotide sequence comprises any of SEQ ID NOs: 19, 29, 35, 39, 47, 51, 55, 63, 71, 75, 79, 83, 87, 95, 103, 117 or 122.

In other embodiments, the isolated nucleic acid comprises a nucleotide sequence encoding a light chain variable domain, wherein the nucleotide sequence is at least 85% identical to any of SEQ ID NOs: 15, 21, 41, 57, 65, 89, 97, 105, 118, 123, 125, or 127.

In other embodiments, the isolated nucleic acid comprises a nucleotide sequence encoding a light chain variable domain, wherein the nucleotide sequence comprises any of SEQ ID NOs: 15, 21, 41, 57, 65, 89, 97, 105, 118, 123, 125, or 127.

In other embodiments, the isolated nucleic acid comprises a nucleotide sequence encoding a light chain, wherein the nucleotide sequence is at least 85% identical to any of SEQ ID NOs: 23, 43, 59, 67, 91, 99, 107, 119, 124, 126, or 128.

In other embodiments, the isolated nucleic acid comprises a nucleotide sequence encoding a light chain, wherein the nucleotide sequence comprises any of SEQ ID NOs: 23, 43, 59, 67, 91, 99, 107, 119, 124, 126, or 128.

Pharmaceutical Compositions and Kits

In some aspects, this disclosure provides compositions, *e.g.*, pharmaceutically acceptable compositions, which include an anti-TIM-3 antibody molecule described herein, formulated together with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, isotonic and absorption delaying agents, and the like that are physiologically compatible. The carrier can be suitable for intravenous, intramuscular, subcutaneous, parenteral, rectal, spinal or epidermal administration (*e.g.* by injection or infusion).

The compositions set out herein may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, liposomes, and suppositories. A suitable form depends on the intended mode of administration and therapeutic application. Typical suitable compositions are in the form of injectable or infusible solutions. One suitable mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In some

embodiments, the antibody molecule is administered by intravenous infusion or injection. In certain embodiments, the antibody is administered by intramuscular or subcutaneous injection.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

Therapeutic compositions typically should be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high antibody concentration. Sterile injectable solutions can be prepared by incorporating the active compound (i.e., antibody or antibody portion) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

The antibody molecules can be administered by a variety of methods. Several are known in the art, and for many therapeutic applications, an appropriate route/mode of administration is intravenous injection or infusion. In an embodiment, the antibody molecules can be administered by intravenous infusion at a rate of more than 20 mg/min, *e.g.*, 20-40 mg/min, and preferably greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m^2, preferably about 70 to 310 mg/m^2, and more preferably, about 110 to 130 mg/m^2. In an embodiment, the antibody molecules can be administered by intravenous infusion at a rate of less than 10mg/min;

preferably less than or equal to 5 mg/min to reach a dose of about 1 to 100 mg/m ^{2}, preferably about 5 to 50 mg/m^2, about 7 to 25 mg/m^2 and more preferably, about 10 mg/m^2. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, *e.g.*, *Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

In certain embodiments, an antibody molecule can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The antibody molecule (and other ingredients, if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the antibody molecule may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer an antibody molecule by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. Therapeutic compositions can also be administered with medical devices, and several are known in the art.

Dosage regimens are adjusted to provide the desired response (*e.g.*, a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be

achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody molecule is 0.1-30 mg/kg, more preferably 1-25 mg/kg. Dosages and therapeutic regimens of the anti-TIM-3 antibody molecule can be determined by a skilled artisan. In certain embodiments, the anti-TIM-3 antibody molecule is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose of about 1 to 40 mg/kg, *e.g.*, 1 to 30 mg/kg, *e.g.*, about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, 1 to 10 mg/kg, 5 to 15 mg/kg, 10 to 20 mg/kg, 15 to 25 mg/kg, or about 3 mg/kg. The dosing schedule can vary from *e.g.*, once a week to once every 2, 3, or 4 weeks. In one embodiment, the anti-TIM-3 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week. The antibody molecule can be administered by intravenous infusion at a rate of more than 20 mg/min, *e.g.*, 20-40 mg/min, and preferably greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m^2, preferably about 70 to 310 mg/m^2, and more preferably, about 110 to 130 mg/m^2. In embodiments, the infusion rate of about 110 to 130 mg/m^2 achieves a level of about 3 mg/kg. In other embodiments, the antibody molecule can be administered by intravenous infusion at a rate of less than 10 mg/min, *e.g.*, less than or equal to 5 mg/min to reach a dose of about 1 to 100 mg/m^2, *e.g.*, about 5 to 50 mg/m^2, about 7 to 25 mg/m^2, or, about 10 mg/m^2. In some embodiments, the antibody is infused over a period of about 30 min. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

The pharmaceutical compositions herein may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody molecule. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the modified antibody or antibody fragment may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or

detrimental effects of the antibody molecule is outweighed by the therapeutically beneficial effects. A "therapeutically effective dosage" preferably inhibits a measurable parameter by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects. The measurable parameter may be, *e.g.*, tumor growth rate or pathogen growth rate. The ability of a compound to inhibit a measurable parameter can be evaluated in an animal model system predictive of efficacy in the corresponding human disease. Alternatively, this property of a composition can be evaluated by examining the ability of the compound to inhibit, such inhibition *in vitro* by assays known to the skilled practitioner.

A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

Also within this disclosure is a kit comprising an antibody molecule described herein. The kit can include one or more other elements including: instructions for use; other reagents, *e.g.*, a label, a therapeutic agent, or an agent useful for chelating, or otherwise coupling, an antibody to a label or therapeutic agent, or a radioprotective composition; devices or other materials for preparing the antibody molecule for administration; pharmaceutically acceptable carriers; and devices or other materials for administration to a subject.

Uses of Anti-TIM-3 Antibody Molecules

TIM-3 is a coinhibitory protein expressed, *e.g.,* on activated T helper 1 (Th1) CD4+ and cytotoxic CD8+ T cells that secrete IFN-γ. TIM-3 is largely co-expressed on PD-1+ exhausted T cells as shown in preclinical models of cancer and viral exhaustion. Co-blockade of these pathways can restore effector T cell function (*e.g.,* IFN-γ secretion, proliferation) in several models as well as human PBMCs derived from metastatic melanoma patients and patients with HIV or HCV. TIM-3 is also enriched on Fox-P3+ natural regulatory T cells (and FoxP3-negative induced regulatory cells), and the nTreg expression correlates with disease severity in NSCLC, hepatocellular and ovarian carcinoma. In mouse models, TIM-3+ nTregs have been shown to be more immunosuppressive (secrete higher levels of IL-10 and TGF-β).

In addition, TIM-3 can play an important role on innate immune cells, including NK cells, monocytes/macrophages and dendritic cells (DCs). TIM-3 is constitutively expressed on macrophages and DCs, and blockade can enhance TNF-α secretion from human monocytes and increase NF-κB expression in a mouse dendritic cell line. TIM-3 can also contribute to expansion of myeloid-derived suppressor cells (MDSCs). Constitutive expression of TIM-3 on macrophages is associated with less IL-12 secretion, and downregulation of TIM-3 post-TLR activation can lead to enhanced IL-12 and subsequent effector T cell responses.

The antibody molecules disclosed herein have *in vitro* and *in vivo* diagnostic, as well as therapeutic and prophylactic utilities. In some embodiments, the antibody molecules modulate (*e.g.*, enhance or inhibit) an immune response in a subject by binding TIM-3. For example, these molecules can be administered to cells in culture, *in vitro* or *ex vivo*, or to a subject, *e.g.*, a human subject, *e.g.*, *in vivo*, to modulate (*e.g.*, enhance or inhibit) immunity.

Accordingly, in some aspects, the disclosure provides a method of modifying an immune response in a subject comprising administering to the subject an antibody molecule described herein, such that the immune response in the subject is modified. In some embodiments, the immune response is enhanced, stimulated or up-regulated. In certain embodiments, the immune response is inhibited or downregulated. For example, these antibody molecules can be administered to cells in culture, *e.g. in vitro* or *ex vivo*, or in a subject, *e.g.*, in vivo, to treat, prevent, and/or diagnose a variety of disorders, such as cancers, immune disorders, and infectious diseases.

As used herein, the term "subject" is intended to include human and non-human animals. In some embodiments, the subject is a human subject, *e.g.*, a human patient having a disorder or condition characterized by abnormal TIM-3 functioning. Generally, the subject has at least some TIM-3 protein, including the TIM-3 epitope that is bound by the antibody molecule, *e.g.*, a high enough level of the protein and epitope to support antibody binding to TIM-3. The term "non-human animals" includes mammals and non-mammals, such as non-human primates. In some embodiments, the subject is a human. In some embodiments, the subject is a human patient in need of enhancement of an immune response. The methods and compositions described herein are suitable for treating human patients having a disorder that can be treated by modulating (*e.g.*, augmenting or inhibiting) an immune response.

Methods of treating immune disorders

TIM-3 is a transmembrane receptor expressed on T cells, *e.g.*, CD4+ T cells, CD8+ T cells, regulatory T cells, and differentiated Th1 cells. TIM-3-dependent trafficking of Th1 cells to target tissue can be inhibited with soluble TIM-3 (see US 7,470,428). Accordingly, modulating TIM-3 function may reduce T-cell trafficking into a target tissue, *e.g.*, in subjects with autoimmune disease. TIM-3 may play an important role in the induction of autoimmune diseases by regulating macrophage activation and/or function. Accordingly, in certain embodiments, the anti-TIM-3 antibody molecules described herein are suitable for use in downregulating an unwanted immune response, *e.g.*, treating autoimmune diseases.

Furthermore, as described in the Examples herein, anti-TIM-3 antibodies can stimulate NK cell-mediated killing of target cells, and can enhance IFN-gamma secretion and proliferation of CD4+ T cells. Accordingly, in certain embodiments, the anti-TIM-3 antibody molecules described herein are suitable for use in stimulating a desired immune response, *e.g.*, an immune response against a cancer cell or pathogen.

The anti-TIM-3 antibodies described herein may be used for treating immune disorders, especially T lymphocyte-related disorders, including, but not limited to, chronic inflammatory diseases and disorders, such as Crohn's disease, reactive arthritis, including Lyme disease, insulin-dependent diabetes, organ-specific autoimmunity, including multiple sclerosis, Hashimoto's thyroiditis and Grave's disease, contact dermatitis, psoriasis, graft rejection, graft versus host disease, sarcoidosis, atopic conditions, such as asthma and allergy, including allergic rhinitis, gastrointestinal allergies, including food allergies, eosinophilia, conjunctivitis, glomerular nephritis (*e.g.*, IgA nephropathy), certain pathogen susceptibilities such as helminthic (*e.g.*, leishmaniasis).

In certain embodiments, the anti-TIM-3 antibody is used to modulate T cell function, *e.g.*, CD4+ T cells, CD8+ T cells, Tregs, Th17, and Th1 function. In some embodiments, the anti-TIM-3 antibody molecule causes TIM-3 blockade, and is used to treat an immune disorder which is not a Th1-dependent disease (see Schroll et al., Am J Pathol 2010 April; 176(4):1716-1742). In certain embodiments, the anti-TIM-3 antibody molecule does not cause TIM-3 blockade.

In some aspects, the present disclosure provides methods of administering an anti-TIM-3 antibody molecule, resulting in promoting or reducing T-cell trafficking to a target tissue, promoting or inhibiting antigen-presenting cell (APC) activation.

In some embodiments the subject is in need of treatment for an autoimmune disease. Autoimmune disease include those in which a subject's own antibodies react with host tissue or in which immune effector T cells are autoreactive to endogenous self-peptides and cause destruction of tissue. Thus an immune response is mounted against a subject's own antigens, referred to as self-antigens. Autoimmune diseases include but are not limited to rheumatoid arthritis, Crohn's disease *e.g.*, pediatric Crohn's disease, multiple sclerosis, systemic lupus erythematosus (SLE), autoimmune encephalomyelitis, myasthenia gravis (MG), Hashimoto's thyroiditis, Goodpasture's syndrome, pemphigus (*e.g.*, pemphigus vulgaris), Grave's disease, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis, pernicious anemia, idiopathic Addison's disease, autoimmune-associated infertility, glomerulonephritis (*e.g.*, crescentic glomerulonephritis, proliferative glomerulonephritis), bullous pemphigoid, Sjogren's syndrome, insulin resistance, autoimmune diabetes mellitus (type 1 diabetes mellitus; insulin-dependent diabetes mellitus), atherosclerosis, and Alzheimer's disease.

In some aspects, an anti-TIM-3 antibody molecule described herein is administered to treat an unwanted immune response to an allergen. Examples of natural animal and plant allergens include proteins specific to the following genuses: Canine (Canis familiaris); Dermatophagoides (*e.g.*, Dermatophagoides farinae); Felis (Felis domesticus); Ambrosia (Ambrosia artemiisfolia; Lolium (*e.g.*, Lolium perenne or Lolium multiflorum); Cryptomeria (Cryptomeria japonica); Alternaria (Alternaria alternata); Alder; Alnus (Alnus gultinosa); Betula (Betula verrucosa); Quercus (Quercus alba); Olea (Olea europa); Artemisia (Artemisia vulgaris); Plantago (*e.g.*, Plantago lanceolata); Parietaria (*e.g.*, Parietaria officinalis or Parietaria judaica); Blattella (*e.g.*, Blattella germanica); Apis (*e.g.*, Apis multiflorum); Cupressus (*e.g.*, Cupressus sempervirens, Cupressus arizonica and Cupressus macrocarpa); Juniperus (*e.g.*, Juniperus sabinoides, Juniperus virginiana, Juniperus communis and Juniperus ashei); Thuya (*e.g.*, Thuya orientalis); Chamaecyparis (*e.g.*, Chamaecyparis obtusa); Periplaneta (*e.g.*, Periplaneta americana); Agropyron (*e.g.*, Agropyron repens); Secale (*e.g.*, Secale cereale); Triticum (*e.g.*, Triticum aestivum); Dactylis (*e.g.*, Dactylis glomerata); Festuca (*e.g.*, Festuca elatior); Poa (*e.g.*, Poa pratensis or Poa compressa); Avena (*e.g.*, Avena sativa); Holcus (*e.g.*, Holcus lanatus); Anthoxanthum (*e.g.*, Anthoxanthum odoratum); Arrhenatherum (*e.g.*, Arrhenatherum elatius); Agrostis (*e.g.*, Agrostis alba); Phleum (*e.g.*, Phleum pratense); Phalaris (*e.g.*, Phalaris

arundinacea); Paspalum (*e.g.*, Paspalum notatum); Sorghum (*e.g.*, Sorghum halepensis); and Bromus (*e.g.*, Bromus inermis).

In some embodiments, the anti-TIM-3 antibody molecule is administered to treat multiple sclerosis, Crohn's disease, sepsis, SIRS (Systemic Inflammatory Response Syndrome), or glomerulonephritis.

Methods of treating cancer

In some aspects, the present disclosure provides methods of administering an anti-TIM-3 antibody molecule to treat cancer. While not wishing to be bound by theory, in some embodiments, an anti-TIM-3 antibody molecule stimulates a patient's immune system to recognize and destroy cancer cells, thereby treating the cancer. In some embodiments, the cancer to be treated expresses TIM-3, and the anti-TIM-3 antibody molecule targets the cancer cells or cells in the cancer microenvironment.

In some aspects, the present disclosure relates to treatment of a subject *in vivo* using an anti-TIM-3 antibody molecule such that growth of cancerous tumors is inhibited. An anti-TIM-3 antibody may be used alone to inhibit the growth of cancerous tumors. Alternatively, an anti-TIM-3 antibody may be used in combination with one or more of: a standard cancer treatment (*e.g.*, for cancer or infectious disorders), or another antibody or antigen-binding fragment thereof, an immunomodulator (*e.g.*, an activator of a costimulatory molecule or an inhibitor of an inhibitory molecule); a vaccine, (*e.g.*, a cancer vaccine); or other forms of cellular immunotherapy , as described below.

Accordingly, in some embodiments, the disclosure provides a method of inhibiting growth of tumor cells in a subject, comprising administering to the subject a therapeutically effective amount of an anti-TIM-3 antibody molecule described herein.

In some embodiments, the methods are suitable for the treatment of cancer *in vivo*. To achieve antigen-specific enhancement of immunity, the anti-TIM-3 antibody molecule can be administered together with an antigen of interest. When antibodies to TIM-3 are administered in combination with one or more agents, the combination can be administered in either order or simultaneously.

Types of Cancer

In certain aspects, a method of treating a subject, *e.g.*, reducing or ameliorating, a hyperproliferative condition or disorder (*e.g.*, a cancer), *e.g.*, solid tumor, a hematological cancer, a soft tissue tumor, or a metastatic lesion, in a subject is provided. The method includes administering to the subject one or more anti-TIM-3 antibody molecules described herein, alone or in combination with other agents or therapeutic modalities.

As used herein, the term "cancer" is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. Examples of cancerous disorders include, but are not limited to, solid tumors, hematological cancers, soft tissue tumors, and metastatic lesions. Examples of solid tumors include malignancies, *e.g.*, sarcomas, and carcinomas (including adenocarcinomas and squamous cell carcinomas) of the various organ systems, such as those affecting liver, lung, breast, lymphoid, gastrointestinal (*e.g.*, colon), genitourinary tract (*e.g.*, renal, urothelial cells), prostate and pharynx. Adenocarcinomas include malignancies such as most colon cancers, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine and cancer of the esophagus. Squamous cell carcinomas include malignancies, *e.g.*, in the lung, esophagus, skin, head and neck region, oral cavity, anus, and cervix. In one embodiment, the cancer is a melanoma, *e.g.*, an advanced stage melanoma. Metastatic lesions of the aforementioned cancers can also be treated or prevented using the methods and compositions described herein.

Exemplary cancers whose growth can be inhibited using the antibody molecules disclosed herein include cancers typically responsive to immunotherapy. Non-limiting examples of suitable cancers for treatment include melanoma (*e.g.*, metastatic malignant melanoma), renal cancer (*e.g.* clear cell carcinoma), prostate cancer (*e.g.* hormone refractory prostate adenocarcinoma), breast cancer, colon cancer and lung cancer (*e.g.* non-small cell lung cancer). Additionally, refractory or recurrent malignancies can be treated using the antibody molecules described herein.

Cancers include, but are not limited to, basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and CNS cancer; primary CNS lymphoma; neoplasm of the central nervous system (CNS); breast cancer; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal

cancer; eye cancer; cancer of the head and neck; gastric cancer; intra-epithelial neoplasm; kidney cancer; larynx cancer; leukemia (including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic or acute leukemias); liver cancer; lung cancer (*e.g.*, small cell and non-small cell); lymphoma including Hodgkin's and non-Hodgkin's lymphoma; lymphocytic lymphoma; melanoma, *e.g.*, cutaneous or intraocular malignant melanoma; myeloma; neuroblastoma; oral cavity cancer (*e.g.*, lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; sarcoma; skin cancer; stomach cancer; testicular cancer; thyroid cancer; uterine cancer; cancer of the urinary system, hepatocarcinoma, cancer of the anal region, carcinoma of the fallopian tubes, carcinoma of the vagina, carcinoma of the vulva, cancer of the small intestine, cancer of the endocrine system, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, as well as other carcinomas and sarcomas, and combinations of said cancers.

In some embodiments, the cancer treated with the antibody molecules, includes but is not limited to, solid tumors, hematological cancers, soft tissue tumors, and metastatic lesions. Examples of solid tumors include malignancies, *e.g.*, sarcomas, adenocarcinomas, and carcinomas, of the various organ systems, such as those affecting lung, breast, lymphoid, gastrointestinal (*e.g.*, colon), genitals and genitourinary tract (*e.g.*, renal, urothelial, bladder cells), pharynx, CNS (*e.g.*, brain, neural or glial cells), skin (*e.g.*, melanoma), and pancreas, as well as adenocarcinomas which include malignancies such as most colon cancers, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell-carcinoma of the lung, cancer of the small intestine and cancer of the esophagus. Methods and compositions disclosed herein are also useful for treating metastatic lesions associated with the aforementioned cancers.

While not wishing to be bound by theory, in some embodiments, a patient is more likely to respond to treatment with an immunomodulator (optionally in combination with one or more agents as described herein) if the patient has a cancer that highly expresses PD-L1, and/or the cancer is infiltrated by anti-tumor immune cells, *e.g.*, TILs. The anti-tumor immunce cells may be positive for CD8, PD-L1, and/or IFN-γ; thus levels of CD8, PD-L1, and/or IFN-γ can serve as

a readout for levels of TILs in the microenvironment. In certain embodiments, the cancer microenvironment is referred to as triple-positive for PD-L1/CD8/IFN-γ.

Accordingly, in certain aspects, this application provides methods of determining whether a tumor sample is positive for one or more of PD-L1, CD8, and IFN-γ, and if the tumor sample is positive for one or more, *e.g.*, two, or all three, of the markers, then administering to the patient a therapeutically effective amount of an anti-PD-1 antibody molecule, optionally in combination with one or more other immunomodulators or anti-cancer agents, *e.g.*, an anti-TIM3 antibody as described herein.

In the following indications, a large fraction of patients are triple-positive for PD-L1/CD8/IFN-γ: Lung cancer (squamous); lung cancer (adenocarcinoma); head and neck cancer; stomach cancer; NSCLC; HNSCC; gastric cancers (*e.g.*, MSIhi and/or EBV+); CRC (*e.g.*, MSIhi); nasopharyngeal cancer (NPC); cervical cancer (*e.g.*, squamous); thyroid cancer *e.g.*, papillary thyroid; melanoma; TN breast cancer; and DLBCL (Diffuse Large B-Cell Lymphoma). In breast cancer generally and in colon cancer generally, a moderate fraction of patients is triple-positive for PD-L1/CD8/IFN-γ. In the following indications, a small fraction of patients are triple-positive for PD-L1/CD8/IFN-γ: ER+ breast cancer, and pancreatic cancer. These findings are discussed further in Example 9. Regardless of whether a large or small fraction of patients is triple-positive for these markers, screening the patients for these markers allows one to identify a fraction of patients that has an especially high likelihood of responding favorably to therapy with a PD-1 antibody (*e.g.*, a blocking PD-1 antibody), optionally in combination with one or more other immunomodulators (*e.g.*, an anti-TIM-3 antibody molecule described herein, an anti-LAG-3 antibody molecule, or an anti-PD-L1 antibody molecule) and/or anti-cancer agents, *e.g.*, those listed in Table 6 and disclosed in the publications listed in Table 6.

In some embodiments, the cancer sample is classified as triple-positive for PDL1/CD8/IFN-γ. This measurement can roughly be broken down into two thresholds: whether an individual cell is classified as positive, and whether the sample as a whole is classified as positive. First, one can measure, within an individual cell, the level of PD-L1, CD8, and/or IFN-γ. In some embodiments, a cell that is positive for one or more of these markers is a cell that has a higher level of the marker compared to a control cell or a reference value. For example, in some embodiments, a high level of PD-L1 in a given cell is a level higher than the level of PD-L1 in a corresponding non-cancerous tissue in the patient. As another example, in some

embodiments, a high level of CD8 or IFN-γ in a given cell is a level of that protein typically seen in a TIL. Second, one can also measure the percentage of cells in the sample that are positive for PD-L1, CD8, and/or IFN-γ. (It is not necessary for a single cell to express all three markers.) In some embodiments, a triple positive sample is one that has a high percentage of cells, *e.g.*, higher than a reference value or higher than a control sample, that are positive for these markers.

In other embodiments, one can measure the levels of PDL1, CD8, and/or IFN-γ overall in the sample. In this case, a high level of CD8 or IFN-γ in the sample can be the level of that protein typically seen in a tumor infiltrated with TIL. Similarly, a high level of PD-L1 can be the level of that protein typically seen in a tumor sample, *e.g.*, a tumor microenvironment.

The identification of subsets of patients that are triple-positive for PD-L1/CD8/IFN-γ, as shown in Example 10 herein, reveals certain sub-populations of patients that are likely to be especially responsive to PD-1 antibody therapy. For instance, many IM-TN (immunomodulatory, triple negative) breast cancer patients are triple-positive for PDL1/CD8/IFN-γ. IM-TN breast cancer is described in, *e.g.*, Brian D. Lehmann *et al.*, "Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies", *J Clin Invest.* Jul 1, 2011; 121(7): 2750–2767. Triple-negative breast cancers are those that do not express estrogen receptor (ER), progesterone receptor (PR) and Her2/neu. These cancers are difficult to treat because they are typically not responsive to agents that target ER, PR, and Her2/neu. Triple-negative breast cancers can be further subdivided into different classes, one of which is immunomodulatory. As described in Lehmann *et al.*, IM-TN breast cancer is enriched for factors involved in immune cell processes, for example, one or more of immune cell signaling (*e.g.*, TH1/TH2 pathway, NK cell pathway, B cell receptor signaling pathway, DC pathway, and T cell receptor signaling), cytokine signaling (*e.g.*, cytokine pathway, IL-12 pathway, and IL-7 pathway), antigen processing and presentation, signaling through core immune signal transduction pathways (*e.g.*, NFKB, TNF, and JAK/STAT signaling), genes involved in T-cell function, immune transcription, interferon (IFN) response and antigen processing. Accordingly, in some embodiments, the cancer treated is a cancer that is, or is determined to be, positive for one or more marker of IM-TN breast cancer, *e.g.*, a factor that promotes one or more of immune cell signaling (*e.g.*, TH1/TH2 pathway, NK cell pathway, B cell receptor signaling pathway, DC pathway, and T cell receptor signaling), cytokine signaling (*e.g.*, cytokine pathway, IL-12 pathway, and IL-7 pathway), antigen processing and

presentation, signaling through core immune signal transduction pathways (*e.g.*, NFKB, TNF, and JAK/STAT signaling), genes involved in T-cell function, immune transcription, interferon (IFN) response and antigen processing.

As another example, it is shown herein that a subset of colon cancer patients having high MSI (microsatellite instability) is also triple-positive for PD-L1/CD8/IFN-γ. Accordingly, in some embodiments, a PD-1 antibody, optionally in combination with one or more immunomodulators such as a TIM-3 antibody described herein, a LAG-3 antibody, or PD-L1 antibody, and one or more anti-cancer agents, *e.g.*, an anti-cancer agent described in Table 6 or in a publication in Table 6, is administered to a patient who has, or who is identified as having, colon cancer with high MSI, thereby treating the cancer. In some embodiments, a cell with high MSI is a cell having MSI at a level higher than a reference value or a control cell, *e.g.*, a non-cancerous cell of the same tissue type as the cancer.

As another example, it is shown herein that a subset of gastric cancer patients having high MSI, and/or which is EBV+, is also triple-positive for PD-L1/CD8/IFN-γ. Accordingly, in some embodiments, a PD-1 antibody, optionally in combination with one or more immunomodulators such as a TIM-3 antibody described herein, a LAG-3 antibody, or PD-L1 antibody, and one or more anti-cancer agents, *e.g.*, an anti-cancer agent described in Table 6 or in a publication in Table 6 is administered to a patient who has, or who is identified as having, gastric cancer with high MSI and/or EBV+, thereby treating the cancer. In some embodiments, a cell with high MSI is a cell having MSI at a level higher than a reference value or a control cell, *e.g.*, a non-cancerous cell of the same tissue type as the cancer.

Additionally disclosed herein are methods of assaying a cancer for PD-L1, and then treating the cancer with a PD-1 antibody, optionally in combination with one or more immunomodulators such as a TIM-3 antibody described herein, a LAG-3 antibody, or PD-L1 antibody. As described in Example 10 herein, a cancer sample can be assayed for PD-L1 protein levels or mRNA levels. A sample having levels of PD-L1 (protein or mRNA) higher than a reference value or a control cell (*e.g.*, a non-cancerous cell) can be classified as PD-L1 positive. Accordingly, in some embodiments, a PD-1 antibody (optionally in combination with one or more anti-cancer agents, optionally in combination with one or more immunomodulators such as a TIM-3 antibody described herein, a LAG-3 antibody, or PD-L1 antibody) is administered to a patient who has, or who is identified as having, a cancer that is PD-L1 positive. The cancer may

be, *e.g.*, non-small cell lung (NSCLC) adenocarcinoma (ACA), NSCLC squamous cell carcinoma (SCC), or hepatocellular carcinoma (HCC).

Based on, *e.g*, Example 9 herein, it was found that certain gastric cancers that are triple-positive for PDL1/CD8/IFN-γ are also positive for PIK3CA. Accordingly, in some embodiments, a cancer can be treated with an anti-PD-1 antibody molecule (optionally in combination with one or more immunomodulators, *e.g.*, an anti-LAG-3 antibody molecule, an anti-TIM-3 antibody molecule as described herein, or an anti-PD-L1 antibody molecule) and an agent that inhibits PIK3CA. Exemplary agents in this category are described in Stein RC (September 2001). "Prospects for phosphoinositide 3-kinase inhibition as a cancer treatment". Endocrine-related Cancer 8 (3): 237–48 and Marone R, Cmiljanovic V, Giese B, Wymann MP (January 2008). "Targeting phosphoinositide 3-kinase: moving towards therapy". Biochimica et Biophysica Acta 1784 (1): 159–85.

Based on, *e.g*, Example 9 herein, CRC, *e.g.*, a patient that has (or is identified as having) MSI-high CRC may be treated with a PD-1 antibody, optionally in combination with a therapeutic that targets one or more of TIM-3, *e.g.*, anti-TIM-3 antibody described herein, LAG-3, RNF43, and BRAF. For instance, these cancers may be treated with a PD-1 antibody, optionally in combination with one or more therapeutics that target one or more of TIM-3, LAG-3, PD-1, RNF43, and BRAF. In embodiments, the one or more therapeutics include an immunomodulators such as an anti-TIM-3 antibody described herein, an anti-LAG-3 antibody molecule, and an anti-cancer agent described in Table 6 or a publication listed in Table 6. LAG-3 inhibitors, *e.g.*, antibodies, are described herein. RNF43 can be inhibited, *e.g.*, with an antibody, small molecule (*e.g.*, 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28)), siRNA, or a Rspo ligand or derivative thereof. BRAF inhibitors (*e.g.*, vemurafenib or dabrafenib) are described herein.

Based on, *e.g*, Example 9 herein, a patient that has (or is identified as having) a squamous cell lung cancer may be treated with a PD-1 antibody molecule in combination with a therapeutic that targets TIM-3, *e.g.*, a TIM-3 antibody molecule, LAG-3, *e.g.*, a LAG-3 antibody molecule, and optionally with one or more anti-cancer agents, *e.g.*, an anti-cancer agent described in Table 6 or in a publication in Table 6.

In some embodiments, a subject that has (or is identified as having) a squamous cell lung cancer may be treated with a PD-1 antibody, optionally in combination with a therapeutic that targets TIM-3, *e.g.*, a TIM-3 antibody described herein.

Based on, *e.g*, Example 9 herein, a patient that has (or is identified as having) a thyroid cancer may be treated with a PD-1 antibody molecule, optionally in combination with a therapeutic that targets BRAF, and optionally in combination with one or more immunomodulators, *e.g.*, an anti-LAG-3 antibody molecule, an anti-TIM-3 antibody molecule described herein, and an anti-PD-L1 antibody molecule. BRAF inhibitors (*e.g.*, vemurafenib or dabrafenib) are described herein, *e.g.*, in Table 6 and the publications listed in Table 6.

In other embodiments, the cancer is a hematological malignancy or cancer including but is not limited to a leukemia or a lymphoma. For example, a anti-TIM-3 antibody molecule can be used to treat cancers and malignancies including, but not limited to, *e.g.*, acute leukemias including but not limited to, *e.g.,* B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to, *e.g.*, chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to, *e.g.*, B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, Follicular lymphoma, Hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like.

In some embodiments, the anti-TIM-3 antibody molecule is used to treat a cancer that expresses TIM-3. TIM-3-expressing cancers include cervical cancer (Cao et al., *PLoS One*. 2013;8(1):e53834), lung cancer (Zhuang et al., *Am J Clin Pathol*. 2012;137(6):978-985) (*e.g.*, non-small cell lung cancer), acute myeloid leukemia (Kikushige et al., *Cell Stem Cell.* 2010 Dec 3;7(6):708-17), diffuse large B cell lymphoma,melanoma (Fourcade et al., *JEM,* 2010; 207 (10): 2175), renal cancer (*e.g.,* renal cell carcinoma (RCC), *e.g.,* kidney clear cell carcinoma, kidney papillary cell carcinoma, or metastatic renal cell carcinoma), squamous cell carcinoma,

esophageal squamous cell carcinoma, nasopharyngeal carcinoma, colorectal cancer, breast cancer (*e.g.*, a breast cancer that does not express one, two or all of estrogen receptor, progesterone receptor, or Her2/neu, *e.g.*, a triple negative breast cancer), mesothelioma, hepatocellular carcinoma, and ovarian cancer. The TIM-3-expressing cancer may be a metastatic cancer. In other embodiments, the anti-TIM-3 antibody molecule is used to treat a cancer that is characterized by macrophage activity or high expression of macrophage cell markers. In an embodiment, the anti-TIM-3 antibody molecule is used to treat a cancer that is characterized by high expression of one or more of the following macrophage cell markers: LILRB4 (macrophage inhibitory receptor), CD14, CD16, CD68, MSR1, SIGLEC1, TREM2, CD163, ITGAX, ITGAM, CD11b, or CD11c. Examples of such cancers include, but are not limited to, diffuse large B-cell lymphoma, glioblastoma multiforme, kidney renal clear cell carcinoma, pancreatic adenocarcinoma, sarcoma, liver heptocellular carcinoma, lung adenocarcinoma, kidney renal papillary cell carcinoma, skin cutaneous melanoma, brain lower grade glioma, lung squamous cell carcinoma, ovarian serious cystadenocarcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, acute myeloid leukemia, cervical squamous cell carcinoma, endocervical adenocarcinoma, uterine carcinoma, colorectal cancer, uterine corpus endometrial carcinoma, thyroid carcinoma, bladder urothelial carcinoma, adrenocortical carcinoma, kidney chromophobe, and prostate adenocarcinoma.

In one embodiment, the cancer is a lung cancer, *e.g.*, a lung adenocarcinoma.

In another embodiment, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.,* a kidney clear cell carcinoma or a kidney papillary cell carcinoma), or a metastatic lesion thereof.

In yet another embodiment, the cancer is a mesothelioma.

In yet another embodiment, the cancer is a nasopharyngeal carcinoma (NPC).

In yet another embodiment, the cancer is a hematological cancer (*e.g.,* a myeloid leukemia, *e.g.,* acute myeloid leukemia (AML)).

In yet another embodiment, the cancer is a lymphoma (*e.g.*, diffuse large B cell lymphoma).

In yet another embodiment, the cancer is a breast cancer, *e.g.*, triple negative (TN) and/or immunomodulatory subtype.

In yet another embodiment, the cancer is glioblastoma multiforme.

In yet another embodiment, the cancer is an ovarian cancer (*e.g.,* ovarian carcinoma).

In certain embodiments, the cancer is a solid tumor and the antibody molecule is administered in combination with an anti-LAG-3 or anti-PD-1 antibody molecule.

Combination of Anti-TIM-3 antibodies with cancer vaccines

Antibody molecules to TIM-3 can be combined with an immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines (He et al (2004) J. Immunol. 173:4919-28). Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MART1 and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF, DNA-based vaccines, RNA-based vaccines, and viral transduction-based vaccines. The cancer vaccine may be prophylactic or therapeutic.

In some embodiments, therapy with an anti-TIM-3 antibody molecule is combined with a vaccination protocol. Many experimental strategies for vaccination against tumors have been devised (see Rosenberg, S., 2000, Development of Cancer Vaccines, ASCO Educational Book Spring: 60-62; Logothetis, C., 2000, ASCO Educational Book Spring: 300-302; Khayat, D. 2000, ASCO Educational Book Spring: 414-428; Foon, K. 2000, ASCO Educational Book Spring: 730-738; see also Restifo, N. and Sznol, M., *Cancer Vaccines*, Ch. 61, pp. 3023-3043 in DeVita, V. et al. (eds.), 1997, Cancer: Principles and Practice of Oncology. Fifth Edition). In one of these strategies, a vaccine is prepared using autologous or allogeneic tumor cells. These cellular vaccines have been shown to be most effective when the tumor cells are transduced to express GM-CSF. GM-CSF has been shown to be a potent activator of antigen presentation for tumor vaccination (Dranoff et al. (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90: 3539-43).

Anti-TIM-3 antibody molecules can be used in conjunction with a collection of recombinant proteins and/or peptides expressed in a tumor in order to generate an immune response to these proteins. These proteins are normally viewed by the immune system as self antigens and are therefore tolerant to them. The tumor antigen may also include the protein telomerase, which is required for the synthesis of telomeres of chromosomes and which is expressed in more than 85% of human cancers and in only a limited number of somatic tissues (Kim, N et al. (1994) *Science* 266: 2011-2013). (These somatic tissues may be protected from

immune attack by various means). Tumor antigens may also be "neo-antigens" expressed in cancer cells because of somatic mutations that alter protein sequence or create fusion proteins between two unrelated sequences (*e.g.*, bcr-abl in the Philadelphia chromosome), or idiotype from B cell tumors.

Other tumor vaccines may include the proteins from viruses implicated in human cancers such a Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV), and Epstein-Barr virus (EBV). Another form of tumor specific antigen which may be used in conjunction with an anti-TIM-3 antibody is purified heat shock proteins (HSP) isolated from the tumor tissue itself. These heat shock proteins contain fragments of proteins from the tumor cells and these HSPs are highly efficient at delivery to antigen presenting cells for eliciting tumor immunity (Suot, R & Srivastava, P (1995) *Science* 269:1585-1588; Tamura, Y. et al. (1997) *Science* 278:117-120).

Dendritic cells (DC) are potent antigen presenting cells that can be used to prime antigen-specific responses. DC's can be produced *ex vivo* and loaded with various protein and peptide antigens as well as tumor cell extracts (Nestle, F. et al. (1998) *Nature Medicine* 4: 328-332). DCs may also be transduced by genetic means to express these tumor antigens as well. DCs have also been fused directly to tumor cells for the purposes of immunization (Kugler, A. et al. (2000) *Nature Medicine* 6:332-336). As a method of vaccination, DC immunization may be effectively combined with an anti-TIM-3 therapy to activate more potent anti-tumor responses.

Alternatively or in combination, the combination further includes an inhibitor or activator of an immune checkpoint modulator, *e.g.*, a LAG-3 inhibitor (*e.g.*, an anti-TIM-3 antibody molecule), a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule), a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule), or a CTLA-4 inhibitor (*e.g.*, an anti-CTLA-4 antibody), or any combination thereof.

TIM-3 blockade may also be combined with a standard cancer treatment. TIM-3 blockade may be effectively combined with chemotherapeutic regimes. In these instances, it may be possible to reduce the dose of chemotherapeutic reagent administered (Mokyr, M. *et al.* (1998) *Cancer Research* 58: 5301-5304). In certain embodiments, the methods and compositions described herein are administered in combination with one or more of other antibody molecules, chemotherapy, other anti-cancer therapy (*e.g.*, targeted anti-cancer

therapies, or oncolytic drugs), cytotoxic agents, immune-based therapies (*e.g.*, cytokines), surgical and/or radiation procedures. Exemplary cytotoxic agents that can be administered in combination with include antimicrotubule agents, topoisomerase inhibitors, anti-metabolites, mitotic inhibitors, alkylating agents, anthracyclines, vinca alkaloids, intercalating agents, agents capable of interfering with a signal transduction pathway, agents that promote apoptosis, proteosome inhibitors, and radiation (*e.g.*, local or whole body irradiation).

Alternatively, or in combination with the aforesaid combinations, the methods and compositions described herein can be administered in combination with one or more of: an immunomodulator (*e.g.*, an activator of a costimulatory molecule or an inhibitor of an inhibitory molecule); a vaccine, *e.g.*, a therapeutic cancer vaccine; or other forms of cellular immunotherapy.

Exemplary non-limiting combinations and uses of the anti-TIM-3 antibody molecules include the following.

In certain embodiments, the anti-TIM-3 antibody molecule is administered in combination with a modulator of a costimulatory molecule or an inhibitory molecule, *e.g.*, a co-inhibitory ligand or receptor.

In one embodiment, the anti-TIM-3 antibody molecule is administered in combination with a modulator, *e.g.*, agonist, of a costimulatory molecule. In one embodiment, the agonist of the costimulatory molecule is chosen from an agonist (*e.g.*, an agonistic antibody or antigen-binding fragment thereof, or soluble fusion) of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand.

In another embodiment, the anti-TIM-3 antibody molecule is used in combination with a costimulatory molecule, *e.g.*, an agonist associated with a positive signal that includes a costimulatory domain of CD28, CD27, ICOS and GITR.

Exemplary GITR agonists include, *e.g.*, GITR fusion proteins and anti-GITR antibodies (*e.g.*, bivalent anti-GITR antibodies), such as, a GITR fusion protein described in U.S. Patent No.: 6,111,090, European Patent No.: 090505B1, U.S Patent No.: 8,586,023, PCT Publication Nos.: WO 2010/003118 and 2011/090754, or an anti-GITR antibody described, *e.g.,* in U.S. Patent No.: 7,025,962, European Patent No.: 1947183B1, U.S. Patent No.: 7,812,135, U.S. Patent No.: 8,388,967, U.S. Patent No.: 8,591,886, European Patent No.: EP 1866339, PCT

Publication No.: WO 2011/028683, PCT Publication No.:WO 2013/039954, PCT Publication No.: WO2005/007190, PCT Publication No.: WO 2007/133822, PCT Publication No.: WO2005/055808, PCT Publication No.: WO 99/40196, PCT Publication No.: WO 2001/03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/115451, U.S. Patent No.: 7,618,632, and PCT Publication No.: WO 2011/051726.

In one embodiment, the anti-TIM-3 antibody molecule is administered in combination with an inhibitor of an immune checkpoint molecule (or immune inhibitory molecule). The term "immune checkpoints" as used herein refers to a group of molecules on the cell surface of immune cells, *e.g.*, CD4 and CD8 T cells that can serve as "brakes" to down-modulate or inhibit an immune response, *e.g.*, an anti-tumor immune response. Immune checkpoint molecules include, but are not limited to, Programmed Death 1 (PD-1), PD-L1, Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), B7-H1, B7-H3, B7-H4, OX-40, 4-1BB (CD137), CD40, T-cell immunoglobulin domain and mucin domain-3 (TIM-3), and Lymphocyte-activation gene 3 (LAG-3), among others. Immunotherapeutic agents that can act as inhibitors of immune checkpoint molecules useful in combination with the anti-PD-1 molecules described herein, include, but are not limited to, inhibitors of PD-L1, PD-L2, CTLA-4, TIM-3, LAG-3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CEACAM (*e.g.*, CEACAM-1, CEACM-3, and/or CEACAM-5), and/or TGFR beta. Inhibition of an immune inhibitory molecule can be performed by inhibition at the DNA, RNA or protein level. In embodiments, an inhibitory nucleic acid (*e.g.*, a dsRNA, siRNA or shRNA), can be used to inhibit expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is, a polypeptide *e.g.*, a soluble ligand, or an antibody or antigen-binding fragment thereof, that binds to the inhibitory molecule.

In one embodiment, the inhibitor is a soluble ligand (*e.g.*, a CTLA-4-Ig or a TIM-3-Ig), or an antibody or antibody fragment that binds to CTLA-4. For example, the anti-TIM-3 antibody molecule can be administered in combination with an anti-CTLA-4 antibody, *e.g.*, ipilimumab, for example, to treat a cancer (*e.g.*, a cancer chosen from: a melanoma, *e.g.*, a metastatic melanoma; a lung cancer, *e.g.*, a non-small cell lung carcinoma; or a prostate cancer). Exemplary anti-CTLA-4 antibodies include Tremelimumab (IgG2 monoclonal antibody available from Pfizer, formerly known as ticilimumab, CP-675,206); and Ipilimumab (CTLA-4 antibody, also known as MDX-010, CAS No. 477202-00-9). In one embodiment, the anti-TIM-3

antibody molecule is administered after treatment, *e.g.*, after treatment of a melanoma, with an anti-CTLA-4 antibody (*e.g.*, ipilimumab) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib). Exemplary doses that can be use include a dose of anti-TIM-3 antibody molecule of about 1 to 30 mg/kg, 1 to 20 mg/kg, or 1 to 10 mg/kg, *e.g.*, 3 mg/kg, and a dose of an anti-CTLA-4 antibody, *e.g.*, ipilimumab, of about 3 mg/kg.

In certain embodiments, immune checkpoint molecules, *e.g.,* PD-1, LAG-3, TIM-3, CEACAM-1/-5, can regulate T-cell function to promote tumoral immune escape. Thus, the anti-TIM-3 antibodies described herein can be used in combination with one or more inhibitors of these immune inhibitor molecules to enhance an anti-tumor response. The combination of antibodies recited herein can be administered separately, *e.g.*, as separate antibodies, or linked, *e.g.*, as a bispecific or trispecific antibody molecule.

In one embodiment, the anti-TIM-3 antibody molecule is administered in combination with an anti-TIM-3 antibody or an antigen-binding fragment thereof. In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with an anti-PD-1 antibody or antigen-binding fragment thereof. In yet other embodiments, the anti-TIM-3 antibody molecule is administered in combination with an anti-TIM-3 antibody and an anti-PD-1 antibody, or antigen-binding fragments thereof. In one embodiment, a bispecific antibody that includes an anti-TIM-3 antibody molecule and an anti-PD-1 or anti-TIM-3 antibody, or antigen-binding fragment thereof, is administered. In certain embodiments, the combination of antibodies recited herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor). The efficacy of the aforesaid combinations can be tested in animal models known in the art. For example, the animal models to test the effect of anti-PD-1 and anti-LAG-3 are described, *e.g.,* in Woo *et al.* (2012) *Cancer Res.* 72(4):917-27).

In some embodiments, the inhibitors of the TIM-3 and PD-1 molecules (*e.g.*, anti-TIM-3 and anti-PD-1 antibody molecules) are administered in combination, *e.g.*, to treat cancer. In some embodiments, the subject is a patient who has progressed (*e.g.*, experienced tumor growth) during therapy with a PD-1 inhibitor (*e.g.*, an antibody molecule as described herein) and/or a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule). In some embodiments, therapy with the PD-1 antibody molecule and/or PD-L1 antibody molecule is continued, and a TIM-3 immune inhibitory molecule (*e.g.*, antibody) is added to the therapy.

In other embodiments, the anti-TIM-3 antibody molecule is administered in combination with a CEACAM inhibitor (*e.g.*, CEACAM-1, CEACAM-3, and/or CEACAM-5 inhibitor). In one embodiment, the inhibitor of CEACAM is an anti-CEACAM antibody molecule. In one embodiment, the anti-TIM-3 antibody molecule is administered in combination with a CEACAM-1 inhibitor, *e.g.*, an anti- CEACAM-1 antibody molecule. In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with a CEACAM-3 inhibitor, *e.g.*, an anti- CEACAM-3 antibody molecule. In another embodiment, the anti-TIM-3 antibody molecule is administered in combination with a CEACAM-5 inhibitor, *e.g.*, an anti- CEACAM-5 antibody molecule. Exemplary anti-CEACAM-1 antibodies are described in WO 2010/125571, WO 2013/082366 and WO 2014/022332, *e.g.,* a monoclonal antibody 34B1, 26H7, and 5F4; or a recombinant form thereof, as described in, *e.g.*, US 2004/0047858, US 7,132,255 and WO 99/052552. In other embodiments, the anti-CEACAM antibody binds to CEACAM-5 as described in, *e.g.*, Zheng et al. *PLoS One*. 2010 Sep 2;5(9). pii: e12529 (DOI:10:1371/journal.pone.0021146), or crossreacts with CEACAM-1 and CEACAM-5 as described in, *e.g.*, WO 2013/054331 and US 2014/0271618.

Without wishing to be bound by theory, carcinoembryonic antigen cell adhesion molecules (CEACAM), such as CEACAM-1 and CEACAM-5, are believed to mediate, at least in part, inhibition of an anti-tumor immune response (*see e.g.*, Markel *et al. J Immunol*. 2002 Mar 15;168(6):2803-10; Markel et al. *J Immunol*. 2006 Nov 1;177(9):6062-71; Markel et al. *Immunology*. 2009 Feb;126(2):186-200; Markel et al. *Cancer Immunol Immunother*. 2010 Feb;59(2):215-30; Ortenberg et al. *Mol Cancer Ther*. 2012 Jun;11(6):1300-10; Stern et al. *J Immunol*. 2005 Jun 1;174(11):6692-701; Zheng et al. *PLoS One*. 2010 Sep 2;5(9). pii: e12529). For example, CEACAM-1 has been described as a heterophilic ligand for TIM-3 and as playing a role in TIM-3-mediated T cell tolerance and exhaustion (*see e.g.*, WO 2014/022332; Huang, *et al.* (2014) *Nature* doi:10.1038/nature13848). In embodiments, co-blockade of CEACAM-1 and TIM-3 has been shown to enhance an anti-tumor immune response in xenograft colorectal cancer models (*see e.g.*, WO 2014/022332; Huang, *et al.* (2014), *supra*). In other embodiments, co-blockade of CEACAM-1 and PD-1 reduce T cell tolerance as described, *e.g.*, in WO 2014/059251. Thus, CEACAM inhibitors can be used with the other immunomodulators described herein (*e.g.*, anti-PD-1 and/or anti-TIM-3 inhibitors) to enhance an immune response

against a cancer, *e.g.*, a melanoma, a lung cancer (*e.g.*, NSCLC), a bladder cancer, a colon cancer an ovarian cancer, and other cancers as described herein.

In some embodiments, the PD-1 and TIM-3 immune inhibitory molecules (*e.g.*, antibody molecules) are administered in combination with each other, *e.g.*, to treat cancer. In some embodiments, the patient is a patient who progressed (*e.g.*, experienced tumor growth) during therapy with a PD-1 inhibitor (*e.g.*, an antibody molecule as described herein) and/or a PDL1 inhibitor (*e.g.*, antibody molecule). In some embodiments, therapy with the PD-1 antibody molecule and/or PDL1 antibody molecule is continued, and a TIM-3 immune inhibitory molecule (*e.g.*, antibody) is added to the therapy.

In some embodiments, the TIM-3 and LAG-3 immune inhibitory molecules (*e.g.*, antibody molecules) are administered in combination with each other, *e.g.*, to treat cancer. In some embodiments, the patient is a patient who progressed (*e.g.*, experienced tumor growth) during therapy with a TIM-3 inhibitor (*e.g.*, an antibody molecule as described herein) and/or a PD-1 inhibitor (*e.g.*, antibody molecule). In some embodiments, therapy with the anti-TIM-3 antibody molecule and/or PDL1 antibody molecule is continued, and a LAG-3 immune inhibitory molecule (*e.g.*, antibody) is added to the therapy.

In other embodiments, the anti-TIM-3 antibody molecule is administered in combination with a cytokine, *e.g.*, interleukin-21, interleukin-2, or interleukin 15. In certain embodiments, the combination of anti-TIM-3 antibody molecule and cytokine described herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor or melanoma).

Exemplary immunomodulators that can be used in combination with anti-TIM-3 antibody molecules include, but are not limited to, *e.g.*, afutuzumab (available from Roche®); pegfilgrastim (Neulasta®); lenalidomide (CC-5013, Revlimid®); thalidomide (Thalomid®), actimid (CC4047); and cytokines, *e.g.*, IL-21 or IRX-2 (mixture of human cytokines including interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics).

In yet other embodiments, the anti-TIM-3 antibody molecule is used in combination with an indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor (*e.g.*, INCB24360) in a subject with advanced or metastatic cancer (*e.g.*, a patient with metastic and recurrent NSCL cancer).

In other embodiments, the anti-TIM-3 antibody molecules are administered to a subject in conjunction with (*e.g.,* before, simultaneously or following) one or more of: bone marrow

transplantation, T cell ablative therapy using chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, and/or antibodies such as OKT3 or CAMPATH. In one embodiment, the anti-TIM-3 antibody molecules are administered following B-cell ablative therapy such as agents that react with CD20, *e.g.*, Rituxan. For example, in one embodiment, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain embodiments, following the transplant, subjects receive the anti-TIM-3 antibody molecules. In an additional embodiment, the anti-TIM-3 antibody molecules are administered before or following surgery.

Another example of a combination is an anti-TIM-3 antibody in combination with decarbazine for the treatment of melanoma. Without being bound by theory, the combined use of TIM-3 blockade and chemotherapy is believed to be facilitated by cell death, that is a consequence of the cytotoxic action of most chemotherapeutic compounds, which can result in increased levels of tumor antigen in the antigen presentation pathway. Other combination therapies that may result in synergy with TIM-3 blockade through cell death are radiation, surgery, and hormone deprivation. Each of these protocols creates a source of tumor antigen in the host. Angiogenesis inhibitors may also be combined with TIM-3 blockade. Inhibition of angiogenesis leads to tumor cell death which may feed tumor antigen into host antigen presentation pathways.

TIM-3 blocking antibodies can also be used in combination with bispecific antibodies. Bispecific antibodies can be used to target two separate antigens. For example anti-Fc receptor/anti tumor antigen (*e.g.*, Her-2/neu) bispecific antibodies have been used to target macrophages to sites of tumor. This targeting may more effectively activate tumor specific responses. The T cell arm of these responses would be augmented by the use of TIM-3 blockade. Alternatively, antigen may be delivered directly to DCs by the use of bispecific antibodies which bind to tumor antigen and a dendritic cell specific cell surface marker.

Tumors evade host immune surveillance by a large variety of mechanisms. Many of these mechanisms may be overcome by the inactivation of proteins which are expressed by the tumors and which are immunosuppressive. These include among others TGF-beta (Kehrl, J. *et al.* (1986) *J. Exp. Med.* 163: 1037-1050), IL-10 (Howard, M. & O'Garra, A. (1992) *Immunology Today* 13: 198-200), and Fas ligand (Hahne, M. *et al.* (1996) *Science* 274: 1363-1365). Antibodies or antigen-binding fragments thereof to each of these entities may be used in

combination with anti-TIM-3 antibody molecules to counteract the effects of the immunosuppressive agent and favor tumor immune responses by the host.

Other antibodies which may be used to activate host immune responsiveness can be used in combination with anti-TIM-3 antibody molecules. These include molecules on the surface of dendritic cells which activate DC function and antigen presentation. Anti-CD40 antibodies are able to substitute effectively for T cell helper activity (Ridge, J. *et al.* (1998) *Nature* 393: 474-478) and can be used in conjunction with PD-1 antibodies (Ito, N. *et al.* (2000) I*mmunobiology* 201 (5) 527-40). Antibodies to T cell costimulatory molecules such as CTLA-4 (*e.g.,* U.S. Pat. No. 5,811,097), OX-40 (Weinberg, A. *et al.* (2000) *Immunol* 164: 2160-2169), 4-1BB (Melero, I. *et al.* (1997) *Nature Medicine* 3: 682-685 (1997), and ICOS (Hutloff, A. *et al.* (1999) *Nature* 397: 262-266) may also provide for increased levels of T cell activation.

Additional exemplary standard of care treatments are described in the section entitled "Combination Therapies" below.

In all of the methods described herein, TIM-3 blockade can be combined with other forms of immunotherapy such as cytokine treatment (*e.g.,* interferons, GM-CSF, G-CSF, IL-2, IL-21), or bispecific antibody therapy, which provides for enhanced presentation of tumor antigens (*see e.g.*, Holliger (1993) *Proc. Natl. Acad. Sci.* USA 90:6444-6448; Poljak (1994) *Structure* 2:1121-1123).

Methods of administering the antibody molecules are known in the art and are described below. Suitable dosages of the molecules used will depend on the age and weight of the subject and the particular drug used. Dosages and therapeutic regimens of the anti-TIM-3 antibody molecule can be determined by a skilled artisan. In certain embodiments, the anti-TIM-3 antibody molecule is administered by injection (*e.g.*, subcutaneously or intravenously) at a dose of about 1 to 30 mg/kg, *e.g.*, about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, or about 3 mg/kg. In some embodiments, the anti-TIM-3 antibody molecule is administered at a dose of about 1 mg/kg, about 3 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg or about 30 mg/kg. In some embodiments, the anti-TIM-3 antibody molecule is administered at a dose of about 1-3 mg/kg, about 3-10 mg/kg, about 3-15 mg/kg, about 10-15 mg/kg, about 10-20 mg/kg, about 10-25 mg/kg, or about 20-30 mg/kg. In some embodiments, the anti-TIM-3 antibody molecule is administered at a dose of about 0.5-2, 2-4, 2-5, or 5-15 mg/kg. The dosing schedule can vary from *e.g.*, once a week to once every 2, 3, or 4 weeks. In

one embodiment, the anti-TIM-3 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week.

The antibody molecules can be used by themselves or conjugated to a second agent, *e.g.*, a cytotoxic drug, radioisotope, or a protein, *e.g.*, a protein toxin or a viral protein. This method includes: administering the antibody molecule, alone or conjugated to a cytotoxic drug, to a subject requiring such treatment. The antibody molecules can be used to deliver a variety of therapeutic agents, *e.g.*, a cytotoxic moiety, *e.g.*, a therapeutic drug, a radioisotope, molecules of plant, fungal, or bacterial origin, or biological proteins (*e.g.*, protein toxins) or particles (*e.g.*, a recombinant viral particles, *e.g.*; via a viral coat protein), or mixtures thereof.

Anti-TIM-3 antibody molecules may also be combined with standard cancer treatments. For instance, anti-TIM-3 antibody molecules may be effectively combined with chemotherapeutic regimes. In these instances, it may be possible to reduce the dose of chemotherapeutic reagent administered (Mokyr, M. et al. (1998) Cancer Research 58: 5301-5304). An example of such a combination is an anti-TIM-3 antibody molecule in combination with decarbazine for the treatment of melanoma. Another example of such a combination is an anti-TIM-3 antibody molecule in combination with interleukin-2 (IL-2) for the treatment of melanoma. In some embodiments the anti-TIM-3 antibody molecule can be combined with IL-21. While not wishing to be bound by theory, one scientific rationale behind the combined use of anti-TIM-3 antibody molecule therapy and chemotherapy is that cell death, that is a consequence of the cytotoxic action of most chemotherapeutic compounds, should result in increased levels of tumor antigen in the antigen presentation pathway. Other combination therapies that may result in synergy with anti-TIM-3 antibody molecule therapy through cell death are radiation, surgery, and hormone deprivation. Each of these protocols creates a source of tumor antigen in the host. Angiogenesis inhibitors may also be combined with anti-TIM-3 antibody molecule therapy. Inhibition of angiogenesis leads to tumor cell death which may feed tumor antigen into host antigen presentation pathways.Anti-TIM-3 antibody molecules can also be used in combination with bispecific antibodies. Bispecific antibodies can be used to target two separate antigens. For example anti-Fc receptor/anti tumor antigen (*e.g.*, Her-2/neu) bispecific antibodies have been used to target macrophages to sites of tumor. This targeting may more effectively activate tumor specific responses. The T cell arm of these responses would be augmented by the use of anti-TIM-3 antibody molecules. Alternatively, antigen may be delivered

directly to DCs by the use of bispecific antibodies which bind to tumor antigen and a dendritic cell specific cell surface marker.

Tumors evade host immune surveillance by a large variety of mechanisms. Many of these mechanisms may be overcome by the inactivation of proteins which are expressed by the tumors and which are immunosuppressive. These include among others TGF-beta (Kehrl, J. et al. (1986) J. Exp. Med. 163: 1037-1050), IL-10 (Howard, M. & O'Garra, A. (1992) Immunology Today 13: 198-200), and Fas ligand (Hahne, M. et al. (1996) Science 274: 1363-1365). Antibodies to each of these entities may be used in combination with anti-TIM-3 antibody molecules to counteract the effects of the immunosuppressive agent and favor tumor immune responses by the host.

Other antibodies which may be used to activate host immune responsiveness can be used in combination with anti-TIM-3 antibody molecules. These include molecules on the surface of dendritic cells which activate DC function and antigen presentation. Anti-CD40 antibodies are able to substitute effectively for T cell helper activity (Ridge, J. et al. (1998) Nature 393: 474-478) and can be used in conjunction with anti-TIM-3 antibody molecules (see Ito, N. et al. (2000) Immunobiology 201 (5) 527-40). Activating antibodies to T cell costimulatory molecules such as CTLA-4 (*e.g.*, U.S. Pat. No. 5,811,097), OX-40 (Weinberg, A. et al. (2000) Immunol 164: 2160-2169), 4-1BB (Melero, I. et al. (1997) Nature Medicine 3: 682-685 (1997), and ICOS (Hutloff, A. et al. (1999) Nature 397: 262-266) may also provide for increased levels of T cell activation.

Additional Combination Therapies

The anti-TIM-3 antibody molecule can be used in combination with other therapies. For example, the combination therapy can include a composition of the present invention co-formulated with, and/or co-administered with, one or more additional therapeutic agents, *e.g.*, one or more anti-cancer agents, cytotoxic or cytostatic agents, hormone treatment, vaccines, and/or other immunotherapies. In other embodiments, the antibody molecules are administered in combination with other therapeutic treatment modalities, including surgery, radiation, cryosurgery, and/or thermotherapy. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

By "in combination with," it is not intended to imply that the therapy or the therapeutic agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope described herein. The anti-TIM-3 antibody molecules can be administered concurrently with, prior to, or subsequent to, one or more other additional therapies or therapeutic agents. The anti-TIM-3 antibody molecule and the other agent or therapeutic protocol can be administered in any order. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutic agent utilized in this combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that additional therapeutic agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

In certain embodiments, the anti-TIM-3 antibody molecules described herein are administered in combination with one or more other inhibitors of TIM-3 or other immune checkpoint molecules, *e.g.*, PD-1, PD-L1, PD-L2, CEACAM (*e.g.*, CEACAM-1, CEACAM-3, or CEACAM-5), or LAG-3.

In certain embodiments, the anti-TIM-3 antibody molecules described herein are administered in combination with one or more other inhibitors of PD-1, PD-L1 and/or PD-L2 known in the art. The antagonist may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or oligopeptide. In some embodiments, the anti-PD-1 antibody is chosen from MDX-1106, Merck 3475 or CT- 011. In some embodiments, the PD-1 inhibitor is an immunoadhesin (*e.g.*, an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-Ll or PD-L2 fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence). In some embodiments, the PD-1 inhibitor is AMP-224. In some embodiments, the PD-Ll inhibitor is anti-PD-Ll antibody. In some embodiments, the anti-PD-Ll binding antagonist is chosen from YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, or MDX-1105. MDX-1105, also known as BMS-936559, is an anti-PD-Ll antibody described in WO2007/005874. Antibody YW243.55.S70 (heavy and light chain variable region sequences shown in SEQ ID Nos. 20 and 21, respectively) is an anti-PD-Ll described in WO 2010/077634.

MDX-1106, also known as MDX-1106-04, ONO-4538 or BMS-936558, is an anti-PD-1 antibody described in WO2006/121168. Merck 3745, also known as MK-3475 or SCH-900475,

is an anti-PD-1 antibody described in WO2009/114335. Pidilizumab (CT-011; Cure Tech) is a humanized IgG1k monoclonal antibody that binds to PD-1. Pidilizumab and other humanized anti-PD-1 monoclonal antibodies are disclosed in WO2009/101611. In other embodiments, the anti-PD-1 antibody is pembrolizumab. Pembrolizumab (Trade name Keytruda formerly lambrolizumab-also known as MK-3475) disclosed, *e.g.*, in Hamid, O. *et al.* (2013) *New England Journal of Medicine* 369 (2): 134–44. AMP-224 (B7-DCIg; Amplimmune; *e.g.*, disclosed in WO2010/027827 and WO2011/066342), is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD-1 and B7-H1. Other anti-PD-1 antibodies include AMP 514 (Amplimmune), among others, *e.g.*, anti-PD-1 antibodies disclosed in US 8,609,089, US 2010028330, and/or US 20120114649.

In some embodiments, the anti-PD-1 antibody is MDX-1106. Alternative names for MDX- 1106 include MDX-1106-04, ONO-4538, BMS-936558 or Nivolumab. In some embodiments, the anti-PD-1 antibody is Nivolumab (CAS Registry Number: 946414-94-4). Nivolumab (also referred to as BMS-936558 or MDX1106; Bristol-Myers Squibb) is a fully human IgG4 monoclonal antibody which specifically blocks PD-1. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD-1 are disclosed in US 8,008,449 and WO2006/121168. Pembrolizumab (Trade name Keytruda formerly lambrolizumab-also known as MK-3475; Merck) is a humanized IgG4 monoclonal antibody that binds to PD-1. Lambrolizumab and other humanized anti-PD-1 antibodies are disclosed in US 8,354,509 and WO2009/114335. MDPL3280A (Genentech / Roche) is a human Fc optimized IgG1 monoclonal antibody that binds to PD-L1. MDPL3280A and other human monoclonal antibodies to PD-L1 are disclosed in U.S. Patent No.: 7,943,743 and U.S Publication No.: 20120039906. Other anti-PD-L1 binding agents include YW243.55.S70 (heavy and light chain variable regions are shown in SEQ ID NOs 20 and 21 in WO2010/077634) and MDX-1105 (also referred to as BMS-936559, and, *e.g.*, anti-PD-L1 binding agents disclosed in WO2007/005874).

Cancer Therapies

Exemplary combinations of anti-TIM-3 antibody molecules (alone or in combination with other stimulatory agents) and standard of care for cancer, include at least the following. In certain embodiments, the anti-TIM-3 antibody molecule, *e.g.*, the anti-TIM-3 antibody molecule described herein, is used in combination with a standard of cancer care

chemotherapeutic agent including, but not limited to, anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®), Ibrutinib, idelalisib, and brentuximab vedotin.

Exemplary alkylating agents include, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): uracil mustard (Aminouracil Mustard®, Chlorethaminacil®, Demethyldopan®, Desmethyldopan®, Haemanthamine®, Nordopan®, Uracil nitrogen mustard®, Uracillost®, Uracilmostaza®, Uramustin®, Uramustine®), chlormethine (Mustargen®), cyclophosphamide (Cytoxan®, Neosar®, Clafen®, Endoxan®, Procytox®, Revimmune™), ifosfamide (Mitoxana®), melphalan (Alkeran®), Chlorambucil (Leukeran®), pipobroman (Amedel®, Vercyte®), triethylenemelamine (Hemel®, Hexalen®, Hexastat®), triethylenethiophosphoramine, Temozolomide (Temodar®), thiotepa (Thioplex®), busulfan (Busilvex®, Myleran®), carmustine (BiCNU®), lomustine (CeeNU®), streptozocin

(Zanosar®), and Dacarbazine (DTIC-Dome®). Additional exemplary alkylating agents include, without limitation, Oxaliplatin (Eloxatin®); Temozolomide (Temodar® and Temodal®); Dactinomycin (also known as actinomycin-D, Cosmegen®); Melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, Alkeran®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Carmustine (BiCNU®); Bendamustine (Treanda®); Busulfan (Busulfex® and Myleran®); Carboplatin (Paraplatin®); Lomustine (also known as CCNU, CeeNU®); Cisplatin (also known as CDDP, Platinol® and Platinol®-AQ); Chlorambucil (Leukeran®); Cyclophosphamide (Cytoxan® and Neosar®); Dacarbazine (also known as DTIC, DIC and imidazole carboxamide, DTIC-Dome®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Ifosfamide (Ifex®); Prednumustine; Procarbazine (Matulane®); Mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, Mustargen®); Streptozocin (Zanosar®); Thiotepa (also known as thiophosphoamide, TESPA and TSPA, Thioplex®); Cyclophosphamide (Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®); and Bendamustine HCl (Treanda®).

Exemplary anthracyclines include, *e.g.*, doxorubicin (Adriamycin® and Rubex®); bleomycin (lenoxane®); daunorubicin (dauorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, Cerubidine®); daunorubicin liposomal (daunorubicin citrate liposome, DaunoXome®); mitoxantrone (DHAD, Novantrone®); epirubicin (Ellence™); idarubicin (Idamycin®, Idamycin PFS®); mitomycin C (Mutamycin®); geldanamycin; herbimycin; ravidomycin; and desacetylravidomycin.

Exemplary vinca alkaloids that can be used in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), include, but ate not limited to, vinorelbine tartrate (Navelbine®), Vincristine (Oncovin®), and Vindesine (Eldisine®)); vinblastine (also known as vinblastine sulfate, vincaleukoblastine and VLB, Alkaban-AQ® and Velban®); and vinorelbine (Navelbine®).

Exemplary proteosome inhibitors that can be used in combination with the anti-PD-1 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-TIM-3 antibody molecule), include, but ate not limited to, bortezomib (Velcade®); carfilzomib (PX-171-007, (*S*)-4-Methyl-*N*-((*S*)-1-(((*S*)-4-methyl-1-((*R*)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)-2-((*S*)-2-(2-

morpholinoacetamido)-4-phenylbutanamido)-pentanamide); marizomib (NPI-0052); ixazomib citrate (MLN-9708); delanzomib (CEP-18770); and *O*-Methyl-*N*-[(2-methyl-5-thiazolyl)carbonyl]-L-seryl-*O*-methyl-*N*-[(1*S*)-2-[(2*R*)-2-methyl-2-oxiranyl]-2-oxo-1-(phenylmethyl)ethyl]- L-serinamide (ONX-0912).

In some embodiments, the anti-TIM-3 antibody molecule, *e.g.*, the anti-TIM-3antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), in combination with a tyrosine kinase inhibitor (*e.g.*, a receptor tyrosine kinase (RTK) inhibitor). Exemplary tyrosine kinase inhibitor include, but are not limited to, an epidermal growth factor (EGF) pathway inhibitor (*e.g.*, an epidermal growth factor receptor (EGFR) inhibitor), a vascular endothelial growth factor (VEGF) pathway inhibitor (*e.g.*, a vascular endothelial growth factor receptor (VEGFR) inhibitor (*e.g.*, a VEGFR-1 inhibitor, a VEGFR-2 inhibitor, a VEGFR-3 inhibitor)), a platelet derived growth factor (PDGF) pathway inhibitor (*e.g.*, a platelet derived growth factor receptor (PDGFR) inhibitor (*e.g.*, a PDGFR-ß inhibitor)), a RAF-1 inhibitor, a KIT inhibitor and a RET inhibitor. In some embodiments, the anti-cancer agent used in combination with the hedgehog inhibitor is selected from the group consisting of: axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTIN™, AZD2171), dasatinib (SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib (IRESSA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN®), bevacizumab (AVASTIN®), rituximab (RITUXAN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), nilotinib (TASIGNA®), sorafenib (NEXAVAR®), alemtuzumab (CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOK™), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, XL228, AEE788, AG-490, AST-6, BMS-599626, CUDC-101, PD153035, pelitinib (EKB-569), vandetanib (zactima), WZ3146, WZ4002, WZ8040, ABT-869 (linifanib), AEE788, AP24534 (ponatinib), AV-951(tivozanib), axitinib, BAY 73-4506 (regorafenib),

brivanib alaninate (BMS-582664), brivanib (BMS-540215), cediranib (AZD2171), CHIR-258 (dovitinib), CP 673451, CYC116, E7080, Ki8751, masitinib (AB1010), MGCD-265, motesanib diphosphate (AMG-706), MP-470, OSI-930, Pazopanib Hydrochloride, PD173074, Sorafenib Tosylate(Bay 43-9006), SU 5402, TSU-68(SU6668), vatalanib, XL880 (GSK1363089, EXEL-2880). Selected tyrosine kinase inhibitors are chosen from sunitinib, erlotinib, gefitinib, or sorafenib.

In certain embodiments, the anti-TIM-3 antibody molecule, *e.g.*, the anti-TIM-3 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), in combination with a Vascular Endothelial Growth Factor (VEGF) receptor inhibitors, including but not limited to, Bevacizumab (Avastin®), axitinib (Inlyta®); Brivanib alaninate (BMS-582664, (*S*)-((*R*)-1-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate); Sorafenib (Nexavar®); Pazopanib (Votrient®); Sunitinib malate (Sutent®); Cediranib (AZD2171, CAS 288383-20-1); Vargatef (BIBF1120, CAS 928326-83-4); Foretinib (GSK1363089); Telatinib (BAY57-9352, CAS 332012-40-5); Apatinib (YN968D1, CAS 811803-05-1); Imatinib (Gleevec®); Ponatinib (AP24534, CAS 943319-70-8); Tivozanib (AV951, CAS 475108-18-0); Regorafenib (BAY73-4506, CAS 755037-03-7); Vatalanib dihydrochloride (PTK787, CAS 212141-51-0); Brivanib (BMS-540215, CAS 649735-46-6); Vandetanib (Caprelsa® or AZD6474); Motesanib diphosphate (AMG706, CAS 857876-30-3, N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, described in PCT Publication No. WO 02/066470); Dovitinib dilactic acid (TKI258, CAS 852433-84-2); Linfanib (ABT869, CAS 796967-16-3); Cabozantinib (XL184, CAS 849217-68-1); Lestaurtinib (CAS 111358-88-4); N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (BMS38703, CAS 345627-80-7); (3R,4R)-4-Amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); *N*-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[(3aα,5β,6aα)-octahydro-2-methylcyclopenta[*c*]pyrrol-5-yl]methoxy]- 4-quinazolinamine (XL647, CAS 781613-23-8); 4-Methyl-3-[[1-methyl-6-(3-pyridinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]amino]-*N*-[3-(trifluoromethyl)phenyl]-benzamide (BHG712, CAS 940310-85-0); and Aflibercept (Eylea®).

Exemplary anti-VEGF antibodies include, but are not limited to, a monoclonal antibody that binds to the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709; a recombinant humanized anti-VEGF monoclonal antibody generated according to Presta *et al.* (1997) *Cancer Res.* 57:4593-4599. In one embodiment, the anti-VEGF antibody is Bevacizumab (BV), also known as rhuMAb VEGF or AVASTIN®. It comprises mutated human IgGl framework regions and antigen-binding complementarity-determining regions from the murine anti-hVEGF monoclonal antibody A.4.6.1 that blocks binding of human VEGF to its receptors. Bevacizumab and other humanized anti-VEGF antibodies are further described in U.S. Pat. No. 6,884,879 issued Feb. 26, 2005. Additional antibodies include the G6 or B20 series antibodies (*e.g.*, G6-31, B20-4.1), as described in PCT Publication No. WO2005/012359, PCT Publication No. WO2005/044853, the contents of these patent applications are expressly incorporated herein by reference. For additional antibodies see U.S. Pat. Nos. 7,060,269, 6,582,959, 6,703,020, 6,054,297, W098/45332, WO 96/30046, WO94/10202, EP 0666868B1, U.S. Patent Application Publication Nos. 2006009360, 20050186208, 20030206899, 20030190317, 20030203409, and 20050112126; and Popkov *et al, Journal of Immunological Methods* 288: 149-164 (2004). Other antibodies include those that bind to a functional epitope on human VEGF comprising of residues F17, Ml 8, D19, Y21, Y25, Q89, 191 , Kl 01, El 03, and C104 or, alternatively, comprising residues F17, Y21, Q22, Y25, D63, 183 and Q89.

In some embodiments, the anti-TIM-3 antibody molecule, *e.g.*, the anti-TIM-3 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), in combination with a PI3K inhibitor. In one embodiment, the PI3K inhibitor is an inhibitor of delta and gamma isoforms of PI3K. Exemplary PI3K inhibitors that can be used in combination are described in, *e.g.*, WO 2010/036380, WO 2010/006086, WO 09/114870, WO 05/113556, GSK 2126458, GDC-0980, GDC-0941, Sanofi XL147, XL756, XL147, PF-46915032, BKM 120, CAL-101, CAL 263, SF1126, PX-886, and a dual PI3K inhibitor (*e.g.*, Novartis BEZ235).

In some embodiments, the anti-TIM-3 antibody molecules described herein is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), in combination with a mTOR inhibitor, *e.g.*, one or more mTOR inhibitors chosen from one or more of rapamycin, temsirolimus (TORISEL®), AZD8055, BEZ235,

BGT226, XL765, PF-4691502, GDC0980, SF1126, OSI-027, GSK1059615, KU-0063794, WYE-354, Palomid 529 (P529), PF-04691502, or PKI-587. ridaforolimus (formally known as deferolimus, (1*R*,2*R*,4*S*)-4-[(2*R*)-2 [(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*, 23*S*,24*E*,26*E*,28*Z*,30*S*,32*S*,35*R*)-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23, 29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$] hexatriaconta-16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669, and described in PCT Publication No. WO 03/064383); everolimus (Afinitor® or RAD001); rapamycin (AY22989, Sirolimus®); simapimod (CAS 164301-51-3); emsirolimus, (5-{2,4-Bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl}-2-methoxyphenyl)methanol (AZD8055); 2-Amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (PF04691502, CAS 1013101-36-4); and N^2-[1,4-dioxo-4-[[4-(4-oxo-8-phenyl-4*H*-1-benzopyran-2-yl)morpholinium-4-yl]methoxy]butyl]-L-arginylglycyl-L-α-aspartylL-serine-, inner salt (SF1126, CAS 936487-67-1), and XL765.

In some embodiments, the anti-TIM-3 antibody molecule, *e.g.*, the anti-TIM-3 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), in combination with a BRAF inhibitor, *e.g.*, GSK2118436, RG7204, PLX4032, GDC-0879, PLX4720, and sorafenib tosylate (Bay 43-9006).

In some embodiments, the anti-TIM-3 antibody molecule, *e.g.*, the anti-TIM-3 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), in combination with a MEK inhibitor. In some embodiments, the combination of the anti-TIM-3 antibody and the MEK inhibitor is used to treat a cancer (*e.g.*, a cancer described herein). In some embodiments, the cancer treated with the combination is chosen from a melanoma, a colorectal cancer, a non-small cell lung cancer, an ovarian cancer, a breast cancer, a prostate cancer, a pancreatic cancer, a hematological malignancy or a renal cell carcinoma. In certain embodiments, the cancer includes a BRAF mutation (*e.g.*, a BRAF V600E mutation), a BRAF wildtype, a KRAS wildtype or an activating KRAS mutation. The cancer may be at an early, intermediate or late stage. Any MEK inhibitor can be used in combination including, but not limited to, ARRY-142886, G02442104 (also known as GSK1120212), RDEA436, RDEA119/BAY 869766, AS703026,

G00039805 (also known as AZD-6244 or selumetinib), BIX 02188, BIX 02189, CI-1040 (PD-184352), PD0325901, PD98059, U0126, GDC-0973 (Methanone, [3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl][3- hydroxy-3-(25)-2-piperidinyl- 1 -azetidinyl]-), G-38963, G02443714 (also known as AS703206), or a pharmaceutically acceptable salt or solvate thereof..Additional examples of MEK inhibitors are disclosed in WO 2013/019906, WO 03/077914, WO 2005/121142, WO 2007/04415, WO 2008/024725 and WO 2009/085983, the contents of which are incorporated herein by reference.

In some embodiments, the anti-TIM-3 antibody molecule, *e.g.*, the anti-TIM-3 antibody molecule described herein, is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), in combination with a JAK2 inhibitor, *e.g.,* CEP-701, INCB18424, CP-690550 (tasocitinib).

In some embodiments, the pharmaceutical composition described herein is used, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), in combination with paclitaxel or a paclitaxel agent, *e.g.,* TAXOL®, protein-bound paclitaxel (*e.g.*, ABRAXANE®). Exemplary paclitaxel agents include, but are not limited to, nanoparticle albumin-bound paclitaxel (ABRAXANE, marketed by Abraxis Bioscience), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin, marketed by Protarga), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX, marketed by Cell Therapeutic), the tumor-activated prodrug (TAP), ANG105 (Angiopep-2 bound to three molecules of paclitaxel, marketed by ImmunoGen), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1; *see* Li *et al., Biopolymers* (2007) 87:225-230), and glucose-conjugated paclitaxel (*e.g.,* 2'-paclitaxel methyl 2-glucopyranosyl succinate, *see* Liu *et al., Bioorganic & Medicinal Chemistry Letters* (2007) 17:617-620).

Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (*e.g.* At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell

conditioner of the present invention include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), *e.g.,* a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

Anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), can be administered in combination with one or more of the existing modalities for treating cancers, including, but not limited to: surgery; radiation therapy (*e.g.,* external-beam therapy which involves three dimensional, conformal radiation therapy where the field of radiation is designed, local radiation (*e.g.,* radition directed to a preselected target or organ), or focused radiation). Focused radiation can be selected from the group consisting of stereotactic radiosurgery, fractionated stereotactic radiosurgery, and intensity-modulated radiation therapy. The focused radiation can have a radiation source selected from the group consisting of a particle beam (proton), cobalt-60 (photon), and a linear accelerator (x-ray), *e.g.,* as decribed in WO 2012/177624.

In certain embodiments, the anti-TIM-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), is administered in combination with an antibody against a Killer-cell Immunoglobulin-like Receptors (also referred to herein as an "anti-KIR antibody"), a pan-KIR antibody, or an anti-NKG2D antibody, and an anti-MICA antibody. In certain embodiments, the combination of anti-TIM-3 antibody molecule and anti-KIR antibody, pan-KIR antibody, or an anti-NKG2D antibody described herein is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a solid tumor, *e.g.*, an advanced solid tumor).

In one embodiment, the anti-TIM-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), is administered in combination with a cellular immunotherapy (*e.g.*, Provenge (*e.g.*, Sipuleucel)), and optionally in combination with cyclophosphamide. In certain embodiments, the combination

of anti-TIM-3 antibody molecule, Provenge and/or cyclophosphamide is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a prostate cancer, *e.g.*, an advanced prostate cancer).

In another embodiment, the anti-TIM-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), is administered in combination with a vaccine, *e.g.*, a dendritic cell renal carcinoma (DC-RCC) vaccine. In certain embodiments, the combination of anti-TIM-3 antibody molecule and the DC-RCC vaccine is used to treat a cancer, *e.g.*, a cancer as described herein (*e.g.*, a renal carcinoma, *e.g.*, metastatic renal cell carcinoma (RCC) or clear cell renal cell carcinoma (CCRCC)).

In yet another embodiment, the anti-TIM-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), is administered in combination with chemotherapy, and/or immunotherapy. For example, the anti-TIM-3 antibody molecule can be used to treat a myeloma, alone or in combination with one or more of: chemotherapy or other anti-cancer agents (*e.g.*, thalidomide analogs, *e.g.*, lenalidomide), an anti-PD-1 antibody, tumor antigen-pulsed dendritic cells, fusions (*e.g.*, electrofusions) of tumor cells and dendritic cells, or vaccination with immunoglobulin idiotype produced by malignant plasma cells. In one embodiment, the anti-TIM-3 antibody molecule is used in combination with an anti-PD-1 antibody to treat a myeloma, *e.g.*, a multiple myeloma.

In one embodiment, the anti-TIM-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), is used in combination with chemotherapy to treat a lung cancer, *e.g.*, non-small cell lung cancer. In one embodiment, the anti-TIM-3 antibody molecule is used with platinum doublet therapy to treat lung cancer.

In yet another embodiment, the anti-TIM-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), is used to treat a renal cancer, *e.g.*, renal cell carcinoma (RCC) (*e.g.,* clear cell renal cell carcinoma (CCRCC) or metastatic RCC. The anti-TIM-3 antibody molecule can be administered in combination with one or more of: an immune-based strategy (*e.g.*, interleukin-2 or interferon-α), a targeted agent (*e.g.*, a VEGF inhibitor such as a monoclonal antibody to VEGF); a VEGF tyrosine kinase inhibitor such as sunitinib, sorafenib, axitinib and pazopanib; an

RNAi inhibitor), or an inhibitor of a downstream mediator of VEGF signaling, *e.g.*, an inhibitor of the mammalian target of rapamycin (mTOR), *e.g.*, everolimus and temsirolimus.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of pancreatic cancer includes, but is not limited to, a chemotherapeutic agent, *e.g.*, paclitaxel or a paclitaxel agent (*e.g.*, a paclitaxel formulation such as TAXOL, an albumin-stabilized nanoparticle paclitaxel formulation (*e.g.*, ABRAXANE) or a liposomal paclitaxel formulation); gemcitabine (*e.g.*, gemcitabine alone or in combination with AXP107-11); other chemotherapeutic agents such as oxaliplatin, 5-fluorouracil, capecitabine, rubitecan, epirubicin hydrochloride, NC-6004, cisplatin, docetaxel (*e.g.*, TAXOTERE), mitomycin C, ifosfamide; interferon; tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib, panitumumab, cetuximab, nimotuzumab); HER2/neu receptor inhibitor (*e.g.*, trastuzumab); dual kinase inhibitor (*e.g.*, bosutinib, saracatinib, lapatinib, vandetanib); multikinase inhibitor (*e.g.*, sorafenib, sunitinib, XL184, pazopanib); VEGF inhibitor (*e.g.*, bevacizumab, AV-951, brivanib); radioimmunotherapy (*e.g.*, XR303); cancer vaccine (*e.g.*, GVAX, survivin peptide); COX-2 inhibitor (*e.g.*, celecoxib); IGF-1 receptor inhibitor (*e.g.*, AMG 479, MK-0646); mTOR inhibitor (*e.g.*, everolimus, temsirolimus); IL-6 inhibitor (*e.g.*, CNTO 328); cyclin-dependent kinase inhibitor (*e.g.*, P276-00, UCN-01); Altered Energy Metabolism-Directed (AEMD) compound (*e.g.*, CPI-613); HDAC inhibitor (*e.g.*, vorinostat); TRAIL receptor 2 (TR-2) agonist (*e.g.*, conatumumab); MEK inhibitor (*e.g.*, AS703026, selumetinib, GSK1120212); Raf/MEK dual kinase inhibitor (*e.g.*, RO5126766); Notch signaling inhibitor (*e.g.,* MK0752); monoclonal antibody-antibody fusion protein (*e.g.,* L19IL2); curcumin; HSP90 inhibitor (*e.g.*, tanespimycin, STA-9090); rIL-2;, denileukin diftitox; topoisomerase 1 inhibitor (*e.g.,* irinotecan, PEP02); statin (*e.g.*, simvastatin); Factor VIIa inhibitor (*e.g.*, PCI-27483); AKT inhibitor (*e.g.,* RX-0201); hypoxia-activated prodrug (*e.g.,* TH-302); metformin hydrochloride, gamma-secretase inhibitor (*e.g.,* RO4929097); ribonucleotide reductase inhibitor (*e.g.*, 3-AP); immunotoxin (*e.g.*, HuC242-DM4); PARP inhibitor (*e.g.,* KU-0059436, veliparib); CTLA-4 inhbitor (*e.g.,* CP-675,206, ipilimumab); AdV-tk therapy; proteasome inhibitor (*e.g.*, bortezomib (Velcade), NPI-0052); thiazolidinedione (*e.g.*, pioglitazone); NPC-1C; Aurora kinase inhibitor (*e.g.*, R763/AS703569), CTGF inhibitor (*e.g.*, FG-3019); siG12D LODER; and radiation therapy (*e.g.,* tomotherapy, stereotactic radiation,

proton therapy), surgery, and a combination thereof. In certain embodiments, a combination of paclitaxel or a paclitaxel agent, and gemcitabine can be used with the anti-TIM-3 antibody molecules described herein.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of small cell lung cancer includes, but is not limited to, a chemotherapeutic agent, *e.g.*, etoposide, carboplatin, cisplatin, oxaliplatin, irinotecan, topotecan, gemcitabine, liposomal SN-38, bendamustine, temozolomide, belotecan, NK012, FR901228, flavopiridol); tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib, gefitinib, cetuximab, panitumumab); multikinase inhibitor (*e.g.*, sorafenib, sunitinib); VEGF inhibitor (*e.g.,* bevacizumab, vandetanib); cancer vaccine (*e.g.,* GVAX); Bcl-2 inhibitor (*e.g.*, oblimersen sodium, ABT-263); proteasome inhibitor (*e.g.*, bortezomib (Velcade), NPI-0052), paclitaxel or a paclitaxel agent; docetaxel; IGF-1 receptor inhibitor (*e.g.*, AMG 479); HGF/SF inhibitor (*e.g.,* AMG 102, MK-0646); chloroquine; Aurora kinase inhibitor (*e.g.,* MLN8237); radioimmunotherapy (*e.g.,* TF2); HSP90 inhibitor (*e.g.*, tanespimycin, STA-9090); mTOR inhibitor (*e.g.*, everolimus); Ep-CAM-/CD3-bispecific antibody (*e.g.,* MT110); CK-2 inhibitor (*e.g.,* CX-4945); HDAC inhibitor (*e.g.,* belinostat); SMO antagonist (*e.g.*, BMS 833923); peptide cancer vaccine, and radiation therapy (*e.g.,* intensity-modulated radiation therapy (IMRT), hypofractionated radiotherapy, hypoxia-guided radiotherapy), surgery, and combinations thereof.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of non-small cell lung cancer includes, but is not limited to, a chemotherapeutic agent, *e.g.*, vinorelbine, cisplatin, docetaxel, pemetrexed disodium, etoposide, gemcitabine, carboplatin, liposomal SN-38, TLK286, temozolomide, topotecan, pemetrexed disodium, azacitidine, irinotecan, tegafur-gimeracil-oteracil potassium, sapacitabine); tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib, gefitinib, cetuximab, panitumumab, necitumumab, PF-00299804, nimotuzumab, RO5083945), MET inhibitor (*e.g.,* PF-02341066, ARQ 197), PI3K kinase inhibitor (*e.g.,* XL147, GDC-0941), Raf/MEK dual kinase inhibitor (*e.g.,* RO5126766), PI3K/mTOR dual kinase inhibitor (*e.g.*, XL765), SRC inhibitor (*e.g.,* dasatinib), dual inhibitor (*e.g.,* BIBW 2992, GSK1363089, ZD6474, AZD0530, AG-013736, lapatinib, MEHD7945A, linifanib), multikinase inhibitor (*e.g.*,

sorafenib, sunitinib, pazopanib, AMG 706, XL184, MGCD265, BMS-690514, R935788), VEGF inhibitor (*e.g.,* endostar, endostatin, bevacizumab, cediranib, BIBF 1120, axitinib, tivozanib, AZD2171), cancer vaccine (*e.g.,* BLP25 liposome vaccine , GVAX, recombinant DNA and adenovirus expressing L523S protein), Bcl-2 inhibitor (*e.g.*, oblimersen sodium), proteasome inhibitor (*e.g.*, bortezomib, carfilzomib, NPI-0052, MLN9708), paclitaxel or a paclitaxel agent, docetaxel, IGF-1 receptor inhibitor (*e.g.*, cixutumumab, MK-0646, OSI 906, CP-751,871, BIIB022), hydroxychloroquine, HSP90 inhibitor (*e.g.*, tanespimycin, STA-9090, AUY922, XL888), mTOR inhibitor (*e.g.*, everolimus, temsirolimus, ridaforolimus), Ep-CAM-/CD3-bispecific antibody (*e.g.*, MT110), CK-2 inhibitor (*e.g.*, CX-4945), HDAC inhibitor (*e.g.*, MS 275, LBH589, vorinostat, valproic acid, FR901228), DHFR inhibitor (*e.g.*, pralatrexate), retinoid (*e.g.*, bexarotene, tretinoin), antibody-drug conjugate (*e.g.*, SGN-15), bisphosphonate (*e.g.*, zoledronic acid), cancer vaccine (*e.g.*, belagenpumatucel-L), low molecular weight heparin (LMWH) (*e.g.*, tinzaparin, enoxaparin), GSK1572932A, melatonin, talactoferrin, dimesna, topoisomerase inhibitor (*e.g.*, amrubicin, etoposide, karenitecin), nelfinavir, cilengitide, ErbB3 inhibitor (*e.g.*, MM-121, U3-1287), survivin inhibitor (*e.g.*, YM155, LY2181308), eribulin mesylate, COX-2 inhibitor (*e.g.*, celecoxib), pegfilgrastim, Polo-like kinase 1 inhibitor (*e.g.*, BI 6727), TRAIL receptor 2 (TR-2) agonist (*e.g.*, CS-1008), CNGRC peptide (SEQ ID NO: 225)-TNF alpha conjugate, dichloroacetate (DCA), HGF inhibitor (*e.g.*, SCH 900105), SAR240550, PPAR-gamma agonist (*e.g.,* CS-7017), gamma-secretase inhibitor (*e.g.*, RO4929097), epigenetic therapy (*e.g.*, 5-azacitidine), nitroglycerin, MEK inhibitor (*e.g.*, AZD6244), cyclin-dependent kinase inhibitor (*e.g.*, UCN-01), cholesterol-Fus1, antitubulin agent (*e.g.*, E7389), farnesyl-OH-transferase inhibitor (*e.g.*, lonafarnib), immunotoxin (*e.g.*, BB-10901, SS1 (dsFv) PE38), fondaparinux, vascular-disrupting agent (*e.g.*, AVE8062), PD-L1 inhibitor (*e.g.*, MDX-1105, MDX-1106), beta-glucan, NGR-hTNF, EMD 521873, MEK inhibitor (*e.g.*, GSK1120212), epothilone analog (*e.g.*, ixabepilone), kinesin-spindle inhibitor (*e.g.*, 4SC-205), telomere targeting agent (*e.g.*, KML-001), P70 pathway inhibitor (*e.g.*, LY2584702), AKT inhibitor (*e.g.*, MK-2206), angiogenesis inhibitor (*e.g.*, lenalidomide), Notch signaling inhibitor (*e.g.*, OMP-21M18), radiation therapy, surgery, and combinations thereof.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of ovarian cancer includes, but is not

limited to, a chemotherapeutic agent (*e.g.*, paclitaxel or a paclitaxel agent; docetaxel; carboplatin; gemcitabine; doxorubicin; topotecan; cisplatin; irinotecan, TLK286, ifosfamide, olaparib, oxaliplatin, melphalan, pemetrexed disodium, SJG-136, cyclophosphamide, etoposide, decitabine); ghrelin antagonist (*e.g.*, AEZS-130), immunotherapy (*e.g.*, APC8024, oregovomab, OPT-821), tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib), dual inhibitor (*e.g.,* E7080), multikinase inhibitor (*e.g.*, AZD0530, JI-101, sorafenib, sunitinib, pazopanib), ON 01910.Na), VEGF inhibitor (*e.g.,* bevacizumab, BIBF 1120, cediranib, AZD2171), PDGFR inhibitor (*e.g.*, IMC-3G3), paclitaxel, topoisomerase inhibitor (*e.g.*, karenitecin, Irinotecan), HDAC inhibitor (*e.g.,* valproate, vorinostat), folate receptor inhibitor (*e.g.,* farletuzumab), angiopoietin inhibitor (*e.g.,* AMG 386), epothilone analog (*e.g.,* ixabepilone), proteasome inhibitor (*e.g.,* carfilzomib), IGF-1 receptor inhibitor (*e.g.,* OSI 906, AMG 479), PARP inhibitor (*e.g.*, veliparib, AG014699, iniparib, MK-4827), Aurora kinase inhibitor (*e.g.,* MLN8237, ENMD-2076), angiogenesis inhibitor (*e.g.,* lenalidomide), DHFR inhibitor (*e.g.,* pralatrexate), radioimmunotherapeutic agnet (*e.g.,* Hu3S193), statin (*e.g.,* lovastatin), topoisomerase 1 inhibitor (*e.g.,* NKTR-102), cancer vaccine (*e.g.,* p53 synthetic long peptides vaccine, autologous OC-DC vaccine), mTOR inhibitor (*e.g.,* temsirolimus, everolimus), BCR/ABL inhibitor (*e.g.,* imatinib), ET-A receptor antagonist (*e.g.,* ZD4054), TRAIL receptor 2 (TR-2) agonist (*e.g.,* CS-1008), HGF/SF inhibitor (*e.g.,* AMG 102), EGEN-001, Polo-like kinase 1 inhibitor (*e.g.,* BI 6727), gamma-secretase inhibitor (*e.g.,* RO4929097), Wee-1 inhibitor (*e.g.,* MK-1775), antitubulin agent (*e.g.*, vinorelbine, E7389), immunotoxin (*e.g.,* denileukin diftitox), SB-485232, vascular-disrupting agent (*e.g.,* AVE8062), integrin inhibitor (*e.g.,* EMD 525797), kinesin-spindle inhibitor (*e.g.,* 4SC-205), revlimid, HER2 inhibitor (*e.g.,* MGAH22), ErrB3 inhibitor (*e.g.,* MM-121), radiation therapy; and combinations thereof.

In one exemplary embodiment, the anti-TIM-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), is used to treat a myeloma, alone or in combination with one or more of: chemotherapy or other anti-cancer agents (*e.g.*, thalidomide analogs, *e.g.*, lenalidomide), HSCT (Cook, R. (2008) *J Manag Care Pharm.* 14(7 Suppl):19-25), an anti-TIM3 antibody (Hallett, WHD *et al.* (2011) *J of American Society for Blood and Marrow Transplantation* 17(8):1133-145), tumor antigen-pulsed dendritic cells, fusions (*e.g.*, electrofusions) of tumor cells and

dendritic cells, or vaccination with immunoglobulin idiotype produced by malignant plasma cells (reviewed in Yi, Q. (2009) *Cancer J.* 15(6):502-10).

In yet another embodiment, the anti-TIM-3 antibody molecule, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), is used to treat a renal cancer, *e.g.*, renal cell carcinoma (RCC) or metastatic RCC. The anti-TIM-3 antibody molecule can be administered in combination with one or more of: an immune-based strategy (*e.g.*, interleukin-2 or interferon-α), a targeted agent (*e.g.*, a VEGF inhibitor such as a monoclonal antibody to VEGF, *e.g.*, bevacizumab (Rini, B.I. *et al.* (2010) *J. Clin. Oncol.* 28(13):2137-2143)); a VEGF tyrosine kinase inhibitor such as sunitinib, sorafenib, axitinib and pazopanib (reviewed in Pal. S.K. *et al.* (2014) *Clin. Advances in Hematology & Oncology* 12(2):90-99)); an RNAi inhibitor), or an inhibitor of a downstream mediator of VEGF signaling, *e.g.*, an inhibitor of the mammalian target of rapamycin (mTOR), *e.g.*, everolimus and temsirolimus (Hudes, G. *et al.* (2007) *N. Engl. J. Med.* 356(22):2271-2281, Motzer, R.J. *et al.* (2008) *Lancet* 372: 449-456).

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of chronic myelogenous leukemia (AML) according to the invention includes, but is not limited to, a chemotherapeutic (*e.g.*, cytarabine, hydroxyurea, clofarabine, melphalan, thiotepa, fludarabine, busulfan, etoposide, cordycepin, pentostatin, capecitabine, azacitidine, cyclophosphamide, cladribine, topotecan), tyrosine kinase inhibitor (*e.g.*, BCR/ABL inhibitor (*e.g.,* imatinib, nilotinib), ON 01910.Na, dual inhibitor (*e.g.*, dasatinib, bosutinib), multikinase inhibitor (*e.g.,* DCC-2036, ponatinib, sorafenib, sunitinib, RGB-286638)), interferon alfa, steroids, apoptotic agent (*e.g.,* omacetaxine mepesuccinat), immunotherapy (*e.g.,* allogeneic CD4+ memory Th1-like T cells/microparticle-bound anti-CD3/anti-CD28, autologous cytokine induced killer cells (CIK), AHN-12), CD52 targeting agent (*e.g.,* alemtuzumab), HSP90 inhibitor (*e.g.*, tanespimycin, STA-9090, AUY922, XL888), mTOR inhibitor (*e.g.,* everolimus), SMO antagonist (*e.g.,* BMS 833923), ribonucleotide reductase inhibitor (*e.g.,* 3-AP), JAK-2 inhibitor (*e.g.,* INCB018424), Hydroxychloroquine, retinoid (*e.g.*, fenretinide), cyclin-dependent kinase inhibitor (*e.g.,* UCN-01), HDAC inhibitor (*e.g.,* belinostat, vorinostat, JNJ-26481585), PARP inhibitor (*e.g.,* veliparib), MDM2 antagonist (*e.g.,* RO5045337), Aurora B kinase inhibitor (*e.g.,* TAK-901), radioimmunotherapy (*e.g.,*

actinium-225-labeled anti-CD33 antibody HuM195), Hedgehog inhibitor (*e.g.,* PF-04449913), STAT3 inhibitor (*e.g.,* OPB-31121), KB004, cancer vaccine (*e.g.,* AG858), bone marrow transplantation, stem cell transplantation, radiation therapy, and combinations thereof.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of chronic lymphocytic leukemia (CLL) includes, but is not limited to, a chemotherapeutic agent (*e.g.*, fludarabine, cyclophosphamide, doxorubicin, vincristine, chlorambucil, bendamustine, chlorambucil, busulfan, gemcitabine, melphalan, pentostatin, mitoxantrone, 5-azacytidine, pemetrexed disodium), tyrosine kinase inhibitor (*e.g.*, EGFR inhibitor (*e.g.*, erlotinib), BTK inhibitor (*e.g.*, PCI-32765), multikinase inhibitor (*e.g.*, MGCD265, RGB-286638), CD-20 targeting agent (*e.g.,* rituximab, ofatumumab, RO5072759, LFB-R603), CD52 targeting agent (*e.g.*, alemtuzumab), prednisolone, darbepoetin alfa, lenalidomide, Bcl-2 inhibitor (*e.g.,* ABT-263), immunotherapy (*e.g.*, allogeneic CD4+ memory Th1-like T cells/microparticle-bound anti-CD3/anti-CD28, autologous cytokine induced killer cells (CIK)), HDAC inhibitor (*e.g.,* vorinostat, valproic acid, LBH589, JNJ-26481585, AR-42), XIAP inhibitor (*e.g.*, AEG35156), CD-74 targeting agent (*e.g.*, milatuzumab), mTOR inhibitor (*e.g.*, everolimus), AT-101, immunotoxin (*e.g.*, CAT-8015, anti-Tac(Fv)-PE38 (LMB-2)), CD37 targeting agent (*e.g.,* TRU-016), radioimmunotherapy (*e.g.,* 131-tositumomab), hydroxychloroquine, perifosine, SRC inhibitor (*e.g.*, dasatinib), thalidomide, PI3K delta inhibitor (*e.g.,* CAL-101), retinoid (*e.g.*, fenretinide), MDM2 antagonist (*e.g.,* RO5045337), plerixafor, Aurora kinase inhibitor (*e.g.*, MLN8237, TAK-901), proteasome inhibitor (*e.g.*, bortezomib), CD-19 targeting agent (*e.g.*, MEDI-551, MOR208), MEK inhibitor (*e.g.,* ABT-348), JAK-2 inhibitor (*e.g.*, INCB018424), hypoxia-activated prodrug (*e.g.,* TH-302), paclitaxel or a paclitaxel agent, HSP90 inhibitor, AKT inhibitor (*e.g.,* MK2206), HMG-CoA inhibitor (*e.g.,* simvastatin), GNKG186, radiation therapy, bone marrow transplantation, stem cell transplantation, and a combination thereof.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of acute lymphocytic leukemia (ALL) includes, but is not limited to, a chemotherapeutic agent (*e.g.*, prednisolone, dexamethasone, vincristine, asparaginase, daunorubicin, cyclophosphamide, cytarabine,

etoposide, thioguanine, mercaptopurine, clofarabine, liposomal annamycin, busulfan, etoposide, capecitabine, decitabine, azacitidine, topotecan, temozolomide), tyrosine kinase inhibitor (*e.g.*, BCR/ABL inhibitor (*e.g.*, imatinib, nilotinib), ON 01910.Na, multikinase inhibitor (*e.g.*, sorafenib)), CD-20 targeting agent (*e.g.,* rituximab), CD52 targeting agent (*e.g.*, alemtuzumab), HSP90 inhibitor (*e.g.,* STA-9090), mTOR inhibitor (*e.g.,* everolimus, rapamycin), JAK-2 inhibitor (*e.g.,* INCB018424), HER2/neu receptor inhibitor (*e.g.,* trastuzumab), proteasome inhibitor (*e.g.*, bortezomib), methotrexate, asparaginase, CD-22 targeting agent (*e.g.*, epratuzumab, inotuzumab), immunotherapy (*e.g.,* autologous cytokine induced killer cells (CIK), AHN-12), blinatumomab, cyclin-dependent kinase inhibitor (*e.g.*, UCN-01), CD45 targeting agent (*e.g.*, BC8), MDM2 antagonist (*e.g.,* RO5045337), immunotoxin (*e.g.*, CAT-8015, DT2219ARL), HDAC inhibitor (*e.g.*, JNJ-26481585), JVRS-100, paclitaxel or a paclitaxel agent, STAT3 inhibitor (*e.g.*, OPB-31121), PARP inhibitor (*e.g.*, veliparib), EZN-2285, radiation therapy, steroid, bone marrow transplantation, stem cell transplantation, or a combination thereof.

An example of suitable therapeutics for use in combination with the anti-TIM-3antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of acute myeloid leukemia (AML) includes, but is not limited to, a chemotherapeutic agent (*e.g.*, cytarabine, daunorubicin, idarubicin, clofarabine, decitabine, vosaroxin, azacitidine, clofarabine, ribavirin, CPX-351, treosulfan, elacytarabine, azacitidine), tyrosine kinase inhibitor (*e.g.,* BCR/ABL inhibitor (*e.g.*, imatinib, nilotinib), ON 01910.Na, multikinase inhibitor (*e.g.,* midostaurin, SU 11248, quizartinib, sorafinib)), immunotoxin (*e.g.,* gemtuzumab ozogamicin), DT388IL3 fusion protein, HDAC inhibitor (*e.g.,* vorinostat, LBH589), plerixafor, mTOR inhibitor (*e.g.*, everolimus), SRC inhibitor (*e.g.,* dasatinib), HSP90 inhbitor (*e.g.,* STA-9090), retinoid (*e.g.,* bexarotene, Aurora kinase inhibitor (*e.g.,* BI 811283), JAK-2 inhibitor (*e.g.,* INCB018424), Polo-like kinase inhibitor (*e.g.,* BI 6727), cenersen, CD45 targeting agent (*e.g.,* BC8), cyclin-dependent kinase inhibitor (*e.g.,* UCN-01), MDM2 antagonist (*e.g.,* RO5045337), mTOR inhibitor (*e.g.,* everolimus), LY573636-sodium, ZRx-101, MLN4924, lenalidomide, immunotherapy (*e.g.,* AHN-12), histamine dihydrochloride, radiation therapy, bone marrow transplantation, stem cell transplantation, and a combination thereof.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules described herein, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of multiple myeloma (MM) includes, but is not limited to, a chemotherapeutic agent (*e.g.*, melphalan, amifostine, cyclophosphamide, doxorubicin, clofarabine, bendamustine, fludarabine, adriamycin, SyB L-0501), thalidomide, lenalidomide, dexamethasone, prednisone, pomalidomide, proteasome inhibitor (*e.g.,* bortezomib, carfilzomib, MLN9708), cancer vaccine (*e.g.*, GVAX), CD-40 targeting agent (*e.g.,* SGN-40, CHIR-12.12), perifosine, zoledronic acid, Immunotherapy (*e.g.,* MAGE-A3, NY-ESO-1 , HuMax-CD38), HDAC inhibitor (*e.g.,* vorinostat, LBH589, AR-42), aplidin, cycline-dependent kinase inhibitor (*e.g.,* PD-0332991, dinaciclib), arsenic trioxide, CB3304, HSP90 inhibitor (*e.g.,* KW-2478), tyrosine kinase inhibitor (*e.g.,* EGFR inhibitor (*e.g.,* cetuximab), multikinase inhibitor (*e.g.*, AT9283)), VEGF inhibitor (*e.g.,* bevacizumab), plerixafor, MEK inhibitor (*e.g.,* AZD6244), IPH2101, atorvastatin, immunotoxin (*e.g.,* BB-10901), NPI-0052, radioimmunotherapeutic (*e.g.,* yttrium Y 90 ibritumomab tiuxetan), STAT3 inhibitor (*e.g.,* OPB-31121), MLN4924, Aurora kinase inhibitor (*e.g.,* ENMD-2076), IMGN901, ACE-041, CK-2 inhibitor (*e.g.,* CX-4945), radiation therapy, bone marrow transplantation, stem cell transplantation, and a combination thereof.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-1 or anti-PD-L1 antibody molecule), for treatment of prostate cancer includes, but is not limited to, a chemotherapeutic agent (*e.g.*, docetaxel, carboplatin, fludarabine), abiraterone, hormonal therapy (*e.g.,* flutamide, bicalutamide, nilutamide, cyproterone acetate, ketoconazole, aminoglutethimide, abarelix, degarelix, leuprolide, goserelin, triptorelin, buserelin), tyrosine kinase inhibitor (*e.g.,* dual kinase inhibitor (*e.g.,* lapatanib), multikinase inhibitor (*e.g.,* sorafenib, sunitinib)), VEGF inhibitor (*e.g.,* bevacizumab), TAK-700, cancer vaccine (*e.g.,* BPX-101, PEP223), lenalidomide, TOK-001, IGF-1 receptor inhibitor (*e.g.,* cixutumumab), TRC105, Aurora A kinase inhibitor (*e.g.,* MLN8237), proteasome inhibitor (*e.g.*, bortezomib), OGX-011, radioimmunotherapy (*e.g.,* HuJ591-GS), HDAC inhibitor (*e.g.,* valproic acid, SB939, LBH589), hydroxychloroquine, mTOR inhibitor (*e.g.*, everolimus), dovitinib lactate, diindolylmethane, efavirenz, OGX-427, genistein, IMC-3G3, bafetinib, CP-675,206, radiation therapy, surgery, or a combination thereof.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), for treatment of HNSCC includes, but is not limited to, one or both of Compound A8 as described herein (or a compound described in PCT Publication No. WO2010/029082) and cetuximab (*e.g.*, Erbitux, marketed by BMS). In some embodiments, the therapeutic (*e.g.*, the Compound A8 or compound related to A8) is a PI3K modulator, *e.g.*, a PI3K inhibitor. In some embodiments, the therapeutic (*e.g.*, cetuximab) modulates, *e.g.*, inhibits, EGFR. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of PI3K or EGFR compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), for treatment of gastric cancer, *e.g.*, MSI-high and/or EBV+ gastric cancer, includes, but is not limited to, Compound A8 as described herein (or a compound described in PCT Publication No. WO2010/029082). In some embodiments, the therapeutic (*e.g.*, the Compound A8 or compound related to A8) is a PI3K modulator, *e.g.*, a PI3K inhibitor. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of PI3K compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), for treatment of gastric cancer, *e.g.*, MSI-high and/or RNF43-inactivated gastric cancer, includes, but is not limited to, Compound A28 as described herein (or a compound described in PCT Publication No. WO2010/101849). In some embodiments, the therapeutic (*e.g.*, the Compound A28 or compound related to A28) is a modulator, *e.g.*, inhibitor, of porcupine. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of porcupine compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), for treatment of GI stromal tumor (GIST), includes, but is not limited to, Compound A16 as described herein (or a compound described in PCT Publication No. WO1999/003854). In some embodiments, the therapeutic (*e.g.*, the Compound A16 or compound related to A16) is a modulator, *e.g.*, inhibitor, of a tyrosine kinase. In some

embodiments, the cancer has, or is determined to have, elevated levels or activity of a tyrosine kinase compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), for treatment of NSCLC, *e.g.*, squamous or adenocarcinoma, includes, but is not limited to, one or both of Compound A17 as described herein (or a compound described in US Patent No. 7,767,675 and 8,420,645) and Compound A23 as described herein (or a compound described in PCT Publication No. WO2003/077914). In some embodiments, the compound (*e.g.*, the Compound A17 or compound related to A17) modulates, *e.g.*, inhibits, c-MET. In some embodiments, the compound (*e.g.*, the Compound A23 or compound related to A23) modulates, *e.g.*, inhibits, Alk. In some embodiments, the cancer has, or is determined to have, elevated levels or activity of one or both of c-MET or Alk compared to a control cell or reference value. In some embodiments, the cancer has, or is identified as having, a mutation in EGFR.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), for treatment of melanoma (*e.g.*, NRAS melanoma) includes, but is not limited to, one or both of Compound A24 as described herein (or a compound described in US Patent Nos. 8,415,355 and 8,685,980) and Compound A34 as described herein (or a compound described in PCT Publication No. WO2003/077914). In some embodiments, the compound (*e.g.*, the Compound A24 or compound related to A24) modulates, *e.g.*, inhibits, one or more of JAK and CDK4/6. In some embodiments, the compound (*e.g.*, the Compound A34 or compound related to A34) modulates, *e.g.*, inhibits, MEK. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of one or more of JAK, CDK4/6, and MEK compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), for treatment of melanoma (*e.g.*, NRAS melanoma) includes, but is not limited to, one or both of Compound A29 as described herein (or a compound described in PCT Publication No. WO2011/025927) and Compound A34 as described herein (or a compound described in PCT Publication No. WO2003/077914). In some embodiments, the

compound (*e.g.*, the Compound A29 or compound related to A29) modulates, *e.g.*, inhibits, BRAF. In some embodiments, the compound (*e.g.*, the Compound A34 or compound related to A34) modulates, *e.g.*, inhibits, MEK. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of one or both of BRAF and MEK compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), for treatment of squamous NSCLC includes, but is not limited to, Compound A5 as described herein (or a compound described in US Patent No. 8,552,002). In some embodiments, the compound (*e.g.*, the Compound A5 or compound related to A5) modulates, *e.g.*, inhibits, FGFR. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of FGFR compared to a control cell or reference value.

An example of suitable therapeutics for use in combination with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), for treatment of colorectal cancer includes, but is not limited to, one or both of Compound A29 as described herein (or a compound PCT Publication No. WO2011/025927) and cetuximab (*e.g.*, Erbitux, marketed by BMS). In some embodiments, the therapeutic (*e.g.*, the Compound A29 or compound related to A29) modulates, *e.g.*, inhibits, BRAF. In some embodiments, the therapeutic (*e.g.*, cetuximab) modulates, *e.g.*, inhibits EGFR. In some embodiments, the cancer has, or is identified as having, elevated levels or activity of BRAF or EGFR compared to a control cell or reference value.

This disclosure also provides a method of treating cancer with Compound A8, cetuximab, and a TIM-3 antibody molecule (optionally in combination with a PD-1 antibody molecule or LAG-3 antibody molecule). In some embodiments, the patient is first treated with Compound A8 and cetuximab. This treatment continues for an amount of time, *e.g.*, a predetermined amount of time, *e.g.*, about 1, 2, 4, 6, 8, 10, or 12 months. Next, the TIM-3 antibody molecule (optionally in combination with a PD-1 antibody molecule or LAG-3 antibody molecule) is administered. The TIM-3 antibody can optionally be administered in combination with cetuximab.

In some embodiments, the patient is first treated with all three of Compound A8, cetuximab, and a TIM-3 antibody molecule (optionally in combination with a PD-1 antibody

molecule or LAG-3 antibody molecule). This treatment continues for an amount of time, *e.g.*, a predetermined amount of time, *e.g.*, about 6, 8, 10, or 12 months. Next, the Compound A8 and/or cetuximab can be tapered off, so that the maintenance phase involves treatment with the TIM-3 antibody molecule (*e.g.*, as a monotherapy, or in combination with a PD-1 antibody molecule or LAG-3 antibody molecule) but not Compound A8 or cetuximab.

In other embodiments, the three compounds (Compound A8, cetuximab, and a TIM-3 antibody molecule, optionally in combination with a PD-1 antibody molecule or LAG-3 antibody molecule) are given sequentially at the outset of the treatment. For instance, Compound A8 and cetuximab can be given first, as described above. Next, the TIM-3 antibody molecule (optionally in combination with a PD-1 antibody molecule or LAG-3 antibody molecule) is added to the regimen. Next, the Compound A8 and/or cetuximab can be tapered off as described above.

Exemplary doses for the three (or more) agent regimens are as follows. The TIM-3 antibody molecule can be administered, *e.g.*, at a dose of about 1 to 40 mg/kg, *e.g.*, 1 to 30 mg/kg, *e.g.*, about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, or about 3 mg/kg. In some embodiments, the Compound A8 is administered at a dose of approximately 200-300, 300-400, or 200-400 mg. In some embodiments, the cetuximab is administered at a 400 mg/m2 initial dose as a 120-minute intravenous infusion followed by 250 mg/m2 weekly infused over 60 minutes. In embodiments, one or more of the Compound A8, cetuximab, and TIM-3 antibody molecule is administered at a dose that is lower than the dose at which that agent is typically administered as a monotherapy, *e.g.*, about 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower than the dose at which that agent is typically administered as a monotherapy. In embodiments, the one or more of the Compound A8, cetuximab, and TIM-3 antibody molecule is administered at a dose that is lower than the dose of that agent recited in this paragraph, *e.g.*, about 0-10%, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, or 80-90% lower than the dose of that agent recited in this paragraph. In certain embodiments, the concentration of the Compound A8 that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the Compound A8 is administered in combination with one or both of the cetuximab and TIM-3 antibody molecule than when the Compound A8 is administered individually. In certain embodiments, the concentration of the cetuximab that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the cetuximab is

administered in combination with one or both of the Compound A8 and TIM-3 antibody molecule than when the cetuximab is administered individually. In certain embodiments, the concentration of the TIM-3 antibody molecule that is required to achieve inhibition, *e.g.*, growth inhibition, is lower when the TIM-3 antibody molecule is administered in combination with one or both of the cetuximab and Compound A8 than when the TIM-3 antibody molecule is administered individually.

Additionally disclosed herein is a method of treating cancer with the anti-TIM-3 antibody molecules, alone or in combination with another immunomodulator (*e.g.,* an anti-LAG-3, anti-PD-L1 or anti-PD-1 antibody molecule), and a targeted anti-cancer agent, *e.g.*, an agent that targets one or more proteins. In some embodiments, the anti-TIM-3 antibody molecule (and optionally other immunomodulator(s)) are administered first, and the targeted anti-cancer agent is administered second. The length of time between administration of the anti-TIM-3 antibody molecule and the targeted anti-cancer agent can be, *e.g.*, 10, 20, or 30 minutes, 1, 2, 4, 6, or 12 hours, or 1, 2, 3, 4, 5, 6, or 7 days, or any span of time within this range. In certain embodiments, the anti-TIM-3 antibody molecule is administered repeatedly over a period of time (*e.g.*, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 4, 8, 12, 16, or 20 weeks, or any span of time within this range) before the targeted anti-cancer agent is administered. In other embodiments, the anti-TIM-3 antibody molecule and the targeted anti-cancer agent are administered at substantially the same time.

Methods of treating infectious diseases

Other methods of the invention are used to treat patients that have been exposed to particular toxins or pathogens. Based on, at least, the Examples herein, anti-TIM-3 antibodies can stimulate NK cell mediated killing of target cells and can enhances IFN-gamma secretion and proliferation of CD4+ T cells. Accordingly, in certain embodiments, the anti-TIM-3 antibody molecules described herein are suitable for use in stimulating an immune response against an infectious agent. Accordingly, another aspect of the invention provides a method of treating an infectious disease in a subject comprising administering to the subject an anti-TIM-3 antibody molecule, such that the subject is treated for the infectious disease. In the treatment of infection (*e.g.*, acute and/or chronic), administration of the anti-TIM-3 antibody molecules can be combined with conventional treatments in addition to or in lieu of stimulating natural host

immune defenses to infection. Natural host immune defenses to infection include, but are not limited to inflammation, fever, antibody-mediated host defense, T-lymphocyte-mediated host defenses, including lymphokine secretion and cytotoxic T-cells (especially during viral infection), complement mediated lysis and opsonization (facilitated phagocytosis), and phagocytosis. The ability of the anti-TIM-3 antibody molecules to reactivate dysfunctional T-cells would be useful to treat chronic infections, in particular those in which cell-mediated immunity is important for complete recovery.

Certain methods described herein are used to treat patients that have been exposed to particular toxins or pathogens. Some aspects provides a method of treating an infectious disease in a subject comprising administering to the subject an anti-TIM-3 antibody molecule, such that the subject is treated for the infectious disease.

Similar to its application to tumors as discussed in the previous section, aIn embodiments, the anti-TIM-3 antibody molecules can be used alone, or as an adjuvant, in combination with vaccines, to stimulate the immune response to, *e.g.*, pathogens or toxins. Examples of pathogens for which this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria, Leishmania, Staphylococcus aureus, Pseudomonas Aeruginosa. Anti-TIM-3 antibody molecule therapy is also useful against established infections by agents such as HIV that present altered antigens over the course of the infections.

Accordingly, in some embodiments an anti-TIM-3 antibody molecule is used to treat a subject that has an infection or is at risk of having an infection. An infection refers to, *e.g.*, a disease or condition attributable to the presence in a host of a foreign organism or agent that reproduces within the host. Infections typically involve breach of a normal mucosal or other tissue barrier by an infectious organism or agent. A subject that has an infection is a subject having objectively measurable infectious organisms or agents present in the subject's body. A subject at risk of having an infection is a subject that is predisposed to develop an infection. Such a subject can include, for example, a subject with a known or suspected exposure to an infectious organism or agent. A subject at risk of having an infection also can include a subject with a condition associated with impaired ability to mount an immune response to an infectious

organism or agent, *e.g.*, a subject with a congenital or acquired immunodeficiency, a subject undergoing radiation therapy or chemotherapy, a subject with a burn injury, a subject with a traumatic injury, a subject undergoing surgery or other invasive medical or dental procedure.

Infections are broadly classified as bacterial, viral, fungal, or parasitic based on the category of infectious organism or agent involved. Other less common types of infection include, *e.g.*, infections involving rickettsiae, mycoplasmas, and agents causing scrapie, bovine spongiform encephalopthy (BSE), and prion diseases (*e.g.*, kuru and Creutzfeldt-Jacob disease). Examples of bacteria, viruses, fungi, and parasites which cause infection are well known in the art. An infection can be acute, subacute, chronic, or latent, and it can be localized or systemic. Furthermore, an infection can be predominantly intracellular or extracellular during at least one phase of the infectious organism's or agent's life cycle in the host.

Viruses

Examples of viruses that have been found to cause infections in humans include but are not limited to: Retroviridae (*e.g.*, human immunodeficiency viruses, such as HIV-1 (also referred to as HTLV-III), HIV-2, LAV or HTLV-III/LAV, or HIV-III, and other isolates, such as HIV-LP; Picornaviridae (*e.g.*, polio viruses, hepatitis A virus; enteroviruses, human Coxsackie viruses, rhinoviruses, echoviruses); Calciviridae (*e.g.*, strains that cause gastroenteritis); Togaviridae (*e.g.*, equine encephalitis viruses, rubella viruses); Flaviviridae (*e.g.*, dengue viruses, encephalitis viruses, yellow fever viruses); Coronaviridae (*e.g.*, coronaviruses); Rhabdoviridae (*e.g.*, vesicular stomatitis viruses, rabies viruses); Filoviridae (*e.g.*, ebola viruses); Paramyxoviridae (*e.g.*, parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (*e.g.*, influenza viruses); Bungaviridae (*e.g.*, Hantaan viruses, bunga viruses, phleboviruses and Nairo viruses); Arena viridae (hemorrhagic fever viruses); Reoviridae (*e.g.*, reoviruses, orbiviurses and rotaviruses); Birnaviridae; Hepadnaviridae (Hepatitis B virus); Parvoviridae (parvoviruses); Papovaviridae (papilloma viruses, polyoma viruses); Adenoviridae (most adenoviruses); Herpesviridae (herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytomegalovirus (CMV), herpes virus; Poxyiridae (variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (*e.g.*, African swine fever virus); and unclassified viruses (*e.g.*, the etiological agents of Spongiform encephalopathies, the agent of delta hepatitis (thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1=enterally transmitted; class 2=parenterally transmitted (i.e., Hepatitis C); Norwalk and related viruses, and

astroviruses). Some examples of pathogenic viruses causing infections treatable by methods herein include HIV, hepatitis (A, B, or C), herpes virus (*e.g.*, VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

For infections resulting from viral causes, the anti-TIM-3 antibody molecules can be combined by application simultaneous with, prior to or subsequent to application of standard therapies for treating viral infections. Such standard therapies vary depending upon type of virus, although in almost all cases, administration of human serum containing antibodies (*e.g.*, IgA, IgG) specific to the virus can be effective.

Some examples of pathogenic viruses causing infections treatable by methods include HIV, hepatitis (A, B, or C), herpes virus (*e.g.*, VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus, arboviral encephalitis virus, and ebolaviruses (*e.g.*, BDBV, EBOV, RESTV, SUDV and TAFV).

In one embodiment, the infection is an influenza infection. Influenza infection can result in fever, cough, myalgia, headache and malaise, which often occur in seasonal epidemics. Influenza is also associated with a number of postinfectious disorders, such as encephalitis, myopericarditis, Goodpasture's syndrome, and Reye's syndrome. Influenza infection also suppresses normal pulmonary antibacterial defenses, such that patient's recovering from influenza have an increased risk of developing bacterial pneumonia. Influenza viral surface proteins show marked antigenic variation, resulting from mutation and recombination. Thus, cytolytic T lymphocytes are the host's primary vehicle for the elimination of virus after infection. Influenza is classified into three primary types: A, B and C. Influenza A is unique in that it infects both humans and many other animals (*e.g.*, pigs, horses, birds and seals) and is the principal cause of pandemic influenza. Also, when a cell is infected by two different influenza A strains, the segmented RNA genomes of two parental virus types mix during replication to create

a hybrid replicant, resulting in new epidemic strains. Influenza B does not replicate in animals and thus has less genetic variation and influenza C has only a single serotype.

Most conventional therapies are palliatives of the symptoms resulting from infection, while the host's immune response actually clears the disease. However, certain strains (*e.g.*, influenza A) can cause more serious illness and death. Influenza A may be treated both clinically and prophylactically by the administration of the cyclic amines inhibitors amantadine and rimantadine, which inhibit viral replication. However, the clinical utility of these drugs is limited due to the relatively high incidence of adverse reactions, their narrow anti-viral spectrum (influenza A only), and the propensity of the virus to become resistant. The administration of serum IgG antibody to the major influenza surface proteins, hemagglutinin and neuraminidase can prevent pulmonary infection, whereas mucosal IgA is required to prevent infection of the upper respiratory tract and trachea. The most effective current treatment for influenza is vaccination with the administration of virus inactivated with formalin or β-propiolactone.

In another embodiment, the infection is a hepatitis infection, *e.g.*, a Hepatitis B or C infection.

Hepatitis B virus (HB-V) is the most infectious known bloodborne pathogen. It is a major cause of acute and chronic heptatis and hepatic carcinoma, as well as life-long, chronic infection. Following infection, the virus replicates in hepatocytes, which also then shed the surface antigen HBsAg. The detection of excessive levels of HBsAg in serum is used a standard method for diagnosing a hepatitis B infection. An acute infection may resolve or it can develop into a chronic persistent infection. Current treatments for chronic HBV include α-interferon, which increases the expression of class I human leukocyte antigen (HLA) on the surface of hepatocytes, thereby facilitating their recognition by cytotoxic T lymphocytes. Additionally, the nucleoside analogs ganciclovir, famciclovir and lamivudine have also shown some efficacy in the treatment of HBV infection in clinical trials. Additional treatments for HBV include pegylated a-interferon, adenfovir, entecavir and telbivudine. While passive immunity can be conferred through parental administration of anti-HBsAg serum antibodies, vaccination with inactivated or recombinant HBsAg also confers resistance to infection. The anti-TIM-3 antibody molecules may be combined with conventional treatments for hepatitis B infections for therapeutic advantage.

Hepatitis C virus (HC-V) infection may lead to a chronic form of hepatitis, resulting in cirrosis. While symptoms are similar to infections resulting from Hepatitis B, in distinct contrast

to HB-V, infected hosts can be asymptomatic for 10-20 years. The anti-TIM-3 antibody molecule can be administered as a monotherapy, or combined with the standard of care for hepatitis C infection. For example, the anti-TIM-3 antibody molecule can be administered with one or more of Sovaldi (sofosbuvir) Olysio (simeprevir), plus ribavirin or pegylated interferon. Although regimens that include Incivek (telaprevir) or Victrelis (boceprevir) plus ribavirin and pegylated interferon are also approved, they are associated with increased side effects and longer duration of treatment and are therefore not considered preferred regimens.

Conventional treatment for HC-V infection includes the administration of a combination of α-interferon and ribavirin. A promising potential therapy for HC-V infection is the protease inhibitor telaprevir (VX-960). Additional treatments include: anti-PD-1 antibody (MDX-1106, Medarex), bavituximab (an antibody that binds anionic phospholipid phosphatidylserine in a B2-glycoprotein I dependent manner, Peregrine Pharmaceuticals), anti-HPV viral coat protein E2 antibod(y)(ies) (*e.g.*, ATL 6865–Ab68+Ab65, XTL Pharmaceuticals) and Civacir® (polyclonal anti-HCV human immune globulin). The anti-PD-L1 antibodies of the invention may be combined with one or more of these treatments for hepatitis C infections for therapeutic advantage. Protease, polymerase and NS5A inhibitors which may be used in combination with the anti-TIM-3 antibody molecules to specifically treat Hepatitis C infection include those described in US 2013/0045202, incorporated herein by reference.

In another embodiment, the infection is a measles virus. After an incubation of 9-11 days, hosts infected with the measles virus develop fever, cough, coryza and conjunctivitis. Within 1-2 days, an erythematous, maculopapular rash develop, which quickly spreads over the entire body. Because infection also suppresses cellular immunity, the host is at greater risk for developing bacterial superinfections, including otitis media, pneumonia and postinfectious encephalomyelitis. Acute infection is associated with significant morbidity and mortality, especially in malnourished adolescents.

Treatment for measles includes the passive administration of pooled human IgG, which can prevent infection in non-immune subjects, even if given up to one week after exposure. However, prior immunization with live, attenuated virus is the most effective treatment and prevents disease in more than 95% of those immunized. As there is one serotype of this virus, a single immunization or infection typically results in protection for life from subsequent infection.

In a small proportion of infected hosts, measles can develop into SSPE, which is a chronic progressive neurologic disorder resulting from a persistent infection of the central nervous system. SSPE is caused by clonal variants of measles virus with defects that interfere with virion assembly and budding. For these patients, reactivation of T-cells with the anti-TIM-3 antibody molecules so as to facilitate viral clearance would be desirable.

In another embodiment, the infection is HIV. HIV attacks $CD4^+$ cells, including T-lymphocytes, monocyte-macrophages, follicular dendritic cells and Langerhan's cells, and $CD4^+$ helper/inducer cells are depleted. As a result, the host acquires a severe defect in cell-mediated immunity. Infection with HIV results in AIDS in at least 50% of individuals, and is transmitted via sexual contact, administration of infected blood or blood products, artificial insemination with infected semen, exposure to blood-containing needles or syringes and transmission from an infected mother to infant during childbirth.

A host infected with HIV may be asymptomatic, or may develop an acute illness that resembling mononucleosis – fever, headache, sore throat, malaise and rash. Symptoms can progress to progressive immune dysfunction, including persistent fever, night sweats, weight loss, unexplained diarrhea, eczema, psoriasis, seborrheic dermatitis, herpes zoster, oral candidiasis and oral hairy leukoplakia. Opportunistic infections by a host of parasites are common in patients whose infections develop into AIDS.

Treatments for HIV include antiviral therapies including nucleoside analogs, zidovudine (AST) either alone or in combination with didanosine or zalcitabine, dideoxyinosine, dideoxycytidine, lamidvudine, stavudine; reverse transcriptive inhibitors such as delavirdine, nevirapine, loviride, and proteinase inhibitors such as saquinavir, ritonavir, indinavir and nelfinavir. The anti-TIM-3 antibody molecules may be combined with conventional treatments for HIV infections for therapeutic advantage.

In another embodiment, the infection is a Cytomegalovirus (CMV). CMV infection is often associated with persistent, latent and recurrent infection. CMV infects and remains latent in monocytes and granulocyte-monocyte progenitor cells. The clinical symptoms of CMV include mononucleosis-like symptoms (*i.e.*, fever, swollen glands, malaise), and a tendancy to develop allergic skin rashes to antibiotics. The virus is spread by direct contact. The virus is shed in the urine, saliva, semen and to a lesser extent in other body fluids. Transmission can also occur from an infected mother to her fetus or newborn and by blood transfusion and organ transplants. CMV

infection results in general impairment of cellular immunity, characterized by impaired blastogenic responses to nonspecific mitogens and specific CMV antigens, diminished cytotoxic ability and elevation of CD8 lymphocyte number of $CD4^+$ lymphocytes.

Treatments of CMV infection include the anti-virals ganciclovir, foscarnet and cidovir, but these druges are typically only prescribed in immunocompromised patients. The anti-TIM-3 antibody molecules may be combined with conventional treatments for cytomegalovirus infections for therapeutic advantage.

In another embodiment, the infection is Epstein-Barr virus (EBV). EBV can establish persistent and latent infections and primarily attacks B cells. Infection with EBV results in the clinical condition of infectious mononucleosis, which includes fever, sore throat, often with exudate, generalized lymphadenopathy and splenomegaly. Hepatitis is also present, which can develop into jaundice.

While typical treatments for EBV infections are palliative of symptoms, EBV is associated with the development of certain cancers such as Burkitt's lymphoma and nasopharyngeal cancer. Thus, clearance of viral infection before these complications result would be of great benefit. The anti-TIM-3 antibody molecules may be combined with conventional treatments for Epstein-Barr virus infections for therapeutic advantage.

In another embodiment, the infection is Herpes simplex virus (HSV). HSV is transmitted by direct contact with an infected host. A direct infection may be asymptomatic, but typically result in blisters containing infectious particles. The disease manifests as cycles of active periods of disease, in which lesions appear and disappear as the viral latently infect the nerve ganglion for subsequent outbreaks. Lesions may be on the face, genitals, eyes and/or hands. In some case, an infection can also cause encephalitis.

Treatments for herpes infections are directed primarily to resolving the symptomatic outbreaks, and include systemic antiviral medicines such as: acyclovir (*e.g.*, Zovirax®), valaciclovir, famciclovir, penciclovir, and topical medications such as docosanol (Abreva®), tromantadine and zilactin. The clearance of latent infections of herpes would be of great clinical benefit. The anti-TIM-3 antibody molecules may be combined with conventional treatments for herpes virus infections for therapeutic advantage.

In another embodiment, the infection is Human T-lymphotrophic virus (HTLV-1, HTLV-2). HTLV is transmitted via sexual contact, breast feeding or exposure to contaminated blood.

The virus activates a subset of T_H cells called Th1 cells, resulting in their overproliferation and overproduction of Th1 related cytokines (*e.g.*, IFN-γ and TNF-α). This in turn results in a suppression of Th2 lymphocytes and reduction of Th2 cytokine production (*e.g.*, IL-4, IL-5, IL-10 and IL-13), causing a reduction in the ability of an infected host to mount an adequate immune response to invading organisms requiring a Th2-dependent response for clearnance (*e.g.*, parasitic infections, production of mucosal and humoral antibodies).

HTLV infections cause lead to opportunistic infections resulting in bronchiectasis, dermatitis and superinfections with *Staphylococcus* spp. and *Strongyloides* spp. resulting in death from polymicrobial sepsis. HTLV infection can also lead directly to adult T-cell leukemia/lymphoma and progressive demyelinating upper motor neuron disease known as HAM/TSP. The clearance of HTLV latent infections would be of great clinical benefit. The anti-TIM-3 antibody molecules may be combined with conventional treatments for HTLV infections for therapeutic advantage.

In another embodiment, the infection is Human papilloma virus (HPV). HPV primarily affects keratinocytes and occurs in two forms: cutaneous and genital. Transmission is believed to occur through direct contact and/or sexual activity. Both cutaneous and genital HPV infection, can result in warts and latent infections and sometimes recurring infections, which are controlled by host immunity which controls the symptoms and blocks the appearance of warts, but leaves the host capable of transmitting the infection to others.

Infection with HPV can also lead to certain cancers, such as cervical, anal, vulvar, penile and oropharynial cancer. There are no known cures for HPV infection, but current treatment is topical application of Imiquimod, which stimulates the immune system to attack the affected area. The clearance of HPV latent infections would be of great clinical benefit. The anti-TIM-3 antibodies of the invention may be combined with conventional treatments for HPV infections for therapeutic advantage.

In another embodiment, the infection is Ebola virus (EBOV). EBOV is one of five known viruses within the Ebolavirus genus. EBOV causes severe and often fatal hemorrhagic fever in humans and mammals, known as Ebola virus disease (EVD). Transmission occurs through contact with blood, secretions, organs, or other boldily fluids of infected patients. Currently, there is no proven treatment or vaccine.

Bacterial Infections

Bacteria include both Gram negative and Gram positive bacteria. Examples of Gram positive bacteria include, but are not limited to Pasteurella species, Staphylococci species, and Streptococcus species. Examples of Gram negative bacteria include, but are not limited to, Escherichia coli, Pseudomonas species, and Salmonella species. Specific examples of infectious bacteria include but are not limited to: Helicobacter pyloris, Borrelia burgdorferi, Legionella pneumophilia, Mycobacteria spp. (*e.g.*, M. tuberculosis, M. avium, M. intracellulare, M. kansasii, M. gordonae), Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes (Group A Streptococcus), Streptococcus agalactiae (Group B Streptococcus), Streptococcus (viridans group), Streptococcus faecalis, Streptococcus bovis, Streptococcus (anaerobic spp.), Streptococcus pneumoniae, pathogenic Campylobacter spp., Enterococcus spp., Haemophilus influenzae, Bacillus anthracis, Corynebacterium diphtheriae, Corynebacterium spp., Erysipelothrix rhusiopathiae, Clostridium perfringens, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, Bacteroides spp., Fusobacterium nucleatum, Streptobacillus moniliformis, Treponema pallidum, Treponema pertenue, Leptospira, Mycobacterium leprae, Rickettsia, and Actinomyces israelii. Some examples of pathogenic bacteria causing infections treatable by methods herein include chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lymes disease bacteria.

Some examples of pathogenic bacteria causing infections treatable by methods of the invention include syphilis, *chlamydia*, *rickettsial bacteria*, *mycobacteria*, *staphylococci*, *streptococci*, *pneumonococci*, *meningococci and conococci*, *klebsiella*, *proteus*, *serratia*, *pseudomonas*, *legionella, diphtheria, salmonella, bacilli*, *cholera, tetanus*, *botulism*, *anthrax*, *plague, leptospirosis*, *and Lymes disease bacteria*. The anti-TIM-3 antibody molecules can be used in combination with existing treatment modalities for the aforesaid infections. For example, Treatments for syphilis include penicillin (*e.g.*, penicillin G.), tetracycline, doxycycline, ceftriaxone and azithromycin.

Lyme disease, caused by *Borrelia burgdorferi* is transmitted into humans through tick bites. The disease manifests initially as a localized rash, followed by flu-like symptoms including

malaise, fever, headache, stiff neck and arthralgias. Later manifestations can include migratory and polyarticular arthritis, neurologic and cardiac involvement with cranial nerve palsies and radiculopathy, myocarditis and arrhythmias. Some cases of Lyme disease become persistent, resulting in irreversible damage analogous to tertiary syphilis. Current therapy for Lyme disease includes primarily the administration of antibiotics. Antibiotic-resistant strains may be treated with hydroxychloroquine or methotrexate. Antibiotic refractory patients with neuropathic pain can be treated with gabapentin. Minocycline may be helpful in late/chronic Lyme disease with neurological or other inflammatory manifestations.

Other forms of borreliois, such as those resulting from *B. recurentis, B. hermsii, B. turicatae, B. parikeri., B. hispanica, B. duttonii* and *B. persica*, as well leptospirosis (*E.g., L. interrogans*), typically resolve spontaneously unless blood titers reach concentrations to cause intrahepatic obstruction.

Fungi and Parasites

Examples of fungi include: Aspergillus spp., Blastomyces dermatitidis, Candida albicans, other Candida spp., Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum, Chlamydia trachomatis, Nocardia spp., Pneumocystis carinii. Some examples of pathogenic fungi causing infections treatable by methods herein include Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum.

Parasites include but are not limited to blood-borne and/or tissues parasites such as Babesia microti, Babesia divergens, Entamoeba histolytica, Giardia lamblia, Leishmania tropica, Leishmania spp., Leishmania braziliensis, Leishmania donovani, Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, Plasmodium vivax, and Toxoplasma gondii, Trypanosoma gambiense and Trypanosoma rhodesiense (African sleeping sickness), Trypanosoma cruzi (Chagas' disease), and Toxoplasma gondii, flat worms, round worms. Some examples of pathogenic parasites causing infections treatable by methods herein include Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma

brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nippostrongylus brasiliensis.

Some examples of pathogenic fungi causing infections treatable by methods of the invention include *Candida* (*albicans, krusei, glabrata, tropicalis, etc.*), *Cryptococcus neoformans, Aspergillus* (*fumigatus, niger, etc.*), *Genus Mucorales* (*mucor, absidia, rhizophus*), *Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis* and *Histoplasma capsulatum*.

Some examples of pathogenic parasites causing infections treatable by methods described herein include *Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nippostrongylus brasiliensis*.

In some embodiments, the infectious disease is chosen from hepatitis (*e.g.*, hepatis C infection), or sepsis.

In all of the above methods, anti-TIM-3 antibody molecule therapy can be combined with other forms of immunotherapy such as cytokine treatment (*e.g.*, interferons, GM-CSF, G-CSF, IL-2, IL-21), or bispecific antibody therapy, which provides for enhanced presentation of tumor antigens (see, *e.g.*, Holliger (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak (1994) Structure 2:1121-1123).

Methods of administering various antibody molecules are known in the art and are described below. Suitable dosages of the antibody molecules used will depend on the age and weight of the subject and the particular drug used. The antibody molecules can be used as competitive agents for ligand binding to inhibit or reduce an undesirable interaction.

The antibody molecules can be used by themselves or conjugated to a second agent, *e.g.*, a cytotoxic drug, radioisotope, or a protein, *e.g.*, a protein toxin or a viral protein. This method includes: administering the antibody molecule, alone or conjugated to a cytotoxic drug, to a subject requiring such treatment. The antibody molecules can be used to deliver a variety of therapeutic agents, *e.g.*, a cytotoxic moiety, *e.g.*, a therapeutic drug, a radioisotope, molecules of plant, fungal, or bacterial origin, or biological proteins (*e.g.*, protein toxins) or particles (*e.g.*, a recombinant viral particles, *e.g.*; via a viral coat protein), or mixtures thereof.

Additional Combination Therapies

The anti-TIM-3 antibody molecules can be used in combination with other therapies. For example, the combination therapy can include an anti-TIM-3 antibody molecule co-formulated with, and/or co-administered with, one or more additional therapeutic agents, *e.g.*, one or more anti-cancer agents, cytotoxic or cytostatic agents, hormone treatment, vaccines, and/or other immunotherapies. In other embodiments, the antibody molecules are administered in combination with other therapeutic treatment modalities, including surgery, radiation, cryosurgery, and/or thermotherapy. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

Administered "in combination", as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, *e.g.*, the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap. This is sometimes referred to herein as "simultaneous" or "concurrent delivery." In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, *e.g.*, an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

Anti-TIM-3 antibody molecules can be administered in combination with one or more of the existing modalities for treating cancers, including, but not limited to: surgery; radiation

therapy (*e.g.*, external-beam therapy which involves three dimensional, conformal radiation therapy where the field of radiation is designed.

In certain aspects, the anti-TIM-3 antibody is co-administered with a second agent that acts on TIM-3 or another element of a TIM-3 pathway.

In some embodiments, *e.g.*, when treating infectious disease, the anti-TIM-3 antibody may be co-administered with, *e.g.*, an antibiotic, an anti-viral agent, or an anti-fungal agent.

In some embodiments, *e.g.*, when treating Crohn's disease, the anti-TIM-3 antibody may be co-administered with, *e.g.* an anti-inflammatory drug such as 5-aminosalicylic acid (5-ASA), prednisone, or hydrocortisone; purine analogs such as azathioprine; antimetabolites such as methotrexate; TNF-alpha inhibitors, *e.g.*, a monoclonal antibody to tumor necrosis factor alpha (TNF-α), *e.g.*, infliximab, adalimumab, or certolizumab; or integrin inhibitors, *e.g.*, a monoclonal antibody to alpha-4-integrin, *e.g.*, natalizumab.

In some embodiments, *e.g.*, when treating multiple sclerosis, the anti-TIM-3 antibody may be co-administered with, *e.g.* an interferon such as interferon beta-1a, interferon beta-1b, an interferon analog, a random amino acid polymer such as glatiramer acetate; a type II topoisomerase inhibitor such as mitoxantrone; an integrin inhibitor, *e.g.*, a monoclonal antibody to alpha-4-integrin, *e.g.*, natalizumab; a sphingosine 1-phosphate receptor modulator, *e.g.*, fingolimod; a pyrimidines synthesis inhibitor, *e.g.*, a dihydroorotate dehydrogenase inhibitor such as teriflunomide; and other immunomodulatory agents such as dimethyl fumarate.

In some embodiments, *e.g.*, when treating sepsis, the anti-TIM-3 antibody may be co-administered with, *e.g.* antibiotics; vasopressors such as norepinephrine or dopamine; steroids; Recombinant activated protein C (drotrecogin alpha); intravenous fluids; and ventilation.

In some embodiments, *e.g.*, when treating SIRS (Systemic Inflammatory Response Syndrome) the anti-TIM-3 antibody may be co-administered with, *e.g.* antibiotics; steroids; antioxidants; or intravenous fluids.

In some embodiments, *e.g.*, when treating glomerulonephritis, the anti-TIM-3 antibody may be co-administered with, *e.g.*, steroids; an alkylating agent such as cyclophosphamide; or a purine analog such as azathioprine.

Combinations of TIM-3 antibody molecules with one or more second therapeutics are provided herein. Many of the combinations in this section are useful in treating cancer, but other

indications are also described. This section focuses on combinations of anti-TIM-3 antibody molecules, optionally in combination with one or more immunomodulators (*e.g.*, an anti-PD-1 antibody molecule, an anti-LAG-3 antibody molecule, or an anti-PD-L1 antibody molecule), with one or more of the agents described in Table 6. In the combinations herein below, in one embodiment, the anti-TIM-3 antibody molecule comprises (i) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3 or SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 10, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 30, or SEQ ID NO: 31; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and (ii) a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6 or SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 7 or SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 8 or SEQ ID NO: 14.

In one embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a PKC inhibitor, Sotrastaurin (Compound A1), or a compound disclosed in PCT Publication No. WO 2005/039549, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PKC inhibitor is disclosed in Table 6, or in a publication recited in Table 6, *e.g.*, in the A1 row of Table 6. In one embodiment, the PKC inhibitor is Sotrastaurin (Compound A1) or a compound disclosed in PCT Publication No. WO 2005/039549. In one embodiment, a TIM-3 antibody molecule is used in combination with Sotrastaurin (Compound A1), or a compound as described in PCT Publication No. WO 2005/039549, to treat a disorder such as a cancer, a melanoma, a non-Hodgkin lymphoma, an inflammatory bowel disease, transplant rejection, an ophthalmic disorder, or psoriasis.

In certain embodiments, Sotrastaurin (Compound A1) is administered at a dose of about 20 to 600 mg, *e.g.,* about 200 to about 600 mg, about 50 mg to about 450 mg, about 100 mg to 400 mg, about 150 mg to 350 mg, or about 200 mg to 300 mg, *e.g.,* about 50 mg, 100 mg, 150mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg. The dosing schedule can vary from *e.g.,* every other day to daily, twice or three times a day.

In one embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a BCR-ABL inhibitor, TASIGNA (Compound A2, or a compound disclosed in PCT Publication No. WO 2004/005281, to treat a disorder, *e.g.*,

a disorder described herein. In one embodiment, the BCR-ABL inhibitor is TASIGNA, or a compound disclosed in PCT Publication No. WO 2004/005281. In one embodiment, a TIM-3 antibody molecule is used in combination with TASIGNA (Compound A2), or a compound as described in PCT Publication No. WO 2004/005281, to treat a disorder such as a lymphocytic leukemia, Parkinson's Disease, a neurologic cancer, a melanoma, a digestive/gastrointestinal cancer, a colorectal cancer, a myeloid leukemia, a head and neck cancer, or pulmonary hypertension.

In one embodiment, the BCR-ABL inhibitor or TASIGNA is administered at a dose of about 300 mg (*e.g.*, twice daily, *e.g.*, for newly diagnosed Ph+ CML-CP), or about 400 mg, *e.g.*, twice daily, *e.g.*, for resistant or intolerant Ph+ CML-CP and CML-AP). BCR-ABL inhibitor or a Compound A2 is administered at a dose of about 300-400 mg.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an HSP90 inhibitor, such as 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(morpholinomethyl)phenyl)isoxazole-3-carboxamide (Compound A3), or a compound disclosed in PCT Publication No. WO 2010/060937 or WO 2004/072051, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the HSP90 inhibitor is 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(morpholinomethyl)phenyl)isoxazole-3-carboxamide (Compound A3), or a compound disclosed in PCT Publication No. WO 2010/060937 or WO 2004/072051. In one embodiment, a TIM-3 antibody molecule is used in combination with 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(morpholinomethyl)phenyl)isoxazole-3-carboxamide (Compound A3), or a compound as described in PCT Publication No. WO 2010/060937 or WO 2004/072051, to treat a disorder such as a cancer, a multiple myeloma, a non-small cell lung cancer, a lymphoma, a gastric cancer, a breast cancer, a digestive/gastrointestinal cancer, a pancreatic cancer, a colorectal cancer, a solid tumor, or a hematopoiesis disorder.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an inhibitor of PI3K and/or mTOR, Dactolisib (Compound A4) or 8-(6-Methoxy-pyridin-3-yl)-3-methyl-1-(4-piperazin-1-yl-3-trifluoromethyl-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one (Compound A41), or a compound disclosed

in PCT Publication No. WO 2006/122806, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PI3K and/or mTOR inhibitor is Dactolisib (Compound A4), 8-(6-Methoxy-pyridin-3-yl)-3-methyl-1-(4-piperazin-1-yl-3-trifluoromethyl-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one (Compound A41), or a compound disclosed in PCT Publication No. WO 2006/122806. In one embodiment, a TIM-3 antibody molecule is used in combination with Dactolisib (Compound A4), 8-(6-Methoxy-pyridin-3-yl)-3-methyl-1-(4-piperazin-1-yl-3-trifluoromethyl-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one (Compound A41), or a compound described in PCT Publication No. WO 2006/122806 , to treat a disorder such as a cancer, a prostate cancer, a leukemia (*e.g.*, lymphocytic leukemia), a breast cancer, a brain cancer, a bladder cancer, a pancreatic cancer, a renal cancer, a solid tumor, or a liver cancer.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an FGFR inhibitor, 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-ethylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-1-methylurea (Compound A5) or a compound disclosed in US Patent 8,552,002, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the FGFR inhibitor is 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-ethylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-1-methylurea (Compound A5) or a compound disclosed in US Patent 8,552,002. In one embodiment, a TIM-3 antibody molecule is used in combination with Compound A5, or a compound as described in US 8,552,002, to treat a disorder such as a digestive/gastrointestinal cancer, a hematological cancer, or a solid tumor.

In one embodiment, the FGFR inhibitor or 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-ethylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-1-methylurea (Compound A5) is administered at a dose of about 100-125 mg (*e.g.*, per day), *e.g.*, about 100 mg or about 125 mg.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a PI3K inhibitor, Buparlisib (Compound A6), or a compound disclosed in PCT Publication No. WO 2007/084786, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PI3K inhibitor is Buparlisib (Compound A6) or a compound disclosed in PCT Publication No. WO 2007/084786. In one embodiment, a TIM-3 antibody molecule is used in combination with Buparlisib (Compound A6), or a compound

disclosed in PCT Publication No. WO 2007/084786, to treat a disorder such as, a prostate cancer, a non-small cell lung cancer, an endocrine cancer, a leukemia, an ovarian cancer, a melanoma, a bladder cancer, a breast cancer, a female reproductive system cancer, a digestive/gastrointestinal cancer, a colorectal cancer, a glioblastoma multiforme, a solid tumor, a non-Hodgkin lymphoma, a hematopoiesis disorder, or a head and neck cancer.

In one embodiment, the PI3K inhibitor or Buparlisib (Compound A6) is administered at a dose of about 100 mg (*e.g.*, per day).

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an FGFR inhibitor, 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide (Compound A7) or a compound disclosed in PCT Publication No. WO 2009/141386 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the FGFR inhibitor is 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide(Compound A7) or a compound disclosed in a PCT Publication No. WO 2009/141386. In one embodiment, the FGFR inhibitor is 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide(Compound A7). In one embodiment, a TIM-3 antibody molecule is used in combination with 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide(Compound A7), or a compound disclosed in PCT Publication No. WO 2009/141386, to treat a disorder such as a cancer characterized by angiogenesis.

In one embodiment, the FGFR inhibitor or 8-(2,6-difluoro-3,5-dimethoxyphenyl)-N-(4-((dimethylamino)methyl)-1H-imidazol-2-yl)quinoxaline-5-carboxamide (Compound A7) is administered at a dose of *e.g.*, from approximately 3 mg to approximately 5 g, more preferably from approximately 10 mg to approximately 1.5 g per person per day, optionally divided into 1 to 3 single doses which may, for example, be of the same size.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a PI3K inhibitor, (S)-N1-(4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-yl)pyrrolidine-1,2-dicarboxamide (Compound A8) or a compound disclosed PCT Publication No. WO 2010/029082 to treat a

disorder, *e.g.*, a disorder described herein. In one embodiment, the PI3K inhibitor is (S)-N1-(4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-yl)pyrrolidine-1,2-dicarboxamide (Compound A8) or a compound disclosed PCT Publication No. WO 2010/029082. In one embodiment, a TIM-3 antibody molecule is used in combination with (S)-N1-(4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-yl)pyrrolidine-1,2-dicarboxamide (Compound A8), or a compound disclosed PCT Publication No. WO 2010/029082, to treat a disorder such as a gastric cancer, a breast cancer, a pancreatic cancer, a digestive/ gastrointestinal cancer, a solid tumor, and a head and neck cancer.

In one embodiment, the PI3K inhibitor or (S)-N1-(4-methyl-5-(2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl)thiazol-2-yl)pyrrolidine-1,2-dicarboxamide (Compound A8) is administered at a dose of about 150-300, 200-300, 200-400, or 300-400 mg (*e.g.*, per day), *e.g.*, about 200, 300, or 400 mg.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an inhibitor of cytochrome P450 (*e.g.*, a CYP17 inhibitor) or a compound disclosed in PCT Publication No. WO 2010/149755, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the cytochrome P450 inhibitor (*e.g.*, the CYP17 inhibitor) is a compound disclosed in PCT Publication No. WO 2010/149755. In one embodiment, a TIM-3 antibody molecule is used in combination with a compound disclosed in PCT Publication No. WO 2010/149755, to treat prostate cancer.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an HDM2 inhibitor, (S)-1-(4-chlorophenyl)-7-isopropoxy-6-methoxy-2-(4-(methyl(((1r,4S)-4-(4-methyl-3-oxopiperazin-1-yl)cyclohexyl)methyl)amino)phenyl)-1,2-dihydroisoquinolin-3(4H)-one(Compound A10) or a compound disclosed in PCT Publication No. WO 2011/076786 to treat a disorder, *e.g.*, a disorder described herein). In one embodiment, the HDM2 inhibitor is (S)-1-(4-chlorophenyl)-7-isopropoxy-6-methoxy-2-(4-(methyl(((1r,4S)-4-(4-methyl-3-oxopiperazin-1-yl)cyclohexyl)methyl)amino)phenyl)-1,2-dihydroisoquinolin-3(4H)-one (Compound A10) or a compound disclosed in PCT Publication No. WO 2011/076786. In one embodiment, a TIM-3 antibody molecule is used in combination with (S)-1-(4-chlorophenyl)-7-isopropoxy-6-methoxy-

2-(4-(methyl(((1r,4S)-4-(4-methyl-3-oxopiperazin-1-yl)cyclohexyl)methyl)amino)phenyl)-1,2-dihydroisoquinolin-3(4H)-one (Compound A10), or a compound disclosed in PCTPublication No. WO 2011/076786, to treat a disorder such as a solid tumor.

In one embodiment, the HDM2 inhibitor or (S)-1-(4-chlorophenyl)-7-isopropoxy-6-methoxy-2-(4-(methyl(((1r,4S)-4-(4-methyl-3-oxopiperazin-1-yl)cyclohexyl)methyl)amino)phenyl)-1,2-dihydroisoquinolin-3(4H)-one (Compound A10) is administered at a dose of about 400 to 700 mg, *e.g.*, administered three times weekly, 2 weeks on and one week off. In some embodiments, the dose is about 400, 500, 600, or 700 mg; about 400-500, 500-600, or 600-700 mg, *e.g.*, administered three times weekly.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an iron chelating agent, Deferasirox (also known as EXJADE; Compound A11), or a compound disclosed in PCT Publication No. WO 1997/049395 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the iron chelating agent is Deferasirox or a compound disclosed in PCT Publication No. WO 1997/049395. In one embodiment, the iron chelating agent is Deferasirox (Compound A11). In one embodiment, a TIM-3 antibody molecule is used in combination with Deferasirox (Compound A11), or a compound disclosed in PCT Publication No. WO 1997/049395, to treat iron overload, hemochromatosis, or myelodysplasia.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an aromatase inhibitor, Letrozole (also known as FEMARA; Compound A12), or a compound disclosed in US 4,978,672 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the aromatase inhibitor is Letrozole (Compound A12) or a compound disclosed in US Patent 4,978,672. In one embodiment, a TIM-3 antibody molecule is used in combination with Letrozole (Compound A12), or a compound disclosed in US Patent 4,978,672, to treat a disorder such as a cancer, a leiomyosarcoma, an endometrium cancer, a breast cancer, a female reproductive system cancer, or a hormone deficiency.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other

immunomodulators, is used in combination with a PI3K inhibitor, *e.g.*, a pan-PI3K inhibitor, (4S,5R)-3-(2'-amino-2-morpholino-4'-(trifluoromethyl)-[4,5'-bipyrimidin]-6-yl)-4-(hydroxymethyl)-5-methyloxazolidin-2-one (Compound A13) or a compound disclosed in PCT Publication No. WO2013/124826 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the PI3K inhibitor is (4S,5R)-3-(2'-amino-2-morpholino-4'-(trifluoromethyl)-[4,5'-bipyrimidin]-6-yl)-4-(hydroxymethyl)-5-methyloxazolidin-2-one (Compound A13) or a compound disclosed in PCT Publication No. WO2013/124826. In one embodiment, a TIM-3 antibody molecule is used in combination with (4S,5R)-3-(2'-amino-2-morpholino-4'-(trifluoromethyl)-[4,5'-bipyrimidin]-6-yl)-4-(hydroxymethyl)-5-methyloxazolidin-2-one (Compound A13), or a compound disclosed in PCT Publication No. WO2013/124826, to treat a disorder such as a cancer or an advanced solid tumor.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an inhibitor of p53 and/or a p53/Mdm2 interaction, (S)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-isopropyl-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one (Compound A14), or a compound disclosed in PCT Publication No. WO2013/111105 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the p53 and/or a p53/Mdm2 interaction inhibitor is (S)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-isopropyl-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one (Compound A14) or a compound disclosed in PCT Publication No. WO2013/111105. In one embodiment, a TIM-3 antibody molecule is used in combination with (S)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-isopropyl-5,6-dihydropyrrolo[3,4-d]imidazol-4(1H)-one (Compound A14), or a compound disclosed in PCT Publication No. WO2013/111105, to treat a disorder such as a cancer or a soft tissue sarcoma.

In another embodiment, anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a CSF-1R tyrosine kinase inhibitor, 4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide (Compound A15), or a compound disclosed in PCT Publication No. WO 2005/073224 to treat a

disorder, *e.g.,* a disorder described herein. In one embodiment, the CSF-1R tyrosine kinase inhibitor is 4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide (Compound A15) or a compound disclosed in PCT Publication No. WO 2005/073224. In one embodiment, anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, is used in combination with 4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide (Compound A15) or a compound disclosed in PCT Publication No. WO 2005/073224, to treat a disorder such as cancer.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an apoptosis inducer and/or an angiogenesis inhibitor, such as Imatinib mesylate (also known as GLEEVEC; Compound A16) or a compound disclosed in PCT Publication No. WO1999/003854 to treat a disorder, *e.g.,* a disorder described. In one embodiment, the apoptosis inducer and/or an angiogenesis inhibitor is Imatinib mesylate (Compound A16) or a compound disclosed in PCT Publication No. WO1999/003854. In one embodiment, a TIM-3 antibody molecule is used in combination with Imatinib mesylate (Compound A16), or a compound disclosed in PCT Publication No. WO1999/003854, to treat a disorder such as a cancer, a multiple myeloma, a prostate cancer, a non-small cell lung cancer, a lymphoma, a gastric cancer, a melanoma, a breast cancer, a pancreatic cancer, a digestive/gastrointestinal cancer, a colorectal cancer, a glioblastoma multiforme, a liver cancer, a head and neck cancer, asthma, multiple sclerosis, allergy, Alzheimer's dementia, amyotrophic lateral sclerosis, or rheumatoid arthritis.

In certain embodiments, Imatinib mesylate (Compound A16) is administered at a dose of about 100 to 1000 mg, *e.g.,* about 200 mg to 800 mg, about 300 mg to 700 mg, or about 400 mg to 600 mg, *e.g.,* about 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, or 700 mg. The dosing schedule can vary from *e.g.,* every other day to daily, twice or three times a day. In one embodiment, Imatinib mesylate is administered at an oral dose from about 100 mg to 600 mg daily, *e.g.*, about 100 mg, 200 mg, 260 mg, 300 mg, 400 mg, or 600 mg daily.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a JAK inhibitor, 2-fluoro-N-methyl-4-(7-

(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide (Compound A17), or a dihydrochloric salt thereof, or a compound disclosed in PCT Publication No. WO 2007/070514, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the JAK inhibitor is 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide (Compound A17), or a dihydrochloric salt thereof, or a compound disclosed in PCT Publication No. WO 2007/070514. In one embodiment, a TIM-3 antibody molecule is used in combination with 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide (Compound A17), or a dihydrochloric salt thereof, or a compound disclosed in PCT Publication No. WO 2007/070514, to treat a disorder such as colorectal cancer, myeloid leukemia, hematological cancer, autoimmune disease, non-Hodgkin lymphoma, or thrombocythemia.

In one embodiment, the JAK inhibitor or a 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide (Compound A17), or a dihydrochloric salt thereof is administered at a dose of about 400-600 mg (*e.g.*, per day), *e.g.*, about 400, 500, or 600 mg, or about 400-500 or 500-600 mg.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a JAK inhibitor, Ruxolitinib Phosphate (also known as JAKAFI; Compound A18) or a compound disclosed in PCT Publication No. WO 2007/070514 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the JAK inhibitor is Ruxolitinib Phosphate (Compound A18) or a compound disclosed in PCT Publication No. WO 2007/070514. In one embodiment, a TIM-3 antibody molecule is used in combination with Ruxolitinib Phosphate (Compound A18), or a compound disclosed in PCT Publication No. WO 2007/070514, to treat a disorder such as a prostate cancer, a lymphocytic leukemia, a multiple myeloma, a lymphoma, a lung cancer, a leukemia, cachexia, a breast cancer, a pancreatic cancer, rheumatoid arthritis, psoriasis, a colorectal cancer, a myeloid leukemia, a hematological cancer, an autoimmune disease, a non-Hodgkin lymphoma, or thrombocythemia.

In one embodiment, the JAK inhibitor or Ruxolitinib Phosphate (Compound A18) is administered at a dose of about 15-25 mg, *e.g.*, twice daily. In some embodiments, the dose is about 15, 20, or 25 mg, or about 15-20 or 20-25 mg.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other

immunomodulators, is used in combination with a deacetylase (DAC) inhibitor, Panobinostat (Compound A19), or a compound disclosed in PCT Publication No. WO 2014/072493 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the DAC inhibitor is Panobinostat (Compound A19) or a compound disclosed in PCT Publication No. WO 2014/072493. In one embodiment, a TIM-3 antibody molecule is used in combination with Panobinostat (Compound A19), a compound disclosed in PCT Publication No. WO 2014/072493, to treat a disorder such as a small cell lung cancer, a respiratory/thoracic cancer, a prostate cancer, a multiple myeloma, myelodysplastic syndrome, a bone cancer, a non-small cell lung cancer, an endocrine cancer, a lymphoma, a neurologic cancer, a leukemia, HIV/AIDS, an immune disorder, transplant rejection, a gastric cancer, a melanoma, a breast cancer, a pancreatic cancer, a colorectal cancer, a glioblastoma multiforme, a myeloid leukemia, a hematological cancer, a renal cancer, a non-Hodgkin lymphoma, a head and neck cancer, a hematopoiesis disorders, or a liver cancer.

In one embodiment, the DAC inhibitor or Panobinostat (Compound A19) is administered at a dose of about 20 mg (*e.g.*, per day).

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an inhibitor of one or more of cytochrome P450 (*e.g.*, 11B2), aldosterone or angiogenesis, Osilodrostat (Compound A20), or a compound disclosed in PCT Publication No. WO2007/024945 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the inhibitor of one or more of cytochrome P450 (*e.g.*, 11B2), aldosterone or angiogenesis is Osilodrostat (Compound A20) or a compound disclosed in PCT Publication No. WO2007/024945. In one embodiment, a TIM-3 antibody molecule is used in combination with Osilodrostat (Compound A20), or a compound disclosed in PCT Publication No. WO2007/024945, to treat a disorder such as Cushing's syndrome, hypertension, or heart failure therapy.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a IAP inhibitor, (S)-N-((S)-1-cyclohexyl-2-((S)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-2-(methylamino)propanamide (Compound A21) or a compound disclosed in US 8,552,003 to treat a disorder, *e.g.*, a disorder

described herein. In one embodiment, the IAP inhibitor is (S)-N-((S)-1-cyclohexyl-2-((S)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-2-(methylamino)propanamide (Compound A21) or a compound disclosed in US Patent 8,552,003. In one embodiment, a TIM-3 antibody molecule is used in combination with (S)-N-((S)-1-cyclohexyl-2-((S)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-2-(methylamino)propanamide (Compound A21), or a compound disclosed in US Patent 8,552,003, to treat a disorder such as a multiple myeloma, a breast cancer, an ovarian cancer, a pancreatic cancer, or a hematopoiesis disorder.

In one embodiment, the IAP inhibitor or (S)-N-((S)-1-cyclohexyl-2-((S)-2-(4-(4-fluorobenzoyl)thiazol-2-yl)pyrrolidin-1-yl)-2-oxoethyl)-2-(methylamino)propanamide (Compound A21) or a compound disclosed in US 8,552,003 is administered at a dose of approximately 1800 mg, *e.g.*, once weekly.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a Smoothened (SMO) inhibitor, Sonidegib phosphate (Compound A22), (R)-2-(5-(4-(6-benzyl-4,5-dimethylpyridazin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)propan-2-ol (Compound A25), or a compound disclosed in PCT Publication No. WO 2007/131201 or WO 2010/007120 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the SMO inhibitor is Sonidegib phosphate (Compound A22), (R)-2-(5-(4-(6-benzyl-4,5-dimethylpyridazin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)propan-2-ol (Compound A25), or a compound disclosed in PCT Publication No. WO 2007/131201 or WO 2010/007120. In one embodiment, a TIM-3 antibody molecule is used in combination with Sonidegib phosphate (Compound A22), (R)-2-(5-(4-(6-benzyl-4,5-dimethylpyridazin-3-yl)-2-methylpiperazin-1-yl)pyrazin-2-yl)propan-2-ol (Compound A25), or a compound disclosed in PCT Publication No. WO 2007/131201 or WO 2010/007120 to treat a disorder such as a cancer, a medulloblastoma, a small cell lung cancer, a prostate cancer, a basal cell carcinoma, a pancreatic cancer, or an inflammation.

In certain embodiments, Sonidegib phosphate (Compound A22) is administered at a dose of about 20 to 500 mg, *e.g.,* about 40 mg to 400 mg, about 50 mg to 300 mg, or about 100 mg to 200 mg, *e.g.,* about 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, or 300 mg. The dosing schedule can vary from *e.g.,* every other day to daily, twice or three times a day.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an Alk inhibitor, ceritinib (also known as ZYKADIA; Compound A23) or a compound disclosed in PCT Publication No. WO 2007/131201 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the Alk inhibitor is ceritinib (Compound A23) or a compound disclosed in PCT Publication No. WO 2007/131201. In one embodiment, a TIM-3 antibody molecule is used in combination with ceritinib (Compound A23), or a compound disclosed in PCT Publication No. WO 2007/131201, to treat a disorder such as non-small cell lung cancer or solid tumors.

In one embodiment, the Alk inhibitor or ceritinib (Compound A23) is administered at a dose of approximately 750 mg, *e.g.*, once daily.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a JAK and/or CDK4/6 inhibitor, 7-cyclopentyl-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A24), or a compound disclosed in US Patent 8,415,355 or US Patent 8,685,980 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the JAK and/or CDK4/6 inhibitor is 7-cyclopentyl-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A24) or a compound disclosed in US Patent 8,415,355 or US Patent 8,685,980. In one embodiment, a TIM-3 antibody molecule is used in combination with 7-cyclopentyl-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A24), or a compound disclosed in US 8,415,355 or US 8,685,980, to treat a disorder such as a lymphoma, a neurologic cancer, a melanoma, a breast cancer, or a solid tumor.

In one embodiment, the JAK and/or CDK4/6 inhibitor or 7-cyclopentyl-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A24) is administered at a dose of approximately 200-600 mg, *e.g.*, per day. In one embodiment, the compound is administered at a dose of about 200, 300, 400, 500, or 600 mg, or about 200-300, 300-400, 400-500, or 500-600 mg.

In another embodiment, the antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in

combination a prolactin receptor (PRLR) inhibitor, a human monoclonal antibody molecule (Compound A26) as disclosed in US Patent 7,867,493), to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the PRLR inhibitor is a human monoclonal antibody (Compound A26) disclosed in US 7,867,493. In one embodiment, a TIM-3 antibody molecule is used in combination with human monoclonal antibody molecule (Compound A26) described in US Patent 7,867,493 to treat a disorder such as, a cancer, a prostate cancer, or a breast cancer.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a PIM Kinase inhibitor, N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide (Compound A27) or a compound disclosed in PCT Publication No. WO 2010/026124 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the PIM Kinase inhibitor is N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide (Compound A27) or a compound disclosed in PCT Publication No. WO 2010/026124. In one embodiment, a TIM-3 antibody molecule is used in combination with N-(4-((1R,3S,5S)-3-amino-5-methylcyclohexyl)pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide (Compound A27), or a compound disclosed in PCT Publication No. WO 2010/026124, to treat a disorder such as a multiple myeloma, myelodysplastic syndrome, a myeloid leukemia, or a non-Hodgkin lymphoma.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a Wnt signaling inhibitor, 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28) or a compound disclosed in PCT publication No. WO 2010/101849 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the Wnt signaling inhibitor is 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28) or a compound disclosed in PCT publication No. WO 2010/101849. In one embodiment, the Wnt signaling inhibitor is 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28). In one embodiment, a TIM-3 antibody molecule is used in combination with 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28), or a compound disclosed in PCT publication No. WO 2010/101849, to treat a disorder such as a

solid tumor (*e.g.*, a head and neck cancer, a squamous cell carcinoma, a breast cancer, a pancreatic cancer, or a colon cancer).

In certain embodiments, 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide (Compound A28) is administered at a dose of about 1 to 50 mg, *e.g.*, about 2 mg to 45 mg, about 3 mg to 40 mg, about 5 mg to 35 mg, 5 mg to 10 mg, or about 10 mg to 30 mg, *e.g.*, about 2 mg, 5 mg, 10 mg, 20 mg, 30 mg, or 40 mg. The dosing schedule can vary from *e.g.*, every other day to daily, twice or three times a day.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a BRAF inhibitor, Encorafenib (Compound A29), or a compound disclosed in PCT Publication No. WO 2011/025927 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the BRAF inhibitor is Encorafenib (Compound A29) or a compound disclosed in PCT Publication No. WO 2011/025927. In one embodiment, a TIM-3 antibody molecule is used in combination with Encorafenib (Compound A29), or a compound disclosed in PCT Publication No. WO 2011/025927, to treat a disorder such as a non-small cell lung cancer, a melanoma, or a colorectal cancer.

In one embodiment, the BRAF inhibitor or Encorafenib (Compound A29) is administered at a dose of about 200-300, 200-400, or 300-400 mg, *e.g.*, per day. In one embodiment, the compound is administered at a dose of about 200, about 300 or about 400 mg.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a CDK4/6 inhibitor, 7-cyclopentyl-N,N-dimethyl-2-((5-((1R,6S)-9-methyl-4-oxo-3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A30), or a compound disclosed in PCT publication No. WO 2011/101409 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the CDK4/6 inhibitor is 7-cyclopentyl-N,N-dimethyl-2-((5-((1R,6S)-9-methyl-4-oxo-3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A30) or a compound disclosed in PCT publication No. WO 2011/101409. In one embodiment, a TIM-3 antibody molecule is used in combination with 7-cyclopentyl-N,N-dimethyl-2-((5-((1R,6S)-9-methyl-4-oxo-3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound A30), or a

compound disclosed in PCT publication No. WO 2011/101409, to treat a disorder such as a cancer, a mantle cell lymphoma, a liposarcoma, a non-small cell lung cancer, a melanoma, a squamous cell esophageal cancer, or a breast cancer.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a HER3 inhibitor, Compound A31, or a compound disclosed in PCT Publication No. WO 2012/022814, to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the HER3 inhibitor is Compound A31 or a compound disclosed in PCT Publication WO 2012/022814. In one embodiment, a TIM-3 antibody molecule is used in combination with Compound A31, or a compound disclosed in PCT Publication WO 2012/022814, to treat a disorder such as a gastric cancer, an esophageal cancer, a head and neck cancer, a squamous cell carcinoma, a stomach cancer, a breast cancer (*e.g.*, metastatic breast cancer), or a digestive/gastrointestinal cancer.

In some embodiments, Compound A31 is a human monoclonal antibody molecule.

In one embodiment, the HER3 inhibitor or Compound A31 is administered at a dose of about 3, 10, 20, or 40 mg/kg, *e.g.*, once weekly (QW). In one embodiment, the compound is administered at a dose of about 3-10, 10-20, or 20-40 mg/kg.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an FGFR2 and/or FGFR4 inhibitor, Compound A32, or a compound disclosed in a publication PCT Publication No. WO 2014/160160 (*e.g.*, an antibody molecule drug conjugate against an FGFR2 and/or FGFR4, *e.g.*, mAb 12425), to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the FGFR2 and/or FGFR4 inhibitor is Compound A32 or a compound disclosed in a publication PCT Publication No. WO 2014/160160. In one embodiment, a TIM-3 antibody molecule is used in combination with Compound A32, or a compound as described in Table 6, to treat a disorder such as a cancer, a gastric cancer, a breast cancer, a rhabdomyosarcoma, a liver cancer, an adrenal cancer, a lung cancer, an esophageal cancer, a colon cancer, or an endometrial cancer.

In some embodiments, Compound A32 is an antibody molecule drug conjugate against an FGFR2 and/or FGFR4, *e.g.*, mAb 12425.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an M-CSF inhibitor, Compound A33, or a compound disclosed in PCT Publication No. WO 2004/045532 (*e.g.*, an antibody molecule or Fab fragment against M-CSF), to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the M-CSF inhibitor is Compound A33 or a compound disclosed in PCT Publication No. WO 2004/045532. In one embodiment, a TIM-3 antibody molecule is used in combination with Compound A33, or a compound as described in PCT Publication No. WO 2004/045532, to treat a disorder such as a cancer, a prostate cancer, a breast cancer, or pigmented villonodular synovitis (PVNS).

In embodiments, Compound A33 is a monoclonal antibody molecule against M-CSF or a fragment (*e.g.*, Fab fragment) thereof. In embodiments, the M-CSF inhibitor or Compound A33 is administered at an average dose of about 10mg/kg.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a MEK inhibitor, Binimetinib (Compound A34), or a compound disclosed in PCT Publication No. WO 2003/077914 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the MEK inhibitor is Binimetinib (Compound A34), or a compound disclosed in PCT Publication No. WO 2003/077914. In one embodiment, a TIM-3 antibody molecule is used in combination with Binimetinib (Compound A34), or a compound disclosed in PCT Publication No. WO 2003/077914, to treat a disorder such as a non-small cell lung cancer, a multisystem genetic disorder, a melanoma, an ovarian cancer, a digestive/gastrointestinal cancer, a rheumatoid arthritis, or a colorectal cancer.

In one embodiment, the MEK inhibitor or Binimetinib (Compound A34) is administered at a dose of about 45 mg, *e.g.*, twice daily.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an inhibitor of one or more of c-KIT, histamine release, Flt3 (*e.g.*, FLK2/STK1) or PKC, Midostaurin (Compound A35) or a compound disclosed in PCT Publication No. WO 2003/037347 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the inhibitor is Midostaurin (Compound A35) or compound

disclosed in PCT Publication No. WO 2003/037347. In one embodiment, the inhibitor of one or more of c-KIT, histamine release, Flt3 (*e.g.*, FLK2/STK1) or PKC is Midostaurin. In one embodiment, a TIM-3 antibody molecule is used in combination with Midostaurin (Compound A35), or compound disclosed in PCT Publication No. WO 2003/037347, to treat a disorder such as a cancer, a colorectal cancer, a myeloid leukemia, myelodysplastic syndrome, an age-related mascular degeration, a diabetic complication, or a dermatologic disorder.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a TOR inhibitor (*e.g.*, mTOR inhibitor), Everolimus (also known as AFINITOR; Compound A36) or a Compound disclosed in PCT Publication No. WO 2014/085318 to treat a disorder, *e.g.*, a disorder described herein). In one embodiment, the TOR inhibitor is Everolimus (Compound A36) or a Compound disclosed in PCT Publication No. WO 2014/085318. In one embodiment, a TIM-3 antibody molecule is used in combination with Everolimus (Compound A36) to treat a disorder such as an interstitial lung disease, a small cell lung cancer, a respiratory/thoracic cancer, a prostate cancer, a multiple myeloma, a sarcoma, an age-related macular degeneration,a bone cancer, tuberous sclerosis, a non-small cell lung cancer, an endocrine cancer, a lymphoma, a neurologic disorders, an astrocytoma, a cervical cancer, a neurologic cancer, a leukemia, an immune disorders, transplant rejection, a gastric cancer, a melanoma, epilepsy, a breast cancer, or a bladder cancer.

In one embodiment, the TOR inhibitor or Everolimusis (Compound A36) administered at a dose of about 2.5-20 mg/day. In one embodiment, the compound is administered at a dose of about 2.5, 5, 10, or 20 mg/day, *e.g.*, about 2.5-5, 5-10, or 10-20 mg/day.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an inhibitor of one or more of VEGFR-2, PDGFRbeta, KIT or Raf kinase C, 1-methyl-5-((2-(5-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yl)oxy)-N-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-2-amine (Compound A37) or a compound disclosed in PCT Publication No. WO 2007/030377 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the inhibitor of one or more of VEGFR-2, PDGFRbeta, KIT or Raf kinase C is 1-methyl-5-((2-(5-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yl)oxy)-N-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-2-amine (Compound

A37) or a compound disclosed in PCT Publication No. WO 2007/030377. In one embodiment, a TIM-3 antibody molecule is used in combination with 1-methyl-5-((2-(5-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yl)oxy)-N-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-2-amine (Compound A37), or a compound disclosed in PCT Publication No. WO 2007/030377, to treat a disorder such as a cancer, a melanoma, or a solid tumor.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a somatostatin agonist and/or growth hormone release inhibitor, Pasireotide diaspartate (also known as SIGNIFOR; Compound A38) or a compound disclosed in PCT Publication No. WO2002/010192 or US Patent No. 7,473,761 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the somatostatin agonist and/or growth hormone release inhibitor is Pasireotide diaspartate (Compound A38) or a compound disclosed in PCT Publication No. WO2002/010192 or US Patent No. 7,473,761. In one embodiment, a TIM-3 antibody molecule is used in combination with Pasireotide diaspartate (Compound A38), or a compound disclosed in PCT Publication No. WO2002/010192 or US Patent No. 7,473,761, to treat a disorder such as a prostate cancer, an endocrine cancer, a nurologic cancer, a skin cancer (*e.g.*, a melanoma), a pancreatic cancer, a liver cancer, Cushing's syndrome, a gastrointestinal disorder, acromegaly, a liver and biliary tract disorder, or liver cirrhosis.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a signal transduction modulator and/or angiogenesis inhibitor, Dovitinib (Compound A39) or a compound disclosed in PCT Publication No. WO 2009/115562 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the signal transduction modulator and/or angiogenesis inhibitor is Dovitinib (Compound A39) or a compound disclosed in PCT Publication No. WO 2009/115562. In one embodiment, a TIM-3 antibody molecule is used in combination with Dovitinib (Compound A39), or a compound disclosed in PCT Publication No. WO 2009/115562, to treat a disorder such as a cancer, a respiratory/thoracic cancer, a multiple myeloma, a prostate cancer, a non-small cell lung cancer, an endocrine cancer, or a neurological genetic disorder.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an EGFR inhibitor, (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40) or a compound disclosed in PCT Publication No. WO 2013/184757 to treat a disorder, *e.g.*, a disorder described herein. In one embodiment, the EGFR inhibitor is (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40) or a compound disclosed in PCT Publication No. WO 2013/184757. In one embodiment, a TIM-3 antibody molecule is used in combination with (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40), or a compound disclosed in PCT Publication No. WO 2013/184757, to treat a disorder such as a cancer, *e.g.*, a solid tumor.

In one embodiment, the EGFR inhibitor or (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40) is administered at a dose of 150-250 mg, *e.g.*, per day. In one embodiment, the compound is administered at a dose of about 150, 200, or 250 mg, or about 150-200 or 200-250 mg.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an ALK inhibitor, N^6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N^4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine (Compound A42) or a compound disclosed in PCT Publication No. WO 2008/073687 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the ALK inhibitor is N^6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N^4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine (Compound A42) or a compound disclosed in PCT Publication No. WO 2008/073687. In one embodiment, a TIM-3 antibody molecule is used in combination with N^6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N^4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine (Compound A42), or a compound disclosed in PCT Publication No. WO 2008/073687, to treat a disorder such as a cancer, an anaplastic large-cell lymphoma (ALCL), a non-small cell lung carcinoma (NSCLC), or a neuroblastoma.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination an IGF-1R inhibitor, 3-(4-(4-((5-chloro-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)-5-fluoro-2-methylphenyl)piperidin-1-yl)thietane 1,1-dioxide (Compound A43), 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A44), or 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A45) or a compound disclosed in PCT Publication No. WO 2010/002655 to treat a disorder, *e.g.,* a disorder described. In one embodiment, the IGF-1R inhibitor is 3-(4-(4-((5-chloro-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)-5-fluoro-2-methylphenyl)piperidin-1-yl)thietane 1,1-dioxide (Compound A43), 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A44), 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A45), or a compound disclosed in PCT Publication No. WO 2010/002655. In one embodiment, a TIM-3 antibody molecule is used in combination with 3-(4-(4-((5-chloro-4-((5-methyl-1H-pyrazol-3-yl)amino)pyrimidin-2-yl)amino)-5-fluoro-2-methylphenyl)piperidin-1-yl)thietane 1,1-dioxide (Compound A43), 5-chloro-N^2-(2-fluoro-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)phenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A44), 5-chloro-N2-(4-(1-ethylpiperidin-4-yl)-2-fluoro-5-methylphenyl)-N^4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (Compound A45), or a compound disclosed in PCT Publication No. WO 2010/002655, to treat a disorder such as a cancer or a sarcoma.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination a P-Glycoprotein 1 inhibitor, Valspodar (also known as AMDRAY; Compound A46) or a compound disclosed in EP 296122 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the P-Glycoprotein 1 inhibitor is Valspodar (Compound A46) or a compound disclosed in EP 296122. In one embodiment, a TIM-3 antibody molecule is used in combination with Valspodar (Compound A46), or a compound disclosed in EP 296122, to treat a disorder such as a cancer or a drug-resistant tumor.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination one or more of a VEGFR inhibitor, Vatalanib succinate (Compound A47) or a compound disclosed in EP 296122 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the VEGFR inhibitor is Vatalanib succinate (Compound A47) or a compound disclosed in EP 296122. In one embodiment, a TIM-3 antibody molecule is used in combination with Vatalanib succinate (Compound A47), or a compound disclosed in EP 296122, to treat cancer.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an IDH inhibitor or a compound disclosed in WO2014/141104 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the IDH inhibitor is a compound disclosed in PCT Publication No. WO2014/141104. In one embodiment, a TIM-3 antibody molecule is used in combination with a compound disclosed in WO2014/141104 to treat a disorder such as a cancer.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a BCL-ABL inhibitor or a compound disclosed in PCT Publication No. WO2013/171639, WO2013/171640, WO2013/171641, or WO2013/171642 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the BCL-ABL inhibitor is a compound disclosed in PCT Publication No. WO2013/171639, WO2013/171640, WO2013/171641, or WO2013/171642. In one embodiment, a TIM-3 antibody molecule is used in combination with a compound disclosed in PCT Publication No. WO2013/171639, WO2013/171640, WO2013/171641, or WO2013/171642 to treat a disorder such as a cancer.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with a c-RAF inhibitor or a compound disclosed in PCT Publication No. WO2014/151616 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the c-RAF inhibitor is Compound A50 or a compound disclosed in PCT Publication No. WO2014/151616. In one embodiment, a TIM-3 antibody molecule is used in

combination with a compound disclosed in PCT Publication No. WO2014/151616 to treat a disorder such as a cancer.

In another embodiment, the anti-TIM-3 antibody molecule, *e.g.*, an anti-TIM-3 antibody molecule as described herein, alone or in combination with one or more other immunomodulators, is used in combination with an ERK1/2 ATP competitive inhibitor or a compound disclosed in International Patent Application No. PCT/US2014/062913 to treat a disorder, *e.g.,* a disorder described herein. In one embodiment, the ERK1/2 ATP competitive inhibitor is a compound disclosed in International Patent Application No. PCT/US2014/062913. In one embodiment, a TIM-3 antibody molecule is used in combination with Compound A51 or a compound disclosed in International Patent Application No. PCT/US2014/062913 to treat a disorder such as a cancer.

In some embodiments, the TIM-3 antibody molecule is administerd in combination with one or more agents selected from , Compound A8, Compound A17, Compound A23, Compound A24, Compound A27, Compound A29, and Compound A33.

In some embodiments, a TIM-3 antibody molecule is administered in combination with an anti-cancer agent having a known activity in an immune cell assay, *e.g.*, in one or more of a huMLR assay, a T cell proliferation assay, and a B-cell proliferation assay. Exemplary assays are described below. Based on the assay, an IC50 for can be calculated for each test agent. In embodiments, the anti-cancer agent has an IC50 of, *e.g.*, 0-1 μM, 1-4 μM, or greater than 4 μM, *e.g.*, 4-10 μM or 4-20 μM. In embodiments, the second therapeutic agent is chosen from one or more of: Compound A9, Compound A16, Compound A17, Compound A21, Compound A22, Compound A25, Compound A28, Compound A48, and Compound 49.

In some embodiments, the Compound A28 (or a compound related to Compound A28) is administered at a dose of approximately 5-10 or 10-30 mg. In some embodiments, the Compound A22 (or compound related to Compound A22) is administered at a dose of about 200 mg. In some embodiments, the Compound A17 (or compound related to Compound A17) is administered at a dose of approximately 400-600 mg. In some embodiments, the Compound A16 (or compound related to Compound A16) is administered at a dose of approximately 400-600 mg PO qDay. In some embodiments, the Compound A29 (or compound related to Compound A29) is administered at a dose of approximately 200-400 or 300-400 mg. In some embodiments, the Compound A24 (or compound related to Compound A24) is administered at a

dose of approximately 200-600 mg. In some embodiments, the Compound A23 (ceritinib) (or compound related to ceritinib) is administered at a dose of approximately 750 mg once daily. In some embodiments, the Compound A8 (or compound related to Compound A8) is administered at a dose of approximately 200-400 or 300-400 mg. In some embodiments, the Compound A5 (or compound related to Compound A5) is administered at a dose of approximately 100-125 mg. In some embodiments, the Compound A6 (or compound related to Compound A6) is administered at a dose of about 100 mg. In some embodiments, the Compound A1 (or compound related to Compound A1) is administered at a dose of approximately 200-300 or 200-600 mg. In some embodiments, the Compound A40 (or compound related to Compound A40) is administered at a dose of approximately 150-250 mg. In embodiments, the Compound A10 (or compound related to Compound A10) is administered at a dose of approximately 400 to 700 mg, *e.g.*, administered three times weekly, 2 weeks on and one week off. In embodiments, the BCR-ABL inhibitor is administered at a dose of approximately 20 mg bid-80 mg bid.

Exemplary huMLR assay and B or T cell proliferation assays are provided below.

Human mixed lymphocyte reaction

The Mixed Lymphocyte Reaction (MLR) is a functional assay which measures the proliferative response of lymphocytes from one individual (the responder) to lymphocytes from another individual (the stimulator). To perform an allogeneic MLR, peripheral blood mononuclear cells (PBMC) from three donors were isolated from buffy-coats of unknown HLA type (Kantonspital Blutspendezentrum from Bern and Aarau, Switzerland). The cells were prepared at 2.105 in 0.2mL of culture medium containing RPMI 1640 GlutaMAX™ with 10% fetal calf serum (FCS), 100U penicillin/ 100µg streptomycin, 50µM 2-Mercaptoethanol. Individual 2-way reactions were set up by mixing PBMC from two different donors at a 1:1 ratio and co-cultures were done in triplicates in flat-bottomed 96-well tissue culture plates for 6 days at 37°C, 5% CO2, in presence or not of an 8-point concentration range of test compounds. Cells were pulsed with 3H-TdR (1 µCi/0.2mL) for the last 16h of culture and incorporated radioactivity was used as a measure of cell proliferation. The concentration that inhibited 50% of the maximal huMLR response (IC50) was calculated for each compound. Cyclosporine was used as a positive control of huMLR inhibition.

Human B cell proliferation assay

PBMC were freshly isolated by Ficoll-Paque density gradient from human blood and subjected to negative B-cell isolation. B cells were resuspended in culture medium (RPMI 1640, HEPES, 10% FCS, 50μg/mL gentamicine, 50μM 2-Mercaptoethanol, 1x ITS (Insulin, Transferrin and Sodium Selenite), 1x Non-Essential Amino-Acids) at a concentration of 9.104 per well in a flat-bottom 96-well culture plate. B cell stimulation was performed by human anti-IgM antibody molecule (30ug/mL) and IL-4 (75ng/mL) or by CD40 ligand (3ug/mL) and IL-4 (75ng/mL) in presence or not of a 7-point concentration range of test compounds. After 72h of culture at 37°C, 10% CO2, cells were pulsed with 3H-TdR (1 μCi/well) for the last 6h of culture. B cells were then harvested and the incorporation of thymidine was measured using a scintillation counter. Of each duplicate treatment, the mean was calculated and these data were plotted in XLfit 4 to determine the respective IC50 values.

Human T cell proliferation assay

PBMC were freshly isolated by Ficoll-Paque density gradient from human blood and subjected to negative isolation of T cells. T cells were prepared in culture medium (RPMI 1640, HEPES, 10% FCS, 50μg/mL gentamicine, 50μM 2-Mercaptoethanol, 1x ITS (Insulin, Transferrin and Sodium Selenite), 1x Non-Essential Amino-Acids) at a concentration of 8.104 per well in a flat-bottom 96-well culture plate. T cell stimulation was performed by human anti-CD3 antibody molecule (10ug/mL) or by human anti-CD3 antibody molecule (5μg/mL) and anti-CD28 antibody molecule (1μg/mL) in presence or not of a 7-point concentration range of test compounds. After 72h of culture at 37°C, 10% CO2, cells were pulsed with 3H-TdR (1 μCi/well) for the last 6h of culture. Cell proliferation was measured by the incorporation of thymidine allowing IC50 determination for each tested compound.

Down-Modulators of the Immune System

In an alternative embodiment, the anti-TIM-3 antibody molecules disclosed herein are used to produce anti-idiotypic peptides or antibodies (Wallmann, J. *et al.* (2010) "Anti-Ids in Allergy: Timeliness of a Classic Concept," *World Allergy Organiz. J.* 3(6):195-201; Nardi, M. *et al.* (2000) "Antiidiotype Antibody Against Platelet Anti-Gpiiia Contributes To The Regulation Of Thrombocytopenia In HIV-1-ITP Patients," *J. Exp. Med.* 191(12):2093-2100) or mimetics (Zang, Y. C. *et al.* (2003) "Human Anti-Idiotypic T Cells Induced By TCR Peptides Corresponding To A Common CDR3Sequence Motif In Myelin Basic Protein-Reactive T Cells,"

Int. Immunol. 15(9):1073-1080; Loiarro, M. *et al.* (Epub 2010 Apr. 8) "Targeting TLR/IL-1R Signalling In Human Diseases," *Mediators Inflamm.* 2010:674363) of TIM-3. Such molecules serve as surrogates for TIM-3, and thus their administration to a subject down-modulates the immune system of such subject by mimicking or facilitating ligand-TIM-3 binding. Such molecules have utility in the treatment of graft vs. host disease. Similarly, agonist antibodies that i) enhance binding between such antibodies and such receptor/ligand or ii) trigger signal transduction when bound directly to a TIM-3 ligand or TIM-3, have utility as agonists of TIM-3 signaling and thus have utility in the treatment of inflammation and autoimmune disease, by directly or indirectly agonizing receptor activity.

Bispecific antibodies, exhibiting immunospecific binding to both TIM-3 and TIM-3 ligands are capable of binding to both APC and T-cells, and thus facilitate the co-localization of APCs and T-cells. Such co-localization facilitates the ability of such cells to bind together via TIM-3 ligand and TIM-3 molecules that are not complexed with antibody, or by co-inhibitory molecules. Such binding provides down modulation of the immune system of the recipient.

Down-modulation of the immune system is desirable in the treatment of inflammatory and auto-immune diseases, and graft vs. host disease (GvHD). Examples of autoimmune disorders that may be treated by administering the antibodies of the present invention include, but are not limited to, alopecia greata, ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune diseases of the adrenal gland, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune oophoritis and orchitis, autoimmune thrombocytopenia, Behcet's disease, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatrical pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, glomerulonephritis, Graves' disease, Guillain-Barre, Hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura (ITP), IgA neuropathy, juvenile arthritis, lichen planus, lupus erthematosus, Meniere's disease, mixed connective tissue disease, multiple sclerosis, Neuromyelitis optica (NMO), type 1 or immune-mediated diabetes mellitus, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychrondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis and dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis,

psoriasis, psoriatic arthritis, Raynauld's phenomenon, Reiter's syndrome, Rheumatoid arthritis, sarcoidosis, scleroderma, Sjogren's syndrome, stiff-man syndrome, systemic lupus erythematosus, lupus erythematosus, takayasu arteritis, temporal arteristis/giant cell arteritis, transverse myelitis, ulcerative colitis, uveitis, vasculitides such as dermatitis herpetiformis vasculitis, vitiligo, and Wegener's granulomatosis.

Examples of inflammatory disorders which can be prevented, treated or managed in accordance with the methods of the invention include, but are not limited to, asthma, encephilitis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), allergic disorders, septic shock, pulmonary fibrosis, undifferentiated spondyloarthropathy, undifferentiated arthropathy, arthritis, inflammatory osteolysis, and chronic inflammation resulting from chronic viral or bacterial infections.

Thus, the antibodies and antigen-binding fragments of the present invention have utility in the treatment of inflammatory and autoimmune diseases.

Diagnostic Uses

In some aspects, the present disclosure provides a diagnostic method for detecting the presence of a TIM-3 protein *in vitro* (*e.g.*, in a biological sample, such as a tissue biopsy, *e.g.*, from a cancerous tissue) or *in vivo* (*e.g.*, in vivo imaging in a subject). The method includes: (i) contacting the sample with an antibody molecule described herein, or administering to the subject, the antibody molecule; (optionally) (ii) contacting a reference sample, *e.g.*, a control sample (*e.g.*, a control biological sample, such as plasma, tissue, biopsy) or a control subject with an antibody molecule described herein; and (iii) detecting formation of a complex between the antibody molecule, and the sample or subject, or the control sample or subject, wherein a change, *e.g.*, a statistically significant change, in the formation of the complex in the sample or subject relative to the control sample or subject is indicative of the presence of TIM-3 in the sample. The antibody molecule can be directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials, as described above and described in more detail below.

The term "sample," as it refers to samples used for detecting polypeptides includes, but is not limited to, cells, cell lysates, proteins or membrane extracts of cells, body fluids such as blood, or tissue samples.

Complex formation between the antibody molecule and TIM-3 can be detected by measuring or visualizing either the antibody molecule bound to the TIM-3 antigen or unbound antibody molecule. Any suitable detection assays can be used, and conventional detection assays include an enzyme-linked immunosorbent assays (ELISA), a radioimmunoassay (RIA) or tissue immunohistochemistry. Alternative to labeling the antibody molecule, the presence of TIM-3 can be assayed in a sample by a competition immunoassay utilizing standards labeled with a detectable substance and an unlabeled antibody molecule. In this assay, the biological sample, the labeled standards and the antibody molecule are combined and the amount of labeled standard bound to the unlabeled binding molecule is determined. The amount of TIM-3 in the sample is inversely proportional to the amount of labeled standard bound to the antibody molecule.

In some aspects, the present disclosure provides methods of using an anti-TIM-3 antibody molecule to diagnose sepsis, SIRS (Systemic Inflammatory Response Syndrome), preeclampsia, or glomerulonephritis. Sepsis is often accompanied by a downregulation of TIM-3 (Yang et al., J Immunol. 2013 Mar 1;190(5):2068-79) so lowered levels of TIM-3 are indicative of sepsis while normal levels of TIM-3 are an indication that sepsis is not present. In SIRS and preeclampsia, TIM-3 levels are downregulated in peripheral lymphocytes (Miko et al., PLoS ONE 8(8): e71811), so lowered levels of TIM-3 are indicative of SIRS or preeclampsia, while normal levels of TIM-3 are an indication that SIRS and preeclampsia are not present. In glomerulonephritis, TIM-3 can be upregulated (see Schroll et al., Am J Pathol 2010 April; 176(4):1716-1742) so elevated levels of TIM-3 are indicative of glomerulonephritis, while normal levels are an indication that glomerulonephritis is not present.

Nucleic Acids

The present disclosure also features nucleic acids comprising nucleotide sequences that encode heavy and light chain variable regions and CDRs of the anti-TIM-3 antibody molecules, as described herein. For example, the present disclosure features a first and second nucleic acid

encoding heavy and light chain variable regions, respectively, of an anti-TIM-3 antibody molecule chosen from one or more of the antibody molecules disclosed herein, *e.g.*, an antibody of Tables 1-4. The nucleic acid can comprise a nucleotide sequence encoding any one of the amino acid sequences in the tables herein, or a sequence substantially identical thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences provided in Tables 1-4.

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a heavy chain variable region having an amino acid sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, *e.g.*, conserved substitutions). In some embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a light chain variable region having an amino acid sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, *e.g.*, conserved substitutions). In some embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs from heavy and light chain variable regions having an amino acid sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, *e.g.*, conserved substitutions).

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a heavy chain variable region having the nucleotide sequence as set forth in Tables 1-4, a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In some embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs from a light chain variable region having the nucleotide sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs from heavy and light chain variable regions having the

nucleotide sequence as set forth in Tables 1-4, or a sequence substantially homologous thereto (*e.g.*, a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein).The nucleic acids disclosed herein include deoxyribonucleotides or ribonucleotides, or analogs thereof. The polynucleotide may be either single-stranded or double-stranded, and if single-stranded may be the coding strand or non-coding (antisense) strand. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. The nucleic acid may be a recombinant polynucleotide, or a polynucleotide of genomic, cDNA, semisynthetic, or synthetic origin which either does not occur in nature or is linked to another polynucleotide in a nonnatural arrangement.

In some aspects, the application features host cells and vectors containing the nucleic acids described herein. The nucleic acids may be present in a single vector or separate vectors present in the same host cell or separate host cell, as described in more detail hereinbelow.

Vectors

Further provided herein are vectors comprising nucleotide sequences encoding an antibody molecule described herein. In some embodiments, the vectors comprise nucleotides encoding an antibody molecule described herein. In some embodiments, the vectors comprise the nucleotide sequences described herein. The vectors include, but are not limited to, a virus, plasmid, cosmid, lambda phage or a yeast artificial chromosome (YAC).

Numerous vector systems can be employed. For example, one class of vectors utilizes DNA elements which are derived from animal viruses such as, for example, bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (Rous Sarcoma Virus, MMTV or MOMLV) or SV40 virus. Another class of vectors utilizes RNA elements derived from RNA viruses such as Semliki Forest virus, Eastern Equine Encephalitis virus and Flaviviruses.

Additionally, cells which have stably integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow for the selection of transfected host cells. The marker may provide, for example, prototropy to an auxotrophic host, biocide

resistance, (*e.g.*, antibiotics), or resistance to heavy metals such as copper, or the like. The selectable marker gene can be either directly linked to the DNA sequences to be expressed, or introduced into the same cell by cotransformation. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include splice signals, as well as transcriptional promoters, enhancers, and termination signals.

Once the expression vector or DNA sequence containing the constructs has been prepared for expression, the expression vectors may be transfected or introduced into an appropriate host cell. Various techniques may be employed to achieve this, such as, for example, protoplast fusion, calcium phosphate precipitation, electroporation, retroviral transduction, viral transfection, gene gun, lipid based transfection or other conventional techniques. In the case of protoplast fusion, the cells are grown in media and screened for the appropriate activity.

Methods and conditions for culturing the resulting transfected cells and for recovering the antibody molecule produced are known to those skilled in the art, and may be varied or optimized depending upon the specific expression vector and mammalian host cell employed, based upon the present description.

Cells

The present disclosure also provides host cells comprising a nucleic acid encoding an antibody molecule as described herein.

In some embodiments, the host cells are genetically engineered to comprise nucleic acids encoding the antibody molecule.

In certain embodiments, the host cells are genetically engineered by using an expression cassette. The phrase "expression cassette," refers to nucleotide sequences, which are capable of affecting expression of a gene in hosts compatible with such sequences. Such cassettes may include a promoter, an open reading frame with or without introns, and a termination signal. Additional factors necessary or helpful in effecting expression may also be used, such as, for example, an inducible promoter.

The disclosure also provides host cells comprising the vectors described herein.

The cell can be, but is not limited to, a eukaryotic c

ell, a bacterial cell, an insect cell, or a human cell. Suitable eukaryotic cells include, but are not limited to, Vero cells, HeLa cells, COS cells, CHO cells, HEK293 cells, BHK cells and MDCKII cells. Suitable insect cells include, but are not limited to, Sf9 cells.

Exemplary sequences of anti-TIM-3 antibodies are described in the Tables 1-4 below.

Table 1. Summary of the sequences of the murine antibody ABTIM3.

Antibody designation	SEQ ID NO	Description
ABTIM3	1	VH amino acid sequence
	2	VL amino acid sequence
	3	VHCDR1 amino acid sequence
	4	VHCDR2 amino acid sequence
	5	VHCDR3 amino acid sequence
	6	VLCDR1 amino acid sequence
	7	VLCDR2 amino acid sequence
	8	VLCDR3 amino acid sequence

Table 2. Depiction of the amino acid sequences of the murine antibody ABTIM3 heavy chain variable domain and light chain variable domain. CDRs are shown in white text on a black background.

SEQ ID NO	Sequence
1	QVQLQQPGAE LVKPGASVKM SCKASGYTFT SYNMHWIKQT PGQGLEWIGD IYPGNGDTSY NQKFKGKATL TADKSSSTVY MQLSSLTSED SAVYYCARVG GAFPMDYWGQ GTSVTVSS
2	DIVLTQSPAS LAVSLGQRAT ISCRASESVE YYGTSLMQWY QQKPGQPPKL LIYAASNVES GVPARFSGSG SGTDFSLNIH PVEEDDIAIY FCQQSRKDPS TFGGGTKLEI K

Table 3. Depiction of the amino acid sequences of the murine antibody ABTIM3 heavy chain CDRs and light chain CDRs.

SEQ ID NO	Sequence
3	SYNMH
4	DIYPGNGDTSYNQKFKG
5	VGGAFPMDY
6	RASESVEYYGTSLMQ

7	AASNVES
8	QQSRKDPST

Exemplary sequences of anti-TIM-3 antibodies are described in Table 4. The antibody molecules include murine ABTIM3, and humanized antibody molecules. The amino acid and nucleotide sequences of the heavy and light chain CDRs, the heavy and light chain variable regions, and the heavy and light chains are shown.

Table 4. Summary of the sequences of exemplary anti-TIM-3 antibodies.

Hybridoma clone		
ABTIM3		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 1	VH	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWIKQTPGQGLEWIGDIY PGNGDTSYNQKFKGKATLTADKSSSTVYMQLSSLTSEDSAVYYCARVGGAFP MDYWGQGTSVTVSS
SEQ ID NO: 11	DNA VH	CAGGTGCAACTGCAGCAGCCTGGGGCTGAGCTGGTGAAGCCTGGGGCCTCAG TGAAGATGTCCTGCAAGGCTTCTGGCTACACATTTACCAGTTACAATATGCA CTGGATAAAGCAGACACCTGGACAGGGCCTGGAATGGATTGGAGATATTTAT CCAGGAAATGGTGATACTTCCTACAATCAGAAATTCAAAGGCAAGGCCACAT TGACTGCAGACAAATCCTCCAGCACAGTCTACATGCAGCTCAGCAGCCTGAC ATCTGAGGACTCTGCGGTCTATTACTGTGCAAGAGTGGGGGGTGCCTTTCCT ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 2	VL	DIVLTQSPASLAVSLGQRATISCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPARFSGSGSGTDFSLNIHPVEEDDIAIYFCQQSRKDPSTFGG GTKLEIK
SEQ ID NO: 15	DNA VL	GACATTGTGCTCACCCAATCTCCAGCTTCTTTGGCTGTGTCTCTAGGGCAGA GAGCCACCATCTCCTGCAGAGCCAGTGAAAGTGTTGAATATTATGGCACAAG TTTAATGCAGTGGTACCAACAGAAACCAGGACAGCCACCCAAACTCCTCATC

		TATGCTGCATCCAACGTAGAATCTGGGGTCCCTGCCAGGTTTAGTGGCAGTG GGTCTGGGACAGACTTCAGCCTCAACATCCATCCTGTGGAGGAGGATGATAT TGCAATATATTTCTGTCAGCAAAGTAGGAAGGATCCTTCGACGTTCGGTGGA GGCACCAAGCTGGAGATCAAA
ABTIM3-hum01		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 16	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGNGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSS
SEQ ID NO: 17	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTCTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGGTTCGCCAGGCCCCAGGGCAGGGCCTCGAGTGGATCGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACTA TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCTAGC
SEQ ID NO: 18	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGNGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 19	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTCTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGGTTCGCCAGGCCCCAGGGCAGGGCCTCGAGTGGATCGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACTA TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCTAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG

		ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 20	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 21	DNA VL	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTACTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO: 22	Light Chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 23	DNA Light Chain	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTACTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum02		

SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 24 (Kabat)	HCDR2	DIYPGSGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 25 (Chothia)	HCDR2	YPGSGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 26	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGSGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSS
SEQ ID NO: 27	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTTAGCTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGGTTCGCCAGGCCCCAGGTCAAGGCCTCGAGTGGATCGGCGATATCTAC CCCGGTAGCGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACTA TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAAGATACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCTAGC
SEQ ID NO: 28	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGSGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 29	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTTAGCTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGGTTCGCCAGGCCCCAGGTCAAGGCCTCGAGTGGATCGGCGATATCTAC CCCGGTAGCGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACTA TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAAGATACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCTAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA

		CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 20	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 21	DNA VL	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTACTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO: 22	Light Chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 23	DNA Light Chain	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTACTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum03		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 30 (Kabat)	HCDR2	DIYPGQGDTSYNQKFKG

SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 31 (Chothia)	HCDR2	YPGQGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 32	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGQGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSS
SEQ ID NO: 33	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTTAGCTGTAAAGCTAGTGGCTATACTTTCACTTCTTATAATATGCA CTGGGTCCGCCAGGCCCCAGGTCAAGGCCTCGAGTGGATCGGCGATATCTAC CCCGGTCAAGGCGACACTTCCTATAATCAGAAGTTTAAGGGTAGAGCTACTA TGACCGCCGATAAGTCTACTTCTACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCA ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCTAGC
SEQ ID NO: 34	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGQGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 35	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTTAGCTGTAAAGCTAGTGGCTATACTTTCACTTCTTATAATATGCA CTGGGTCCGCCAGGCCCCAGGTCAAGGCCTCGAGTGGATCGGCGATATCTAC CCCGGTCAAGGCGACACTTCCTATAATCAGAAGTTTAAGGGTAGAGCTACTA TGACCGCCGATAAGTCTACTTCTACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCA ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCTAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6	LCDR1	RASESVEYYGTSLMQ

(Kabat)		
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 20	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 21	DNA VL	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTACTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO: 22	Light Chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 23	DNA Light Chain	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTACTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum04		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9	HCDR1	GYTFTSY

(Chothia)		
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 36	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWIRQAPGQGLEWIGDIY PGNGDTSYNQKFKGRATLTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSS
SEQ ID NO: 37	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTTTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGATTAGACAGGCCCCAGGGCAGGGCCTCGAGTGGATCGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACCC TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGGCAGGGCACCCTGGTCACCGTGTCTAGC
SEQ ID NO: 38	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWIRQAPGQGLEWIGDIY PGNGDTSYNQKFKGRATLTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 39	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTTTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGATTAGACAGGCCCCAGGGCAGGGCCTCGAGTGGATCGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACCC TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGGCAGGGCACCCTGGTCACCGTGTCTAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES

SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 40	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 41	DNA VL	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO: 42	Light Chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 43	DNA Light Chain	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum05		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 24 (Kabat)	HCDR2	DIYPGSGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO:	HCDR2	YPGSGD

25(Chothia)		
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 44	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWIRQAPGQGLEWIGDIY PGSGDTSYNQKFKGRATLTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSS
SEQ ID NO: 45	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCAAGCG TTAAAGTCTCATGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGATTAGACAGGCCCCAGGGCAAGGCCTGGAGTGGATCGGCGATATCTAC CCCGGTAGCGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACCC TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GAGTGAAGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCAAGC
SEQ ID NO: 46	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWIRQAPGQGLEWIGDIY PGSGDTSYNQKFKGRATLTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 47	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCAAGCG TTAAAGTCTCATGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGATTAGACAGGCCCCAGGGCAAGGCCTGGAGTGGATCGGCGATATCTAC CCCGGTAGCGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACCC TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GAGTGAAGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCAAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST

SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 40	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 41	DNA VL	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO: 42	Light Chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 43	DNA Light Chain	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum06		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 30 (Kabat)	HCDR2	DIYPGQGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 31 (Chothia)	HCDR2	YPGQGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY

SEQ ID NO: 48	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWIRQAPGQGLEWIGDIY PGQGDTSYNQKFKGRATLTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSS
SEQ ID NO: 49	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTCTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGATTAGACAGGCCCCAGGTCAAGGCCTCGAGTGGATCGGCGATATCTAC CCCGGTCAAGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACCC TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCTAGC
SEQ ID NO: 50	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWIRQAPGQGLEWIGDIY PGQGDTSYNQKFKGRATLTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 51	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCGCTAGTG TGAAAGTCTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGATTAGACAGGCCCCAGGTCAAGGCCTCGAGTGGATCGGCGATATCTAC CCCGGTCAAGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGCTACCC TGACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACCCTGGTCACCGTGTCTAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO:	LCDR2	AAS

13 (Chothia)		
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 40	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 41	DNA VL	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO: 42	Light Chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 43	DNA Light Chain	GATATCGTCCTGACTCAGTCACCCGATAGCCTGGCCGTCAGCCTGGGCGAGC GGGCTACTATTAACTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAACCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCGATAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATTAGTAGCCTGCAGGCCGAGGACGT GGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum07		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 36	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWIRQAPGQGLEWIGDIY PGNGDTSYNQKFKGRATLTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSS

SEQ ID NO: 115	DNA VH	CAGGTCCAGCTGGTCCAGAGCGGAGCAGAGGTCAAAAAGCCCGGAGCAAGCG TGAAGGTCTCATGCAAAGCAAGCGGATACACATTTACATCATACAACATGCA CTGGATCAGGCAGGCTCCAGGACAGGGACTGGAGTGGATCGGGGACATCTAC CCTGGAAACGGCGATACTAGCTATAATCAGAAGTTCAAAGGCCGGGCCACCC TGACAGCTGACAAGTCTACTAGTACCGTGTATATGGAGCTGAGCTCCCTGCG GTCTGAAGATACCGCAGTGTACTATTGCGCCAGAGTCGGGGGGGCATTTCCT ATGGATTATTGGGGGCAGGGGACTCTGGTCACTGTCTCCTCC
SEQ ID NO: 116	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWIRQAPGQGLEWIGDIY PGNGDTSYNQKFKGRATLTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 117	DNA Heavy Chain	CAGGTCCAGCTGGTCCAGAGCGGAGCAGAGGTCAAAAAGCCCGGAGCAAGCG TGAAGGTCTCATGCAAAGCAAGCGGATACACATTTACATCATACAACATGCA CTGGATCAGGCAGGCTCCAGGACAGGGACTGGAGTGGATCGGGGACATCTAC CCTGGAAACGGCGATACTAGCTATAATCAGAAGTTCAAAGGCCGGGCCACCC TGACAGCTGACAAGTCTACTAGTACCGTGTATATGGAGCTGAGCTCCCTGCG GTCTGAAGATACCGCAGTGTACTATTGCGCCAGAGTCGGGGGGGCATTTCCT ATGGATTATTGGGGGCAGGGGACTCTGGTCACTGTCTCCTCCGCTAGCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAG CACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACG GTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTG TCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGC AACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCAC CATGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCC AAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTG GTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGG ATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAA CAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG AACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCA TCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTA CACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACC TGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCA ATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGA CGGCTCCTTCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAG GAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACACAGAAGAGCCTCTCCCTGTCTCTGGGTAAA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS

SEQ ID NO: 20	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 118	DNA VL	GACATCGTCCTGACACAGTCTCCTGACAGCCTGGCAGTGAGCCTGGGCGAAA GGGCAACCATTAATTGTAGAGCTTCCGAGTCCGTCGAGTACTATGGCACTAG TCTGATGCAGTGGTACCAGCAGAAGCCAGGGCAGCCCCCTAAACTGCTGATC TATGCAGCTAGCAACGTGGAGTCCGGAGTCCCAGACCGGTTCTCTGGAAGTG GGTCAGGAACCGATTTTACCCTGACAATTAGCTCCCTGCAGGCAGAAGACGT GGCCGTCTACTATTGTCAGCAGAGCCGCAAGGACCCAAGCACATTCGGAGGG GGGACCAAAGTGGAAATCAAG
SEQ ID NO: 22	Light Chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 119	DNA Light Chain	GACATCGTCCTGACACAGTCTCCTGACAGCCTGGCAGTGAGCCTGGGCGAAA GGGCAACCATTAATTGTAGAGCTTCCGAGTCCGTCGAGTACTATGGCACTAG TCTGATGCAGTGGTACCAGCAGAAGCCAGGGCAGCCCCCTAAACTGCTGATC TATGCAGCTAGCAACGTGGAGTCCGGAGTCCCAGACCGGTTCTCTGGAAGTG GGTCAGGAACCGATTTTACCCTGACAATTAGCTCCCTGCAGGCAGAAGACGT GGCCGTCTACTATTGTCAGCAGAGCCGCAAGGACCCAAGCACATTCGGAGGG GGGACCAAAGTGGAAATCAAGCGGACTGTTGCTGCACCATCTGTCTTCATCT TCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCT GCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGTTCACCG GTGACAAAGAGCTTCAACAGGGGAGAGTGT
ABTIM3-hum08		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 16	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGNGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSS
SEQ ID NO: 120	DNA VH	CAGGTCCAGCTGGTCCAGAGCGGAGCAGAGGTCAAAAAGCCCGGAGCAAGCG TGAAGGTCTCATGCAAAGCAAGCGGATACACATTTACATCATACAACATGCA CTGGGTCAGGCAGGCTCCAGGACAGGGACTGGAGTGGATCGGGGACATCTAC CCTGGAAACGGCGATACTAGCTATAATCAGAAGTTCAAAGGCCGGGCCACCA TGACAGCTGACAAGTCTACTAGTACCGTGTATATGGAGCTGAGCTCCCTGCG GTCTGAAGATACCGCAGTGTACTATTGCGCCAGAGTCGGGGGGGCATTTCCT

		ATGGATTATTGGGGGCAGGGGACTCTGGTCACTGTCTCCTCC
SEQ ID NO: 121	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGNGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 122	DNA Heavy Chain	CAGGTCCAGCTGGTCCAGAGCGGAGCAGAGGTCAAAAAGCCCGGAGCAAGCG TGAAGGTCTCATGCAAAGCAAGCGGATACACATTTACATCATACAACATGCA CTGGGTCAGGCAGGCTCCAGGACAGGGACTGGAGTGGATCGGGGACATCTAC CCTGGAAACGGCGATACTAGCTATAATCAGAAGTTCAAAGGCCGGGCCACCA TGACAGCTGACAAGTCTACTAGTACCGTGTATATGGAGCTGAGCTCCCTGCG GTCTGAAGATACCGCAGTGTACTATTGCGCCAGAGTCGGGGGGGCATTTCCT ATGGATTATTGGGGGCAGGGGACTCTGGTCACTGTCTCCTCCGCTAGCACCA AGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAG CACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACG GTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTG TCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGC AACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCAC CATGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCC AAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTG GTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGG ATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAA CAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG AACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCA TCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTA CACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACC TGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCA ATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGA CGGCTCCTTCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAG GAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT ACACACAGAAGAGCCTCTCCCTGTCTCTGGGTAAA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 40	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO:	DNA VL	GACATCGTCCTGACACAGTCTCCTGACAGCCTGGCAGTGAGCCTGGGCGAAA GGGCAACCATTAATTGTAGAGCTTCCGAGTCCGTCGAGTACTATGGCACTAG

123		TCTGATGCAGTGGTACCAGCAGAAGCCAGGGCAGCCCCCTAAACTGCTGATC TATGCAGCTAGCAACGTGGAGTCCGGAGTCCCAGACCGGTTCTCTGGAAGTG GGTCAGGAACCGATTTTACCCTGACAATTAGCTCCCTGCAGGCAGAAGACGT GGCCGTCTACTTTTGTCAGCAGAGCCGCAAGGACCCAAGCACATTCGGAGGG GGGACCAAAGTGGAAATCAAG
SEQ ID NO: 42	Light Chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 124	DNA Light Chain	GACATCGTCCTGACACAGTCTCCTGACAGCCTGGCAGTGAGCCTGGGCGAAA GGGCAACCATTAATTGTAGAGCTTCCGAGTCCGTCGAGTACTATGGCACTAG TCTGATGCAGTGGTACCAGCAGAAGCCAGGGCAGCCCCCTAAACTGCTGATC TATGCAGCTAGCAACGTGGAGTCCGGAGTCCCAGACCGGTTCTCTGGAAGTG GGTCAGGAACCGATTTTACCCTGACAATTAGCTCCCTGCAGGCAGAAGACGT GGCCGTCTACTTTTGTCAGCAGAGCCGCAAGGACCCAAGCACATTCGGAGGG GGGACCAAAGTGGAAATCAAGCGGACTGTTGCTGCACCATCTGTCTTCATCT TCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCT GCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGG ACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGTTCACCG GTGACAAAGAGCTTCAACAGGGGAGAGTGT
ABTIM3-hum09		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 52	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGNGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 53	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCTCTAGCG TGAAAGTTTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGGTTCGCCAGGCCCCAGGGCAAGGCCTCGAGTGGATGGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGTCACTA TCACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACTACCGTGACCGTGTCTAGC
SEQ ID NO: 54	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGNGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV

		VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 55	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCTCTAGCG TGAAAGTTTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGGTTCGCCAGGCCCCAGGGCAAGGCCTCGAGTGGATGGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGTCACTA TCACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACTACCGTGACCGTGTCTAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 56	VL	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 57	DNA VL	GAGATCGTCCTGACTCAGTCACCCGCTACCCTGAGCCTGAGCCCTGGCGAGA GAGCTACACTGAGCTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAAGCCCCTAGACTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGGATCCCCGCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATCTCTAGCCTGGAACCCGAGGATAT CGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO:	Light	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI

58	Chain	YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 59	DNA Light Chain	GAGATCGTCCTGACTCAGTCACCCGCTACCCTGAGCCTGAGCCCTGGCGAGA GAGCTACACTGAGCTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAAGCCCCTAGACTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGGATCCCCGCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATCTCTAGCCTGGAACCCGAGGATAT CGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum10		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 60	VH	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGNGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 61	DNA VH	GAAGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAGCCCGGCGAGTCAC TGAAGATTAGCTGTAAAGGTTCAGGCTACACCTTCACTAGCTATAATATGCA CTGGGTCCGCCAGATGCCCGGGAAAGGCCTCGAGTGGATGGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGGCAAGTCACAA TTAGCGCCGATAAGTCTATTAGCACCGTCTACCTGCAGTGGTCTAGCCTGAA GGCTAGTGACACCGCTATGTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACTACCGTGACCGTGTCTAGC
SEQ ID NO: 62	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGNGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO:	DNA Heavy	GAAGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAGCCCGGCGAGTCAC TGAAGATTAGCTGTAAAGGTTCAGGCTACACCTTCACTAGCTATAATATGCA

63	Chain	CTGGGTCCGCCAGATGCCCGGGAAAGGCCTCGAGTGGATGGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGGCAAGTCACAA TTAGCGCCGATAAGTCTATTAGCACCGTCTACCTGCAGTGGTCTAGCCTGAA GGCTAGTGACACCGCTATGTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACTACCGTGACCGTGTCTAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 56	VL	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 57	DNA VL	GAGATCGTCCTGACTCAGTCACCCGCTACCCTGAGCCTGAGCCCTGGCGAGA GAGCTACACTGAGCTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAAGCCCCTAGACTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGGATCCCCGCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATCTCTAGCCTGGAACCCGAGGATAT CGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO: 58	Light Chain	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO:	DNA Light	GAGATCGTCCTGACTCAGTCACCCGCTACCCTGAGCCTGAGCCCTGGCGAGA GAGCTACACTGAGCTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG

59	Chain	CCTGATGCAGTGGTATCAGCAGAAGCCCGGTCAAGCCCCTAGACTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGGATCCCCGCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATCTCTAGCCTGGAACCCGAGGATAT CGCCGTCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum11		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 52	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGNGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 53	DNA VH	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCTCTAGCG TGAAAGTTTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGGTTCGCCAGGCCCCAGGGCAAGGCCTCGAGTGGATGGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGTCACTA TCACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACTACCGTGACCGTGTCTAGC
SEQ ID NO: 54	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGNGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 55	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAACCCGGCTCTAGCG TGAAAGTTTCTTGTAAAGCTAGTGGCTACACCTTCACTAGCTATAATATGCA CTGGGTTCGCCAGGCCCCAGGGCAAGGCCTCGAGTGGATGGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGTAGAGTCACTA TCACCGCCGATAAGTCTACTAGCACCGTCTATATGGAACTGAGTTCCCTGAG GTCTGAGGACACCGCCGTCTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACTACCGTGACCGTGTCTAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC

		GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 64	VL	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 65	DNA VL	GCTATTCAGCTGACTCAGTCACCTAGTAGCCTGAGCGCTAGTGTGGGCGATA GAGTGACTATCACCTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGGAAAGCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCGAGGACTT CGCTACCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO: 66	Light Chain	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 67	DNA Light Chain	GCTATTCAGCTGACTCAGTCACCTAGTAGCCTGAGCGCTAGTGTGGGCGATA GAGTGACTATCACCTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGGAAAGCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCGAGGACTT CGCTACCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC

		GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum12		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 60	VH	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGNGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 61	DNA VH	GAAGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAGCCCGGCGAGTCAC TGAAGATTAGCTGTAAAGGTTCAGGCTACACCTTCACTAGCTATAATATGCA CTGGGTCCGCCAGATGCCCGGGAAAGGCCTCGAGTGGATGGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGGCAAGTCACAA TTAGCGCCGATAAGTCTATTAGCACCGTCTACCTGCAGTGGTCTAGCCTGAA GGCTAGTGACACCGCTATGTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACTACCGTGACCGTGTCTAGC
SEQ ID NO: 62	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGNGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 63	DNA Heavy Chain	GAAGTGCAGCTGGTGCAGTCAGGCGCCGAAGTGAAGAAGCCCGGCGAGTCAC TGAAGATTAGCTGTAAAGGTTCAGGCTACACCTTCACTAGCTATAATATGCA CTGGGTCCGCCAGATGCCCGGGAAAGGCCTCGAGTGGATGGGCGATATCTAC CCCGGGAACGGCGACACTAGTTATAATCAGAAGTTTAAGGGGCAAGTCACAA TTAGCGCCGATAAGTCTATTAGCACCGTCTACCTGCAGTGGTCTAGCCTGAA GGCTAGTGACACCGCTATGTACTACTGCGCTAGAGTGGGCGGAGCCTTCCCT ATGGACTACTGGGGTCAAGGCACTACCGTGACCGTGTCTAGCGCTAGCACTA AGGGCCCGTCCGTGTTCCCCCTGGCACCTTGTAGCCGGAGCACTAGCGAATC CACCGCTGCCCTCGGCTGCCTGGTCAAGGATTACTTCCCGGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCACACCTTCCCCGCTG TGCTGCAGAGCTCCGGGCTGTACTCGCTGTCGTCGGTGGTCACGGTGCCTTC ATCTAGCCTGGGTACCAAGACCTACACTTGCAACGTGGACCACAAGCCTTCC AACACTAAGGTGGACAAGCGCGTCGAATCGAAGTACGGCCCACCGTGCCCGC CTTGTCCCGCGCCGGAGTTCCTCGGCGGTCCCTCGGTCTTTCTGTTCCCACC GAAGCCCAAGGACACTTTGATGATTTCCCGCACCCCTGAAGTGACATGCGTG GTCGTGGACGTGTCACAGGAAGATCCGGAGGTGCAGTTCAATTGGTACGTGG

		ATGGCGTCGAGGTGCACAACGCCAAAACCAAGCCGAGGGAGGAGCAGTTCAA CTCCACTTACCGCGTCGTGTCCGTGCTGACGGTGCTGCATCAGGACTGGCTG AACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGGACTTCCTAGCTCAA TCGAAAAGACCATCTCGAAAGCCAAGGGACAGCCCCGGGAACCCCAAGTGTA TACCCTGCCACCGAGCCAGGAAGAAATGACTAAGAACCAAGTCTCATTGACT TGCCTTGTGAAGGGCTTCTACCCATCGGATATCGCCGTGGAATGGGAGTCCA ACGGCCAGCCGGAAAACAACTACAAGACCACCCCTCCGGTGCTGGACTCAGA CGGATCCTTCTTCCTCTACTCGCGGCTGACCGTGGATAAGAGCAGATGGCAG GAGGGAAATGTGTTCAGCTGTTCTGTGATGCATGAAGCCCTGCACAACCACT ACACTCAGAAGTCCCTGTCCCTCTCCCTGGGA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 64	VL	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 65	DNA VL	GCTATTCAGCTGACTCAGTCACCTAGTAGCCTGAGCGCTAGTGTGGGCGATA GAGTGACTATCACCTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGGAAAGCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCGAGGACTT CGCTACCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAG
SEQ ID NO: 66	Light Chain	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 67	DNA Light Chain	GCTATTCAGCTGACTCAGTCACCTAGTAGCCTGAGCGCTAGTGTGGGCGATA GAGTGACTATCACCTGTAGAGCTAGTGAATCAGTCGAGTACTACGGCACTAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGGAAAGCCCCTAAGCTGCTGATC TACGCCGCCTCTAACGTGGAATCAGGCGTGCCCTCTAGGTTTAGCGGTAGCG GTAGTGGCACCGACTTCACCCTGACTATCTCTAGCCTGCAGCCCGAGGACTT CGCTACCTACTTCTGTCAGCAGTCTAGGAAGGACCCTAGCACCTTCGGCGGA GGCACTAAGGTCGAGATTAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC
ABTIM3-hum13		

SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 24 (Kabat)	HCDR2	DIYPGSGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 25 (Chothia)	HCDR2	YPGSGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 68	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGSGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 69	DNA VH	CAGGTGCAATTGGTTCAGTCAGGAGCAGAAGTTAAGAAGCCAGGATCATCCG TCAAGGTGTCCTGCAAAGCATCTGGCTACACCTTCACCAGCTACAATATGCA CTGGGTCCGACAAGCCCCTGGGCAGGGCTTGGAGTGGATGGGAGACATTTAC CCCGGCAGTGGTGACACTTCCTATAACCAGAAGTTCAAGGGCCGAGTCACTA TTACCGCTGACAAGTCCACCTCCACAGTCTACATGGAACTCTCTTCTCTGAG ATCCGAGGACACTGCCGTCTATTACTGCGCTCGCGTGGGCGGTGCTTTCCCA ATGGACTATTGGGGACAGGGCACAACCGTGACCGTCAGCTCA
SEQ ID NO: 70	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGSGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 71	DNA Heavy Chain	CAGGTGCAATTGGTTCAGTCAGGAGCAGAAGTTAAGAAGCCAGGATCATCCG TCAAGGTGTCCTGCAAAGCATCTGGCTACACCTTCACCAGCTACAATATGCA CTGGGTCCGACAAGCCCCTGGGCAGGGCTTGGAGTGGATGGGAGACATTTAC CCCGGCAGTGGTGACACTTCCTATAACCAGAAGTTCAAGGGCCGAGTCACTA TTACCGCTGACAAGTCCACCTCCACAGTCTACATGGAACTCTCTTCTCTGAG ATCCGAGGACACTGCCGTCTATTACTGCGCTCGCGTGGGCGGTGCTTTCCCA ATGGACTATTGGGGACAGGGCACAACCGTGACCGTCAGCTCAGCCTCTACAA AGGGCCCCTCCGTCTTTCCACTCGCGCCGTGCTCTCGCTCCACCTCAGAGTC AACTGCCGCTCTGGGTTGCCTGGTCAAGGACTACTTCCCAGAGCCGGTGACA GTGAGCTGGAACAGTGGGGCCCTGACATCCGGCGTTCATACCTTCCCCGCAG TCCTCCAGTCCTCAGGCCTGTATTCCCTGAGCAGCGTTGTCACAGTGCCCTC CAGCTCTCTTGGCACGAAAACCTACACATGCAACGTTGATCATAAGCCGTCT AATACCAAGGTGGATAAAAGAGTGGAGAGCAAGTACGGCCCACCCTGCCCGC CTTGCCCAGCTCCGGAGTTCCTGGGCGGACCATCCGTTTTCTTGTTTCCACC CAAACCTAAAGACACTCTGATGATTTCCCGAACCCCTGAAGTGACTTGCGTT GTGGTGGACGTCTCCCAGGAGGACCCAGAAGTGCAATTCAACTGGTACGTGG ACGGGGTGGAGGTGCACAATGCAAAAACCAAACCAAGGGAGGAACAGTTTAA TTCAACATATAGGGTTGTGTCTGTGCTGACGGTTCTGCATCAGGACTGGCTG AACGGAAAGGAATACAAGTGCAAGGTGTCCAACAAAGGACTGCCAAGCTCTA TCGAGAAAACAATCTCTAAGGCCAAGGGACAACCTAGAGAGCCCCAAGTTTA CACCCTGCCACCATCACAGGAAGAGATGACCAAAAATCAGGTGAGCTTGACA TGCCTGGTGAAGGGCTTCTACCCTAGCGATATTGCGGTTGAGTGGGAGTCAA ATGGCCAGCCTGAGAACAACTATAAGACTACTCCTCCCGTGCTGGACTCCGA

		CGGGAGCTTTTTCCTGTATTCCAGGCTTACAGTCGATAAGAGCAGATGGCAA GAGGGGAATGTGTTTTCCTGCTCCGTGATGCACGAGGCTCTCCATAACCATT ATACTCAGAAAAGTCTCTCTCTGTCACTGGGCAAA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 64	VL	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 125	DNA VL	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAA
SEQ ID NO: 66	Light Chain	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 126	DNA Light Chain	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAACGTACGGTGGCAGCTCCGTCTGTTTTCATCT TTCCACCTAGCGACGAGCAACTCAAAAGTGGTACAGCATCCGTGGTTTGTCT GCTGAACAATTTTTACCCCAGGGAGGCTAAGGTCCAGTGGAAAGTCGATAAC GCTCTTCAGTCTGGCAACAGTCAGGAGAGCGTCACAGAGCAGGACTCTAAGG ATAGCACTTATAGTCTGTCCTCCACGCTGACACTGTCTAAAGCGGATTATGA GAAGCACAAGGTTTACGCCTGTGAGGTAACGCACCAAGGACTCTCCTCCCCA GTTACCAAATCTTTCAACAGAGGAGAATGT
ABTIM3-hum14		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 30 (Kabat)	HCDR2	DIYPGQGDTSYNQKFKG

SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 31 (Chothia)	HCDR2	YPGQGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 72	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGQGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 73	DNA VH	CAGGTGCAATTGGTTCAGTCAGGAGCAGAAGTTAAGAAGCCAGGATCATCCG TCAAGGTGTCCTGCAAAGCATCTGGCTACACCTTCACCAGCTACAATATGCA CTGGGTCCGACAAGCCCCTGGGCAGGGCTTGGAGTGGATGGGAGACATTTAC CCCGGCCAGGGTGACACTTCCTATAACCAGAAGTTCAAGGGCCGAGTCACTA TTACCGCTGACAAGTCCACCTCCACAGTCTACATGGAACTCTCTTCTCTGAG ATCCGAGGACACTGCCGTCTATTACTGCGCTCGCGTGGGCGGTGCTTTCCCA ATGGACTATTGGGGACAGGGCACAACCGTGACCGTCAGCTCA
SEQ ID NO: 74	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGQGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 75	DNA Heavy Chain	CAGGTGCAATTGGTTCAGTCAGGAGCAGAAGTTAAGAAGCCAGGATCATCCG TCAAGGTGTCCTGCAAAGCATCTGGCTACACCTTCACCAGCTACAATATGCA CTGGGTCCGACAAGCCCCTGGGCAGGGCTTGGAGTGGATGGGAGACATTTAC CCCGGCCAGGGTGACACTTCCTATAACCAGAAGTTCAAGGGCCGAGTCACTA TTACCGCTGACAAGTCCACCTCCACAGTCTACATGGAACTCTCTTCTCTGAG ATCCGAGGACACTGCCGTCTATTACTGCGCTCGCGTGGGCGGTGCTTTCCCA ATGGACTATTGGGGACAGGGCACAACCGTGACCGTCAGCTCAGCCTCTACAA AGGGCCCCTCCGTCTTTCCACTCGCGCCGTGCTCTCGCTCCACCTCAGAGTC AACTGCCGCTCTGGGTTGCCTGGTCAAGGACTACTTCCCAGAGCCGGTGACA GTGAGCTGGAACAGTGGGGCCCTGACATCCGGCGTTCATACCTTCCCCGCAG TCCTCCAGTCCTCAGGCCTGTATTCCCTGAGCAGCGTTGTCACAGTGCCCTC CAGCTCTCTTGGCACGAAAACCTACACATGCAACGTTGATCATAAGCCGTCT AATACCAAGGTGGATAAAAGAGTGGAGAGCAAGTACGGCCCACCCTGCCCGC CTTGCCCAGCTCCGGAGTTCCTGGGCGGACCATCCGTTTTCTTGTTTCCACC CAAACCTAAAGACACTCTGATGATTTCCCGAACCCCTGAAGTGACTTGCGTT GTGGTGGACGTCTCCCAGGAGGACCCAGAAGTGCAATTCAACTGGTACGTGG ACGGGGTGGAGGTGCACAATGCAAAAACCAAACCAAGGGAGGAACAGTTTAA TTCAACATATAGGGTTGTGTCTGTGCTGACGGTTCTGCATCAGGACTGGCTG AACGGAAAGGAATACAAGTGCAAGGTGTCCAACAAAGGACTGCCAAGCTCTA TCGAGAAAACAATCTCTAAGGCCAAGGGACAACCTAGAGAGCCCCAAGTTTA CACCCTGCCACCATCACAGGAAGAGATGACCAAAAATCAGGTGAGCTTGACA TGCCTGGTGAAGGGCTTCTACCCTAGCGATATTGCGGTTGAGTGGGAGTCAA ATGGCCAGCCTGAGAACAACTATAAGACTACTCCTCCCGTGCTGGACTCCGA CGGGAGCTTTTTCCTGTATTCCAGGCTTACAGTCGATAAGAGCAGATGGCAA GAGGGGAATGTGTTTTCCTGCTCCGTGATGCACGAGGCTCTCCATAACCATT ATACTCAGAAAAGTCTCTCTCTGTCACTGGGCAAA
SEQ ID NO: 6	LCDR1	RASESVEYYGTSLMQ

(Kabat)		
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 64	VL	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 125	DNA VL	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAA
SEQ ID NO: 66	Light Chain	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 126	DNA Light Chain	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAACGTACGGTGGCAGCTCCGTCTGTTTTCATCT TTCCACCTAGCGACGAGCAACTCAAAAGTGGTACAGCATCCGTGGTTTGTCT GCTGAACAATTTTTACCCCAGGGAGGCTAAGGTCCAGTGGAAAGTCGATAAC GCTCTTCAGTCTGGCAACAGTCAGGAGAGCGTCACAGAGCAGGACTCTAAGG ATAGCACTTATAGTCTGTCCTCCACGCTGACACTGTCTAAAGCGGATTATGA GAAGCACAAGGTTTACGCCTGTGAGGTAACGCACCAAGGACTCTCCTCCCCA GTTACCAAATCTTTCAACAGAGGAGAATGT
ABTIM3-hum15		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 24 (Kabat)	HCDR2	DIYPGSGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9	HCDR1	GYTFTSY

(Chothia)		
SEQ ID NO: 25 (Chothia)	HCDR2	YPGSGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 76	VH	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGSGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 77	DNA VH	GAAGTTCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCAGTGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCA
SEQ ID NO: 78	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGSGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 79	DNA Heavy Chain	GAAGTTCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCAGTGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCAGCCTCTACAA AGGGCCCCTCCGTCTTTCCACTCGCGCCGTGCTCTCGCTCCACCTCAGAGTC AACTGCCGCTCTGGGTTGCCTGGTCAAGGACTACTTCCCAGAGCCGGTGACA GTGAGCTGGAACAGTGGGGCCCTGACATCCGGCGTTCATACCTTCCCCGCAG TCCTCCAGTCCTCAGGCCTGTATTCCCTGAGCAGCGTTGTCACAGTGCCCTC CAGCTCTCTTGGCACGAAAACCTACACATGCAACGTTGATCATAAGCCGTCT AATACCAAGGTGGATAAAAGAGTGGAGAGCAAGTACGGCCCACCCTGCCCGC CTTGCCCAGCTCCGGAGTTCCTGGGCGGACCATCCGTTTTCTTGTTTCCACC CAAACCTAAAGACACTCTGATGATTTCCCGAACCCCTGAAGTGACTTGCGTT GTGGTGGACGTCTCCCAGGAGGACCCAGAAGTGCAATTCAACTGGTACGTGG ACGGGGTGGAGGTGCACAATGCAAAAACCAAACCAAGGGAGGAACAGTTTAA TTCAACATATAGGGTTGTGTCTGTGCTGACGGTTCTGCATCAGGACTGGCTG AACGGAAAGGAATACAAGTGCAAGGTGTCCAACAAAGGACTGCCAAGCTCTA TCGAGAAAACAATCTCTAAGGCCAAGGGACAACCTAGAGAGCCCCAAGTTTA CACCCTGCCACCATCACAGGAAGAGATGACCAAAAATCAGGTGAGCTTGACA TGCCTGGTGAAGGGCTTCTACCCTAGCGATATTGCGGTTGAGTGGGAGTCAA ATGGCCAGCCTGAGAACAACTATAAGACTACTCCTCCCGTGCTGGACTCCGA CGGGAGCTTTTTCCTGTATTCCAGGCTTACAGTCGATAAGAGCAGATGGCAA GAGGGGAATGTGTTTTCCTGCTCCGTGATGCACGAGGCTCTCCATAACCATT ATACTCAGAAAAGTCTCTCTCTGTCACTGGGCAAA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES

SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 56	VL	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 127	DNA VL	GAGATTGTTCTTACGCAAAGTCCCGCCACACTTAGTTTGTCACCAGGAGAGC GCGCCACCCTGAGCTGCAGAGCTTCAGAGAGTGTGGAATACTACGGCACATC CCTGATGCAGTGGTATCAGCAGAAACCAGGACAGGCTCCTCGGCTGCTGATC TACGCAGCCAGCAACGTCGAGTCCGGCATTCCAGCCAGATTTTCTGGGTCAG GATCTGGAACTGACTTTACACTGACAATCTCCAGCCTGGAACCCGAGGACAT TGCTGTGTATTTTTGTCAACAGTCCCGGAAGGACCCCAGTACCTTTGGAGGT GGAACCAAGGTAGAGATAAAG
SEQ ID NO: 58	Light Chain	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 128	DNA Light Chain	GAGATTGTTCTTACGCAAAGTCCCGCCACACTTAGTTTGTCACCAGGAGAGC GCGCCACCCTGAGCTGCAGAGCTTCAGAGAGTGTGGAATACTACGGCACATC CCTGATGCAGTGGTATCAGCAGAAACCAGGACAGGCTCCTCGGCTGCTGATC TACGCAGCCAGCAACGTCGAGTCCGGCATTCCAGCCAGATTTTCTGGGTCAG GATCTGGAACTGACTTTACACTGACAATCTCCAGCCTGGAACCCGAGGACAT TGCTGTGTATTTTTGTCAACAGTCCCGGAAGGACCCCAGTACCTTTGGAGGT GGAACCAAGGTAGAGATAAAGCGTACGGTGGCAGCTCCGTCTGTTTTCATCT TTCCACCTAGCGACGAGCAACTCAAAAGTGGTACAGCATCCGTGGTTTGTCT GCTGAACAATTTTTACCCCAGGGAGGCTAAGGTCCAGTGGAAAGTCGATAAC GCTCTTCAGTCTGGCAACAGTCAGGAGAGCGTCACAGAGCAGGACTCTAAGG ATAGCACTTATAGTCTGTCCTCCACGCTGACACTGTCTAAAGCGGATTATGA GAAGCACAAGGTTTACGCCTGTGAGGTAACGCACCAAGGACTCTCCTCCCCA GTTACCAAATCTTTCAACAGAGGAGAATGT
ABTIM3-hum16		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 30 (Kabat)	HCDR2	DIYPGQGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 31 (Chothia)	HCDR2	YPGQGD

SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 80	VH	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGQGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 81	DNA VH	GAAGTTCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCCAGGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCA
SEQ ID NO: 82	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGQGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 83	DNA Heavy Chain	GAAGTTCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCCAGGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCAGCCTCTACAA AGGGCCCCTCCGTCTTTCCACTCGCGCCGTGCTCTCGCTCCACCTCAGAGTC AACTGCCGCTCTGGGTTGCCTGGTCAAGGACTACTTCCCAGAGCCGGTGACA GTGAGCTGGAACAGTGGGGCCCTGACATCCGGCGTTCATACCTTCCCCGCAG TCCTCCAGTCCTCAGGCCTGTATTCCCTGAGCAGCGTTGTCACAGTGCCCTC CAGCTCTCTTGGCACGAAAACCTACACATGCAACGTTGATCATAAGCCGTCT AATACCAAGGTGGATAAAAGAGTGGAGAGCAAGTACGGCCCACCCTGCCCGC CTTGCCCAGCTCCGGAGTTCCTGGGCGGACCATCCGTTTTCTTGTTTCCACC CAAACCTAAAGACACTCTGATGATTTCCCGAACCCCTGAAGTGACTTGCGTT GTGGTGGACGTCTCCCAGGAGGACCCAGAAGTGCAATTCAACTGGTACGTGG ACGGGGTGGAGGTGCACAATGCAAAAACCAAACCAAGGGAGGAACAGTTTAA TTCAACATATAGGGTTGTGTCTGTGCTGACGGTTCTGCATCAGGACTGGCTG AACGGAAAGGAATACAAGTGCAAGGTGTCCAACAAAGGACTGCCAAGCTCTA TCGAGAAAACAATCTCTAAGGCCAAGGGACAACCTAGAGAGCCCCAAGTTTA CACCCTGCCACCATCACAGGAAGAGATGACCAAAAATCAGGTGAGCTTGACA TGCCTGGTGAAGGGCTTCTACCCTAGCGATATTGCGGTTGAGTGGGAGTCAA ATGGCCAGCCTGAGAACAACTATAAGACTACTCCTCCCGTGCTGGACTCCGA CGGGAGCTTTTTCCTGTATTCCAGGCTTACAGTCGATAAGAGCAGATGGCAA GAGGGGAATGTGTTTTCCTGCTCCGTGATGCACGAGGCTCTCCATAACCATT ATACTCAGAAAAGTCTCTCTCTGTCACTGGGCAAA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO:	LCDR1	SESVEYYGTSL

12 (Chothia)		
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 56	VL	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 127	DNA VL	GAGATTGTTCTTACGCAAAGTCCCGCCACACTTAGTTTGTCACCAGGAGAGC GCGCCACCCTGAGCTGCAGAGCTTCAGAGAGTGTGGAATACTACGGCACATC CCTGATGCAGTGGTATCAGCAGAAACCAGGACAGGCTCCTCGGCTGCTGATC TACGCAGCCAGCAACGTCGAGTCCGGCATTCCAGCCAGATTTTCTGGGTCAG GATCTGGAACTGACTTTACACTGACAATCTCCAGCCTGGAACCCGAGGACAT TGCTGTGTATTTTTGTCAACAGTCCCGGAAGGACCCCAGTACCTTTGGAGGT GGAACCAAGGTAGAGATAAAG
SEQ ID NO: 58	Light Chain	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 128	DNA Light Chain	GAGATTGTTCTTACGCAAAGTCCCGCCACACTTAGTTTGTCACCAGGAGAGC GCGCCACCCTGAGCTGCAGAGCTTCAGAGAGTGTGGAATACTACGGCACATC CCTGATGCAGTGGTATCAGCAGAAACCAGGACAGGCTCCTCGGCTGCTGATC TACGCAGCCAGCAACGTCGAGTCCGGCATTCCAGCCAGATTTTCTGGGTCAG GATCTGGAACTGACTTTACACTGACAATCTCCAGCCTGGAACCCGAGGACAT TGCTGTGTATTTTTGTCAACAGTCCCGGAAGGACCCCAGTACCTTTGGAGGT GGAACCAAGGTAGAGATAAAGCGTACGGTGGCAGCTCCGTCTGTTTTCATCT TTCCACCTAGCGACGAGCAACTCAAAAGTGGTACAGCATCCGTGGTTTGTCT GCTGAACAATTTTTACCCCAGGGAGGCTAAGGTCCAGTGGAAAGTCGATAAC GCTCTTCAGTCTGGCAACAGTCAGGAGAGCGTCACAGAGCAGGACTCTAAGG ATAGCACTTATAGTCTGTCCTCCACGCTGACACTGTCTAAAGCGGATTATGA GAAGCACAAGGTTTACGCCTGTGAGGTAACGCACCAAGGACTCTCCTCCCCA GTTACCAAATCTTTCAACAGAGGAGAATGT
ABTIM3-hum17		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 24 (Kabat)	HCDR2	DIYPGSGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 25 (Chothia)	HCDR2	YPGSGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO:	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGSGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP

68		MDYWGQGTTVTVSS
SEQ ID NO: 69	DNA VH	CAGGTGCAATTGGTTCAGTCAGGAGCAGAAGTTAAGAAGCCAGGATCATCCG TCAAGGTGTCCTGCAAAGCATCTGGCTACACCTTCACCAGCTACAATATGCA CTGGGTCCGACAAGCCCCTGGGCAGGGCTTGGAGTGGATGGGAGACATTTAC CCCGGCAGTGGTGACACTTCCTATAACCAGAAGTTCAAGGGCCGAGTCACTA TTACCGCTGACAAGTCCACCTCCACAGTCTACATGGAACTCTCTTCTCTGAG ATCCGAGGACACTGCCGTCTATTACTGCGCTCGCGTGGGCGGTGCTTTCCCA ATGGACTATTGGGGACAGGGCACAACCGTGACCGTCAGCTCA
SEQ ID NO: 70	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGSGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 71	DNA Heavy Chain	CAGGTGCAATTGGTTCAGTCAGGAGCAGAAGTTAAGAAGCCAGGATCATCCG TCAAGGTGTCCTGCAAAGCATCTGGCTACACCTTCACCAGCTACAATATGCA CTGGGTCCGACAAGCCCCTGGGCAGGGCTTGGAGTGGATGGGAGACATTTAC CCCGGCAGTGGTGACACTTCCTATAACCAGAAGTTCAAGGGCCGAGTCACTA TTACCGCTGACAAGTCCACCTCCACAGTCTACATGGAACTCTCTTCTCTGAG ATCCGAGGACACTGCCGTCTATTACTGCGCTCGCGTGGGCGGTGCTTTCCCA ATGGACTATTGGGGACAGGGCACAACCGTGACCGTCAGCTCAGCCTCTACAA AGGGCCCCTCCGTCTTTCCACTCGCGCCGTGCTCTCGCTCCACCTCAGAGTC AACTGCCGCTCTGGGTTGCCTGGTCAAGGACTACTTCCCAGAGCCGGTGACA GTGAGCTGGAACAGTGGGGCCCTGACATCCGGCGTTCATACCTTCCCCGCAG TCCTCCAGTCCTCAGGCCTGTATTCCCTGAGCAGCGTTGTCACAGTGCCCTC CAGCTCTCTTGGCACGAAAACCTACACATGCAACGTTGATCATAAGCCGTCT AATACCAAGGTGGATAAAAGAGTGGAGAGCAAGTACGGCCCACCCTGCCCGC CTTGCCCAGCTCCGGAGTTCCTGGGCGGACCATCCGTTTTCTTGTTTCCACC CAAACCTAAAGACACTCTGATGATTTCCCGAACCCCTGAAGTGACTTGCGTT GTGGTGGACGTCTCCCAGGAGGACCCAGAAGTGCAATTCAACTGGTACGTGG ACGGGGTGGAGGTGCACAATGCAAAAACCAAACCAAGGGAGGAACAGTTTAA TTCAACATATAGGGTTGTGTCTGTGCTGACGGTTCTGCATCAGGACTGGCTG AACGGAAAGGAATACAAGTGCAAGGTGTCCAACAAAGGACTGCCAAGCTCTA TCGAGAAAACAATCTCTAAGGCCAAGGGACAACCTAGAGAGCCCCAAGTTTA CACCCTGCCACCATCACAGGAAGAGATGACCAAAAATCAGGTGAGCTTGACA TGCCTGGTGAAGGGCTTCTACCCTAGCGATATTGCGGTTGAGTGGGAGTCAA ATGGCCAGCCTGAGAACAACTATAAGACTACTCCTCCCGTGCTGGACTCCGA CGGGAGCTTTTTCCTGTATTCCAGGCTTACAGTCGATAAGAGCAGATGGCAA GAGGGGAATGTGTTTTCCTGCTCCGTGATGCACGAGGCTCTCCATAACCATT ATACTCAGAAAAGTCTCTCTCTGTCACTGGGCAAA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS

SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 56	VL	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 127	DNA VL	GAGATTGTTCTTACGCAAAGTCCCGCCACACTTAGTTTGTCACCAGGAGAGC GCGCCACCCTGAGCTGCAGAGCTTCAGAGAGTGTGGAATACTACGGCACATC CCTGATGCAGTGGTATCAGCAGAAACCAGGACAGGCTCCTCGGCTGCTGATC TACGCAGCCAGCAACGTCGAGTCCGGCATTCCAGCCAGATTTTCTGGGTCAG GATCTGGAACTGACTTTACACTGACAATCTCCAGCCTGGAACCCGAGGACAT TGCTGTGTATTTTTGTCAACAGTCCCGGAAGGACCCCAGTACCTTTGGAGGT GGAACCAAGGTAGAGATAAAG
SEQ ID NO: 58	Light Chain	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 128	DNA Light Chain	GAGATTGTTCTTACGCAAAGTCCCGCCACACTTAGTTTGTCACCAGGAGAGC GCGCCACCCTGAGCTGCAGAGCTTCAGAGAGTGTGGAATACTACGGCACATC CCTGATGCAGTGGTATCAGCAGAAACCAGGACAGGCTCCTCGGCTGCTGATC TACGCAGCCAGCAACGTCGAGTCCGGCATTCCAGCCAGATTTTCTGGGTCAG GATCTGGAACTGACTTTACACTGACAATCTCCAGCCTGGAACCCGAGGACAT TGCTGTGTATTTTTGTCAACAGTCCCGGAAGGACCCCAGTACCTTTGGAGGT GGAACCAAGGTAGAGATAAAGCGTACGGTGGCAGCTCCGTCTGTTTTCATCT TTCCACCTAGCGACGAGCAACTCAAAAGTGGTACAGCATCCGTGGTTTGTCT GCTGAACAATTTTTACCCCAGGGAGGCTAAGGTCCAGTGGAAAGTCGATAAC GCTCTTCAGTCTGGCAACAGTCAGGAGAGCGTCACAGAGCAGGACTCTAAGG ATAGCACTTATAGTCTGTCCTCCACGCTGACACTGTCTAAAGCGGATTATGA GAAGCACAAGGTTTACGCCTGTGAGGTAACGCACCAAGGACTCTCCTCCCCA GTTACCAAATCTTTCAACAGAGGAGAATGT
ABTIM3-hum18		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 30 (Kabat)	HCDR2	DIYPGQGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 31 (Chothia)	HCDR2	YPGQGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 72	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGQGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 73	DNA VH	CAGGTGCAATTGGTTCAGTCAGGAGCAGAAGTTAAGAAGCCAGGATCATCCG TCAAGGTGTCCTGCAAAGCATCTGGCTACACCTTCACCAGCTACAATATGCA CTGGGTCCGACAAGCCCCTGGGCAGGGCTTGGAGTGGATGGGAGACATTTAC

		CCCGGCCAGGGTGACACTTCCTATAACCAGAAGTTCAAGGGCCGAGTCACTA TTACCGCTGACAAGTCCACCTCCACAGTCTACATGGAACTCTCTTCTCTGAG ATCCGAGGACACTGCCGTCTATTACTGCGCTCGCGTGGGCGGTGCTTTCCCA ATGGACTATTGGGGACAGGGCACAACCGTGACCGTCAGCTCA
SEQ ID NO: 74	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGQGDTSYNQKFKGRVTITADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 75	DNA Heavy Chain	CAGGTGCAATTGGTTCAGTCAGGAGCAGAAGTTAAGAAGCCAGGATCATCCG TCAAGGTGTCCTGCAAAGCATCTGGCTACACCTTCACCAGCTACAATATGCA CTGGGTCCGACAAGCCCCTGGGCAGGGCTTGGAGTGGATGGGAGACATTTAC CCCGGCCAGGGTGACACTTCCTATAACCAGAAGTTCAAGGGCCGAGTCACTA TTACCGCTGACAAGTCCACCTCCACAGTCTACATGGAACTCTCTTCTCTGAG ATCCGAGGACACTGCCGTCTATTACTGCGCTCGCGTGGGCGGTGCTTTCCCA ATGGACTATTGGGGACAGGGCACAACCGTGACCGTCAGCTCAGCCTCTACAA AGGGCCCCTCCGTCTTTCCACTCGCGCCGTGCTCTCGCTCCACCTCAGAGTC AACTGCCGCTCTGGGTTGCCTGGTCAAGGACTACTTCCCAGAGCCGGTGACA GTGAGCTGGAACAGTGGGGCCCTGACATCCGGCGTTCATACCTTCCCCGCAG TCCTCCAGTCCTCAGGCCTGTATTCCCTGAGCAGCGTTGTCACAGTGCCCTC CAGCTCTCTTGGCACGAAAACCTACACATGCAACGTTGATCATAAGCCGTCT AATACCAAGGTGGATAAAAGAGTGGAGAGCAAGTACGGCCCACCCTGCCCGC CTTGCCCAGCTCCGGAGTTCCTGGGCGGACCATCCGTTTTCTTGTTTCCACC CAAACCTAAAGACACTCTGATGATTTCCCGAACCCCTGAAGTGACTTGCGTT GTGGTGGACGTCTCCCAGGAGGACCCAGAAGTGCAATTCAACTGGTACGTGG ACGGGGTGGAGGTGCACAATGCAAAAACCAAACCAAGGGAGGAACAGTTTAA TTCAACATATAGGGTTGTGTCTGTGCTGACGGTTCTGCATCAGGACTGGCTG AACGGAAAGGAATACAAGTGCAAGGTGTCCAACAAAGGACTGCCAAGCTCTA TCGAGAAAACAATCTCTAAGGCCAAGGGACAACCTAGAGAGCCCCAAGTTTA CACCCTGCCACCATCACAGGAAGAGATGACCAAAAATCAGGTGAGCTTGACA TGCCTGGTGAAGGGCTTCTACCCTAGCGATATTGCGGTTGAGTGGGAGTCAA ATGGCCAGCCTGAGAACAACTATAAGACTACTCCTCCCGTGCTGGACTCCGA CGGGAGCTTTTTCCTGTATTCCAGGCTTACAGTCGATAAGAGCAGATGGCAA GAGGGGAATGTGTTTTCCTGCTCCGTGATGCACGAGGCTCTCCATAACCATT ATACTCAGAAAAGTCTCTCTCTGTCACTGGGCAAA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 56	VL	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG

		GTKVEIK
SEQ ID NO: 127	DNA VL	GAGATTGTTCTTACGCAAAGTCCCGCCACACTTAGTTTGTCACCAGGAGAGC GCGCCACCCTGAGCTGCAGAGCTTCAGAGAGTGTGGAATACTACGGCACATC CCTGATGCAGTGGTATCAGCAGAAACCAGGACAGGCTCCTCGGCTGCTGATC TACGCAGCCAGCAACGTCGAGTCCGGCATTCCAGCCAGATTTTCTGGGTCAG GATCTGGAACTGACTTTACACTGACAATCTCCAGCCTGGAACCCGAGGACAT TGCTGTGTATTTTTGTCAACAGTCCCGGAAGGACCCCAGTACCTTTGGAGGT GGAACCAAGGTAGAGATAAAG
SEQ ID NO: 58	Light Chain	EIVLTQSPATLSLSPGERATLSCRASESVEYYGTSLMQWYQQKPGQAPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSLEPEDIAVYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 128	DNA Light Chain	GAGATTGTTCTTACGCAAAGTCCCGCCACACTTAGTTTGTCACCAGGAGAGC GCGCCACCCTGAGCTGCAGAGCTTCAGAGAGTGTGGAATACTACGGCACATC CCTGATGCAGTGGTATCAGCAGAAACCAGGACAGGCTCCTCGGCTGCTGATC TACGCAGCCAGCAACGTCGAGTCCGGCATTCCAGCCAGATTTTCTGGGTCAG GATCTGGAACTGACTTTACACTGACAATCTCCAGCCTGGAACCCGAGGACAT TGCTGTGTATTTTTGTCAACAGTCCCGGAAGGACCCCAGTACCTTTGGAGGT GGAACCAAGGTAGAGATAAAGCGTACGGTGGCAGCTCCGTCTGTTTTCATCT TTCCACCTAGCGACGAGCAACTCAAAAGTGGTACAGCATCCGTGGTTTGTCT GCTGAACAATTTTTACCCCAGGGAGGCTAAGGTCCAGTGGAAAGTCGATAAC GCTCTTCAGTCTGGCAACAGTCAGGAGAGCGTCACAGAGCAGGACTCTAAGG ATAGCACTTATAGTCTGTCCTCCACGCTGACACTGTCTAAAGCGGATTATGA GAAGCACAAGGTTTACGCCTGTGAGGTAACGCACCAAGGACTCTCCTCCCCA GTTACCAAATCTTTCAACAGAGGAGAATGT
ABTIM3-hum19		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 24 (Kabat)	HCDR2	DIYPGSGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 25 (Chothia)	HCDR2	YPGSGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 76	VH	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGSGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 77	DNA VH	GAAGTTCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCAGTGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCA

SEQ ID NO: 78	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGSGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 79	DNA Heavy Chain	GAAGTTCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCAGTGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCAGCCTCTACAA AGGGCCCCTCCGTCTTTCCACTCGCGCCGTGCTCTCGCTCCACCTCAGAGTC AACTGCCGCTCTGGGTTGCCTGGTCAAGGACTACTTCCCAGAGCCGGTGACA GTGAGCTGGAACAGTGGGGCCCTGACATCCGGCGTTCATACCTTCCCCGCAG TCCTCCAGTCCTCAGGCCTGTATTCCCTGAGCAGCGTTGTCACAGTGCCCTC CAGCTCTCTTGGCACGAAAACCTACACATGCAACGTTGATCATAAGCCGTCT AATACCAAGGTGGATAAAAGAGTGGAGAGCAAGTACGGCCCACCCTGCCCGC CTTGCCCAGCTCCGGAGTTCCTGGGCGGACCATCCGTTTTCTTGTTTCCACC CAAACCTAAAGACACTCTGATGATTTCCCGAACCCCTGAAGTGACTTGCGTT GTGGTGGACGTCTCCCAGGAGGACCCAGAAGTGCAATTCAACTGGTACGTGG ACGGGGTGGAGGTGCACAATGCAAAAACCAAACCAAGGGAGGAACAGTTTAA TTCAACATATAGGGTTGTGTCTGTGCTGACGGTTCTGCATCAGGACTGGCTG AACGGAAAGGAATACAAGTGCAAGGTGTCCAACAAAGGACTGCCAAGCTCTA TCGAGAAAACAATCTCTAAGGCCAAGGGACAACCTAGAGAGCCCCAAGTTTA CACCCTGCCACCATCACAGGAAGAGATGACCAAAAATCAGGTGAGCTTGACA TGCCTGGTGAAGGGCTTCTACCCTAGCGATATTGCGGTTGAGTGGGAGTCAA ATGGCCAGCCTGAGAACAACTATAAGACTACTCCTCCCGTGCTGGACTCCGA CGGGAGCTTTTTCCTGTATTCCAGGCTTACAGTCGATAAGAGCAGATGGCAA GAGGGGAATGTGTTTTCCTGCTCCGTGATGCACGAGGCTCTCCATAACCATT ATACTCAGAAAAGTCTCTCTCTGTCACTGGGCAAA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 64	VL	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 125	DNA VL	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG

		GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAA
SEQ ID NO: 66	Light Chain	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 126	DNA Light Chain	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAACGTACGGTGGCAGCTCCGTCTGTTTTCATCT TTCCACCTAGCGACGAGCAACTCAAAAGTGGTACAGCATCCGTGGTTTGTCT GCTGAACAATTTTTACCCCAGGGAGGCTAAGGTCCAGTGGAAAGTCGATAAC GCTCTTCAGTCTGGCAACAGTCAGGAGAGCGTCACAGAGCAGGACTCTAAGG ATAGCACTTATAGTCTGTCCTCCACGCTGACACTGTCTAAAGCGGATTATGA GAAGCACAAGGTTTACGCCTGTGAGGTAACGCACCAAGGACTCTCCTCCCCA GTTACCAAATCTTTCAACAGAGGAGAATGT
ABTIM3-hum20		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 30 (Kabat)	HCDR2	DIYPGQGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 31 (Chothia)	HCDR2	YPGQGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 80	VH	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGQGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 81	DNA VH	GAAGTTCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCCAGGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCA
SEQ ID NO: 82	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGQGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT

		CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 83	DNA Heavy Chain	GAAGTTCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCCAGGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCAGCCTCTACAA AGGGCCCCTCCGTCTTTCCACTCGCGCCGTGCTCTCGCTCCACCTCAGAGTC AACTGCCGCTCTGGGTTGCCTGGTCAAGGACTACTTCCCAGAGCCGGTGACA GTGAGCTGGAACAGTGGGGCCCTGACATCCGGCGTTCATACCTTCCCCGCAG TCCTCCAGTCCTCAGGCCTGTATTCCCTGAGCAGCGTTGTCACAGTGCCCTC CAGCTCTCTTGGCACGAAAACCTACACATGCAACGTTGATCATAAGCCGTCT AATACCAAGGTGGATAAAAGAGTGGAGAGCAAGTACGGCCCACCCTGCCCGC CTTGCCCAGCTCCGGAGTTCCTGGGCGGACCATCCGTTTTCTTGTTTCCACC CAAACCTAAAGACACTCTGATGATTTCCCGAACCCCTGAAGTGACTTGCGTT GTGGTGGACGTCTCCCAGGAGGACCCAGAAGTGCAATTCAACTGGTACGTGG ACGGGGTGGAGGTGCACAATGCAAAAACCAAACCAAGGGAGGAACAGTTTAA TTCAACATATAGGGTTGTGTCTGTGCTGACGGTTCTGCATCAGGACTGGCTG AACGGAAAGGAATACAAGTGCAAGGTGTCCAACAAAGGACTGCCAAGCTCTA TCGAGAAAACAATCTCTAAGGCCAAGGGACAACCTAGAGAGCCCCAAGTTTA CACCCTGCCACCATCACAGGAAGAGATGACCAAAAATCAGGTGAGCTTGACA TGCCTGGTGAAGGGCTTCTACCCTAGCGATATTGCGGTTGAGTGGGAGTCAA ATGGCCAGCCTGAGAACAACTATAAGACTACTCCTCCCGTGCTGGACTCCGA CGGGAGCTTTTTCCTGTATTCCAGGCTTACAGTCGATAAGAGCAGATGGCAA GAGGGGAATGTGTTTTCCTGCTCCGTGATGCACGAGGCTCTCCATAACCATT ATACTCAGAAAAGTCTCTCTCTGTCACTGGGCAAA
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 64	VL	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 125	DNA VL	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAA
SEQ ID NO: 66	Light Chain	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN

		ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 126	DNA Light Chain	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAACGTACGGTGGCAGCTCCGTCTGTTTTCATCT TTCCACCTAGCGACGAGCAACTCAAAAGTGGTACAGCATCCGTGGTTTGTCT GCTGAACAATTTTTACCCCAGGGAGGCTAAGGTCCAGTGGAAAGTCGATAAC GCTCTTCAGTCTGGCAACAGTCAGGAGAGCGTCACAGAGCAGGACTCTAAGG ATAGCACTTATAGTCTGTCCTCCACGCTGACACTGTCTAAAGCGGATTATGA GAAGCACAAGGTTTACGCCTGTGAGGTAACGCACCAAGGACTCTCCTCCCCA GTTACCAAATCTTTCAACAGAGGAGAATGT
ABTIM3-hum21		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 30 (Kabat)	HCDR2	DIYPGQGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 31 (Chothia)	HCDR2	YPGQGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 84	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGQGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSS
SEQ ID NO: 85	DNA VH	CAGGTGCAATTGGTGCAGAGCGGAGCAGAGGTCAAAAAGCCCGGAGCAAGCG TGAAGGTCTCATGCAAAGCAAGCGGATACACATTTACATCATACAACATGCA CTGGGTCAGGCAGGCTCCAGGACAGGGACTGGAGTGGATCGGGGACATCTAC CCTGGACAGGGCGATACTAGCTATAATCAGAAGTTCAAAGGCCGGGCCACCA TGACAGCTGACAAGTCTACTAGTACCGTGTATATGGAACTGAGCTCCCTGCG GTCTGAAGATACCGCAGTGTACTATTGCGCCAGAGTCGGGGGGGGCATTTCCT ATGGATTATTGGGGGCAGGGGACTCTGGTCACTGTCAGCTCA
SEQ ID NO: 86	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWIGDIY PGQGDTSYNQKFKGRATMTADKSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALAAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 87	DNA Heavy Chain	CAGGTGCAATTGGTGCAGAGCGGAGCAGAGGTCAAAAAGCCCGGAGCAAGCG TGAAGGTCTCATGCAAAGCAAGCGGATACACATTTACATCATACAACATGCA CTGGGTCAGGCAGGCTCCAGGACAGGGACTGGAGTGGATCGGGGACATCTAC CCTGGACAGGGCGATACTAGCTATAATCAGAAGTTCAAAGGCCGGGCCACCA

		TGACAGCTGACAAGTCTACTAGTACCGTGTATATGGAACTGAGCTCCCTGCG GTCTGAAGATACCGCAGTGTACTATTGCGCCAGAGTCGGGGGGGCATTTCCT ATGGATTATTGGGGGCAGGGGACTCTGGTCACTGTCAGCTCAGCTAGCACCA AGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGG CACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCG TGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAG CAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGC AACACCAAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACA CCTGCCCCCCCTGCCCAGCCCCAGAGCTGCTGGGCGGACCCTCCGTGTTCCT GTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTG ACCTGCGTGGTGGTGGCCGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACT GGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGA GCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAG GACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGG CAGCCCCCATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGCC CCAGGTGTACACCCTGCCCCCCTCCCGGGAGGAGATGACCAAGAACCAGGTG TCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGT GGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCT GGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCC AGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGC ACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 88	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 89	DNA VL	GACATCGTCCTGACACAGTCTCCTGACAGCCTGGCAGTGAGCCTGGGCGAAA GGGCAACCATTAATTGTAGAGCTTCCGAGTCCGTCGAGTACTATGGCACTAG TCTGATGCAGTGGTACCAGCAGAAGCCAGGGCAGCCCCCTAAACTGCTGATC TATGCAGCTAGCAACGTGGAGTCCGGAGTCCCAGACCGGTTCTCTGGAAGTG GGTCAGGAACCGATTTTACCCTGACAATTAGCTCCCTGCAGGCAGAAGACGT GGCCGTCTACTATTGTCAGCAGAGCCGCAAGGACCCAAGCACATTCGGAGGG GGGACCAAAGTGGAAATCAAG
SEQ ID NO: 90	Light Chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 91	DNA Light Chain	GACATCGTCCTGACACAGTCTCCTGACAGCCTGGCAGTGAGCCTGGGCGAAA GGGCAACCATTAATTGTAGAGCTTCCGAGTCCGTCGAGTACTATGGCACTAG TCTGATGCAGTGGTACCAGCAGAAGCCAGGGCAGCCCCCTAAACTGCTGATC TATGCAGCTAGCAACGTGGAGTCCGGAGTCCCAGACCGGTTCTCTGGAAGTG

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ABTIM3-hum22		
SEQ ID NO: 3 (Kabat)	HCDR1	SYNMH
SEQ ID NO: 30 (Kabat)	HCDR2	DIYPGQGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 31 (Chothia)	HCDR2	YPGQGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 92	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGQGDTSYNQKFKGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 93	DNA VH	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCAGGCGCCAGCG TGAAGGTGTCCTGCAAGGCCAGCGGCTACACCTTTACCAGCTACAACATGCA CTGGGTGCGCCAGGCCCCTGGACAGGGACTGGAATGGATGGGCGACATCTAC CCCGGCCAGGGCGACACCTCCTACAACCAGAAATTCAAGGGCAGAGTGACCA TGACCCGGGACACCAGCACCTCCACCGTGTACATGGAACTGAGCAGCCTGCG GAGCGAGGACACCGCCGTGTACTACTGTGCTAGAGTGGGCGGAGCCTTCCCC ATGGACTATTGGGGCCAGGGCACCACCGTGACCGTGAGCTCA
SEQ ID NO: 94	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGDIY PGQGDTSYNQKFKGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALAAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 95	DNA Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCAGGCGCCAGCG TGAAGGTGTCCTGCAAGGCCAGCGGCTACACCTTTACCAGCTACAACATGCA CTGGGTGCGCCAGGCCCCTGGACAGGGACTGGAATGGATGGGCGACATCTAC CCCGGCCAGGGCGACACCTCCTACAACCAGAAATTCAAGGGCAGAGTGACCA TGACCCGGGACACCAGCACCTCCACCGTGTACATGGAACTGAGCAGCCTGCG GAGCGAGGACACCGCCGTGTACTACTGTGCTAGAGTGGGCGGAGCCTTCCCC ATGGACTATTGGGGCCAGGGCACCACCGTGACCGTGAGCTCAGCTAGCACCA AGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGG CACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC

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SEQ ID NO: 6 (Kabat)	LCDR1	RASESVEYYGTSLMQ
SEQ ID NO: 7 (Kabat)	LCDR2	AASNVES
SEQ ID NO: 8 (Kabat)	LCDR3	QQSRKDPST
SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 96	VL	AIRLTQSPSSFSASTGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQSEDFATYYCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 97	DNA VL	GCCATCAGACTGACCCAGAGCCCCAGCTCCTTTAGCGCCAGCACCGGCGACA GAGTGACCATCACCTGTAGAGCCAGCGAGAGCGTGGAATATTACGGCACCAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATC TACGCCGCCAGCAATGTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGCTCTG GCAGCGGCACCGACTTCACCCTGACAATCAGCAGCCTGCAGAGCGAGGACTT CGCCACCTACTACTGCCAGCAGAGCCGGAAGGACCCCAGCACATTTGGCGGA GGCACCAAGGTGGAAATCAAG
SEQ ID NO: 98	Light Chain	AIRLTQSPSSFSASTGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQSEDFATYYCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 99	DNA Light Chain	GCCATCAGACTGACCCAGAGCCCCAGCTCCTTTAGCGCCAGCACCGGCGACA GAGTGACCATCACCTGTAGAGCCAGCGAGAGCGTGGAATATTACGGCACCAG CCTGATGCAGTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATC TACGCCGCCAGCAATGTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGCTCTG GCAGCGGCACCGACTTCACCCTGACAATCAGCAGCCTGCAGAGCGAGGACTT CGCCACCTACTACTGCCAGCAGAGCCGGAAGGACCCCAGCACATTTGGCGGA GGCACCAAGGTGGAAATCAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC

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SEQ ID NO: 4 (Kabat)	HCDR2	DIYPGNGDTSYNQKFKG
SEQ ID NO: 5 (Kabat)	HCDR3	VGGAFPMDY
SEQ ID NO: 9 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO: 10 (Chothia)	HCDR2	YPGNGD
SEQ ID NO: 5 (Chothia)	HCDR3	VGGAFPMDY
SEQ ID NO: 100	VH	QVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGNGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSS
SEQ ID NO: 101	DNA VH	CAGGTGCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCAATGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCA
SEQ ID NO: 102	Heavy Chain	QVQLVQSGAEVKKPGESLKISCKGSGYTFTSYNMHWVRQMPGKGLEWMGDIY PGNGDTSYNQKFKGQVTISADKSISTVYLQWSSLKASDTAMYYCARVGGAFP MDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALAAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 103	DNA Heavy Chain	CAGGTGCAATTGGTACAGTCTGGCGCAGAAGTAAAGAAACCAGGAGAGAGTT TGAAAATTTCCTGCAAGGGCAGTGGGTACACATTCACGTCCTACAATATGCA CTGGGTGAGACAGATGCCAGGCAAGGGCCTGGAGTGGATGGGAGACATATAC CCAGGCAATGGAGACACAAGCTATAATCAGAAATTCAAAGGACAGGTGACGA TCTCCGCAGACAAATCCATATCTACGGTCTACCTCCAGTGGTCCTCACTTAA AGCCTCCGACACCGCCATGTACTATTGCGCTCGGGTAGGTGGCGCGTTTCCA ATGGACTATTGGGGCCAAGGGACCACAGTAACCGTCAGCTCAGCTAGCACCA AGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGG CACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC GTGTCCTGGAACAGCGGAGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCG TGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAG CAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGC AACACCAAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACA CCTGCCCCCCCTGCCCAGCCCCAGAGCTGCTGGGCGGACCCTCCGTGTTCCT GTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTG ACCTGCGTGGTGGTGGCCGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACT

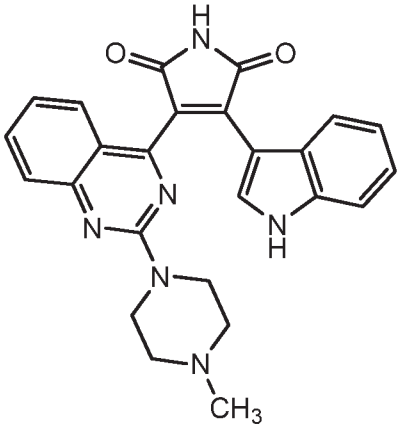
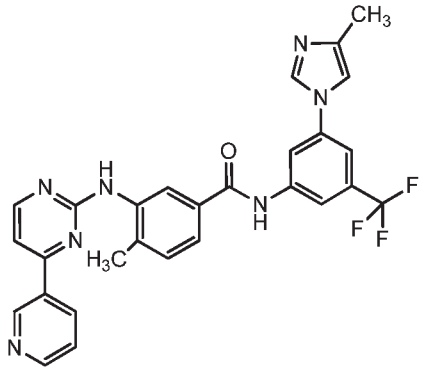
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SEQ ID NO: 12 (Chothia)	LCDR1	SESVEYYGTSL
SEQ ID NO: 13 (Chothia)	LCDR2	AAS
SEQ ID NO: 14 (Chothia)	LCDR3	SRKDPS
SEQ ID NO: 104	VL	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIK
SEQ ID NO: 105	DNA VL	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAA
SEQ ID NO: 106	Light Chain	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQKPGKAPKLLI YAASNVESGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQSRKDPSTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 107	DNA Light Chain	GCAATACAGTTGACACAGAGTCCTTCAAGTTTGTCCGCTTCCGTTGGCGACC GAGTGACAATCACCTGTAGAGCATCCGAGTCAGTGGAGTATTATGGCACTAG CCTGATGCAGTGGTATCAGCAAAAGCCAGGGAAAGCCCCAAAGCTGCTGATA TATGCCGCGAGTAACGTCGAGTCAGGGGTGCCATCAAGATTCTCCGGTTCCG GGTCCGGAACCGACTTCACACTGACCATCTCTTCCCTTCAGCCAGAGGACTT CGCTACGTACTTTTGCCAGCAGTCACGGAAAGATCCCTCTACTTTCGGAGGT GGGACAAAAGTCGAAATTAAACGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAC GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCAAGG ACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGA GAAGCATAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCC GTGACCAAGAGCTTCAACAGGGGCGAGTGC

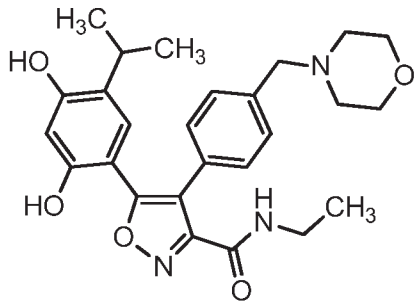
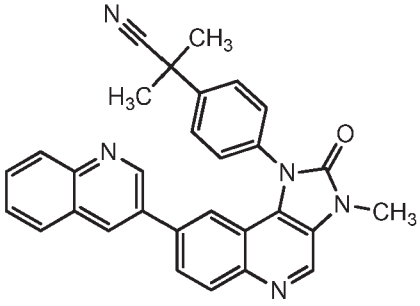
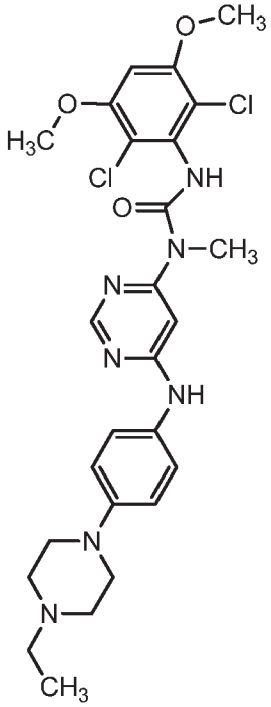
Table 5. Constant region amino acid sequences of human IgG heavy chains and human kappa light chain

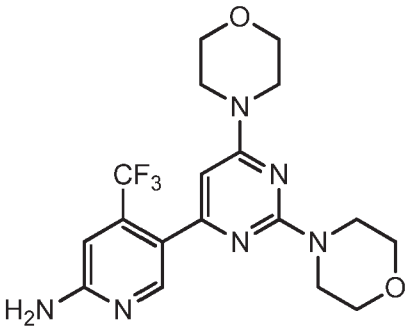
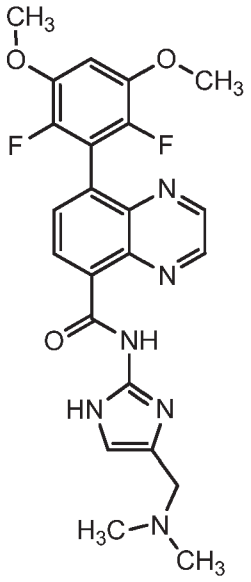
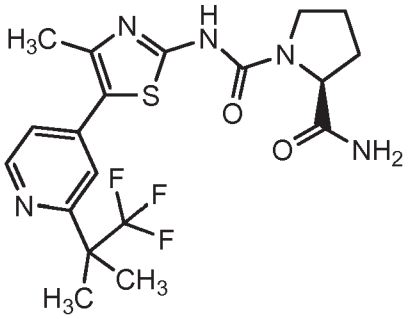
HC	**IgG4 (S228P) mutant constant region amino acid sequence (EU Numbering)** ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK (SEQ ID NO: 108)
LC	**Human kappa constant region amino acid sequence** RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC (SEQ ID NO: 109)
HC	**IgG4 (S228P) mutant constant region amino acid sequence lacing C-terminal lysine (K) (EU Numbering)** ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLG (SEQ ID NO: 110)
HC	**IgG1 wild type** ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 111)
HC	**IgG1 (N297A) mutant constant region amino acid sequence (EU Numbering)** ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 112)
HC	**IgG1 (D265A, P329A) mutant constant region amino acid sequence (EU Numbering)** ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVAVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LAAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 113)

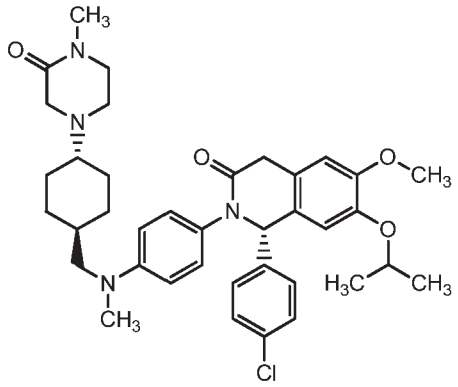
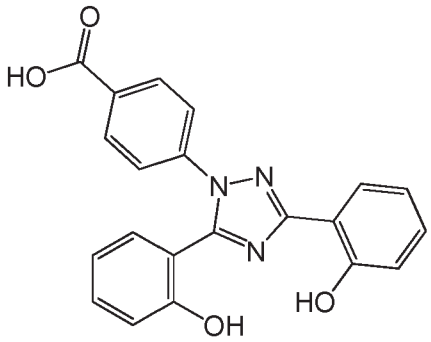
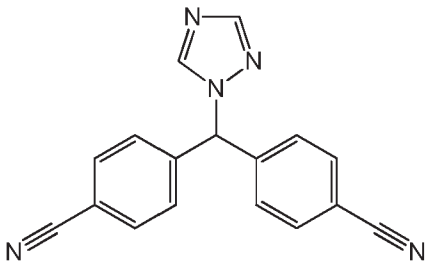
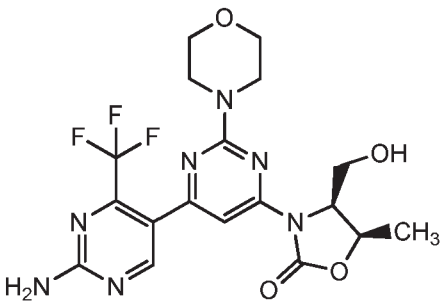
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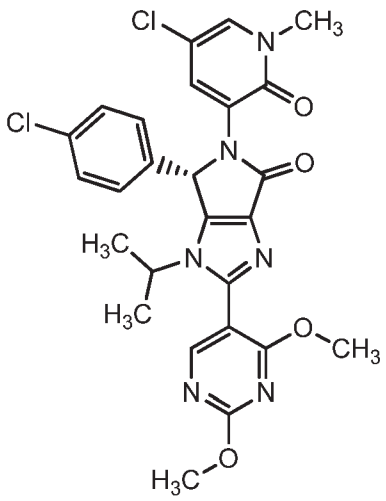
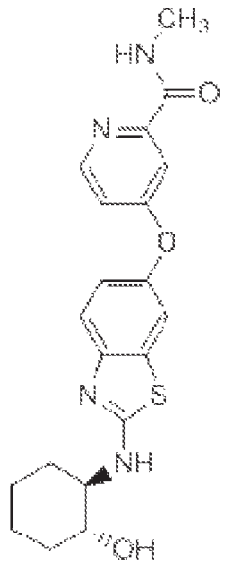
Table 6. Selected therapeutic agents that can be administered in combination with the anti-TIM-3 antibody molecules, *e.g.*, as a single agent or in combination with other immunomodulators described herein. Each publication listed in this Table is herein incorporated by reference in its entirety, including all structural formulae therein.

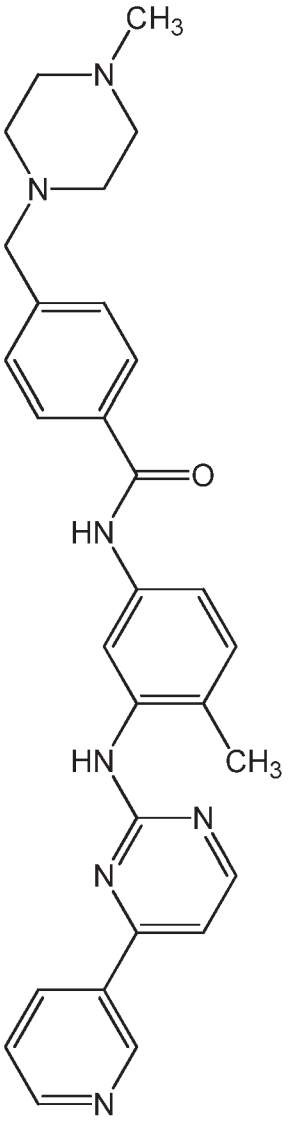
Compound No.	Generic Name Tradename	Compound Structure	Patents / Patent Application Publications
A1	Sotrastaurin		EP 1682103 US 2007/142401 WO 2005/039549
A2	Nilotinib HCl monohydrate TASIGNA®	 HCl • H_2O	WO 2004/005281 US 7,169,791

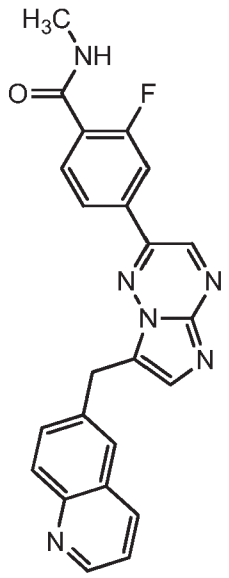
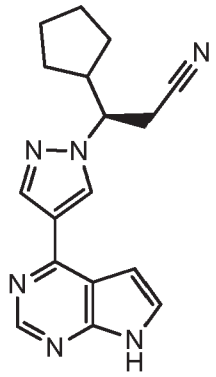
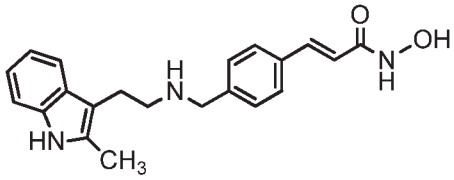
A3			WO 2010/060937 WO 2004/072051 EP 1611112 US 8,450,310
A4	Dactolisib		WO 2006/122806
A5			US 8,552,002

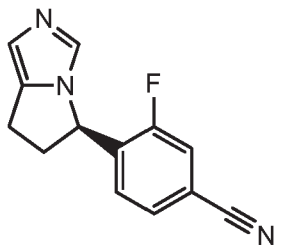
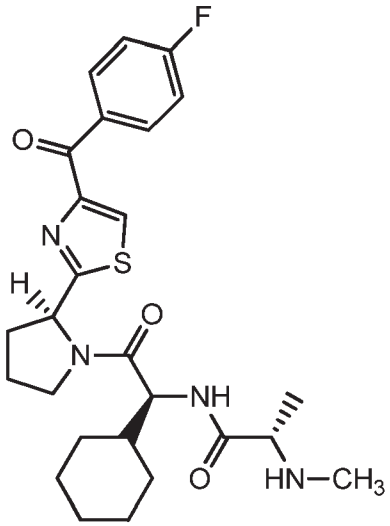
A6	Buparlisib		WO 2007/084786
A7			WO 2009/141386 US 2010/0105667
A8			WO 2010/029082
A9		CYP17 inhibitor	WO 2010/149755 US 8,263,635 B2 EP 2445903 B1

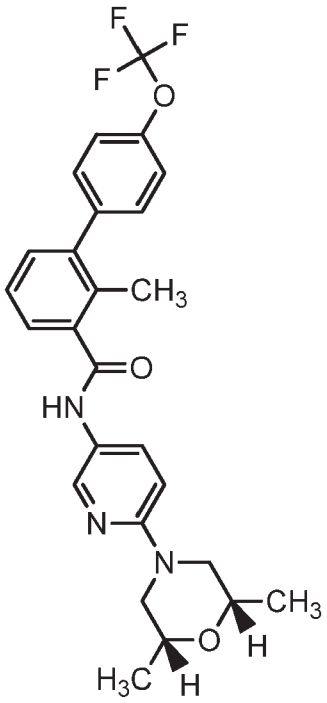
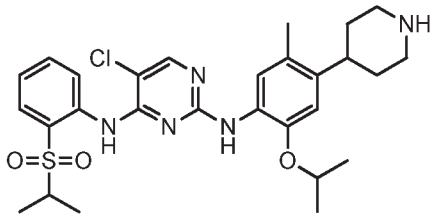
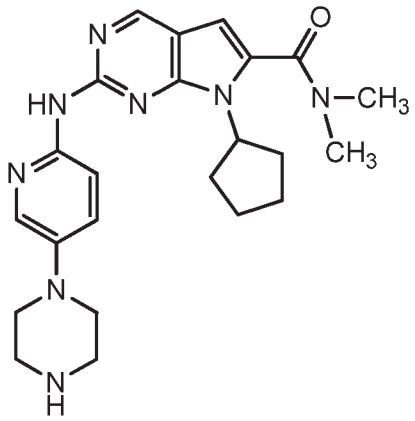
A10			WO 2011/076786
A11	Deferasirox EXJADE®		WO 1997/049395
A12	Letrozole FEMARA®		US 4,978,672
A13			WO 2013/124826 US 2013/0225574

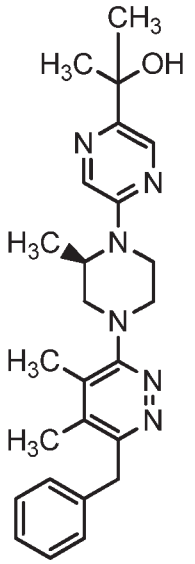
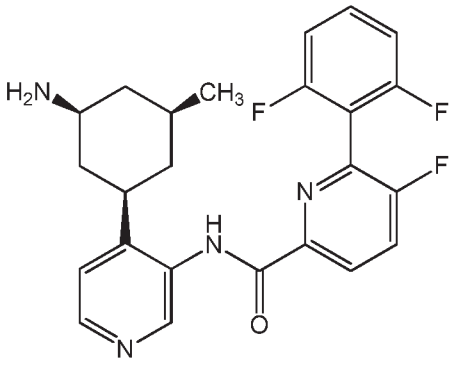
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A15			WO 2005/073224

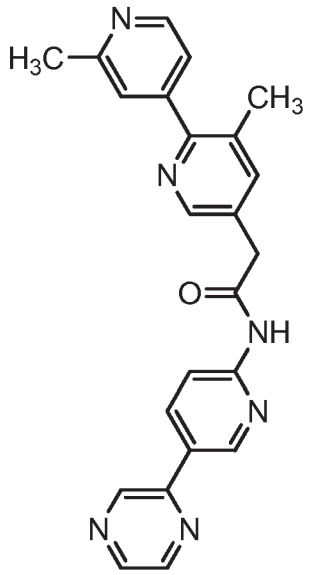
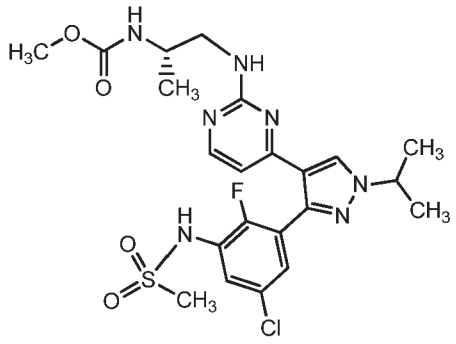
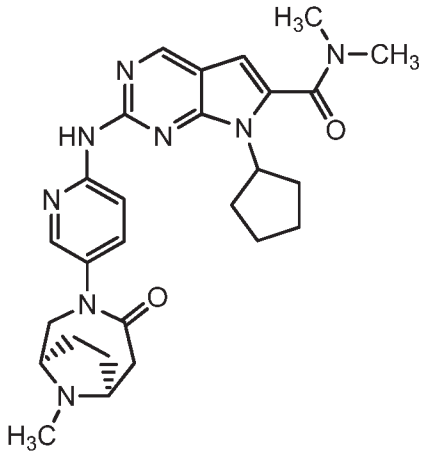
A16	Imatinib mesylate GLEEVEC®	 Mesylate	WO 1999/003854
A17			EP 2099447 US 7,767,675 US 8,420,645

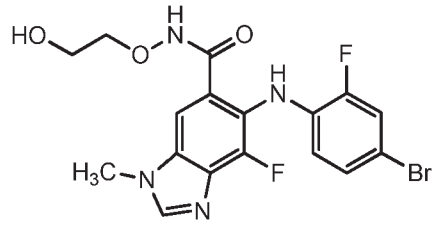
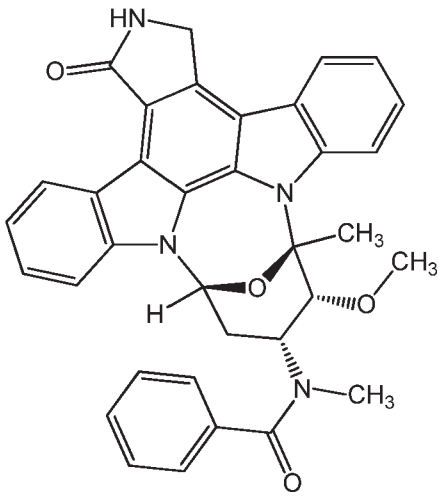
		 Dihydrochloric salt	
A18	Ruxolitinib Phosphate JAKAFI®	 H_3PO_4	WO 2007/070514 EP 2474545 US 7,598,257 WO 2014/018632
A19	Panobinostat		WO 2014/072493 WO 2002/022577 EP 1870399

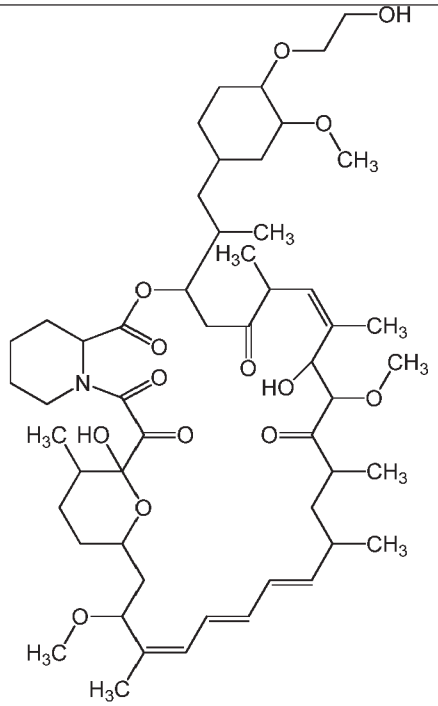
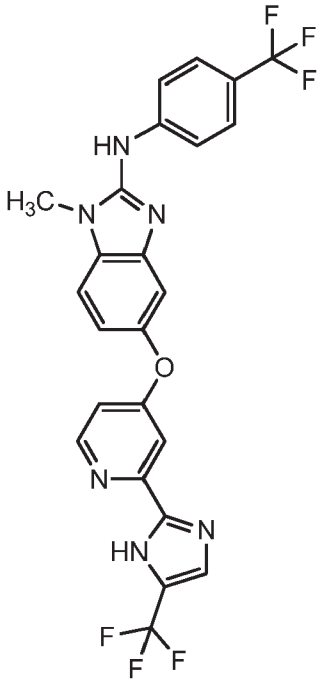
A20	Osilodrostat		WO 2007/024945
A21			WO 2008/016893 EP 2051990 US 8,546,336

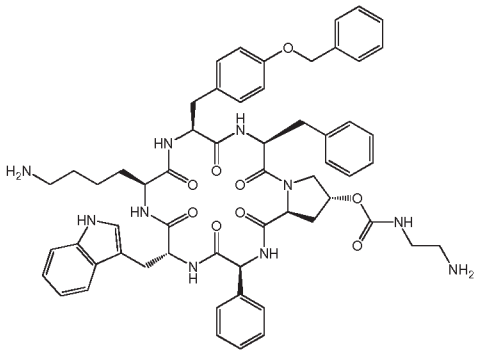
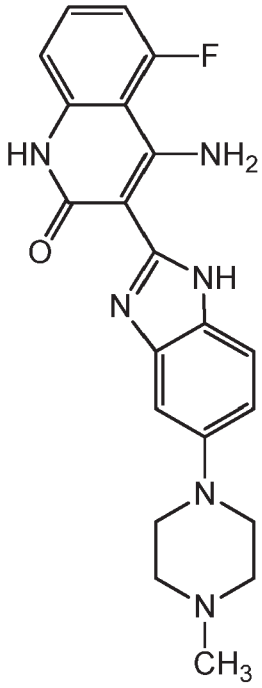
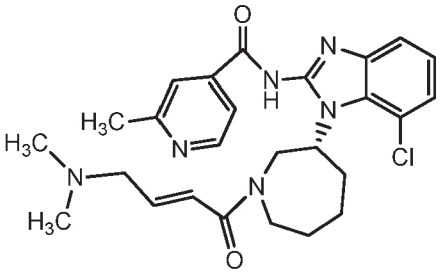
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A23	ceritinib ZYKADIA™		WO 2008/073687 US 8,039,479
A24			US 8,415,355 US 8,685,980

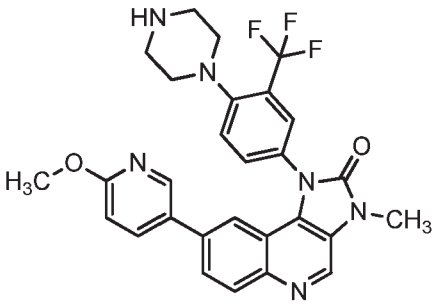
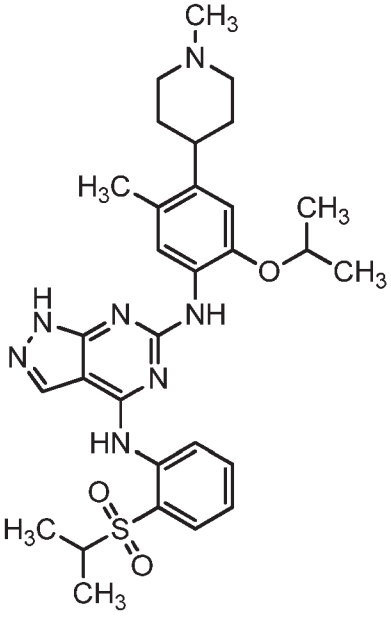
A25			WO 2010/007120
A26		Human monoclonal antibody to PRLR	US 7,867,493
A27			WO 2010/026124 EP 2344474 US 2010/0056576 WO2008/106692

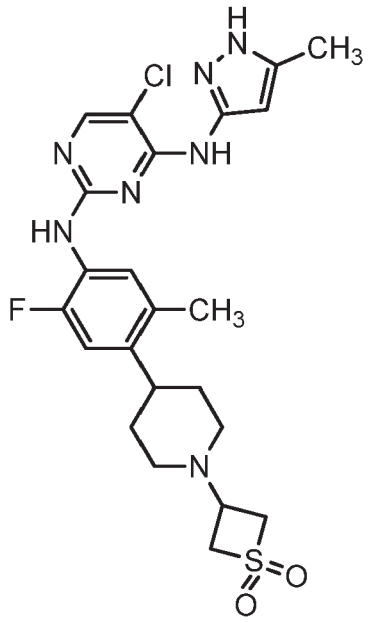
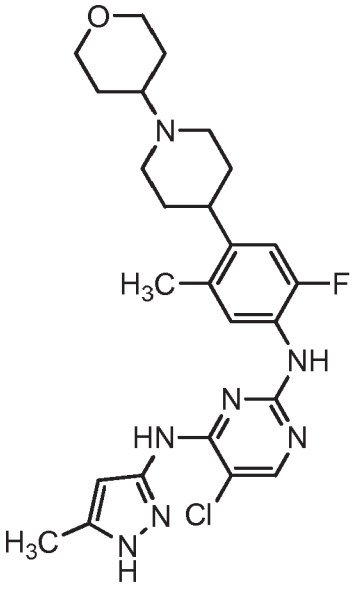
A28			WO 2010/101849
A29	Encorafenib		WO 2011/025927
A30			WO 2011/101409
A31		Human monoclonal antibody to HER3	WO 2012/022814

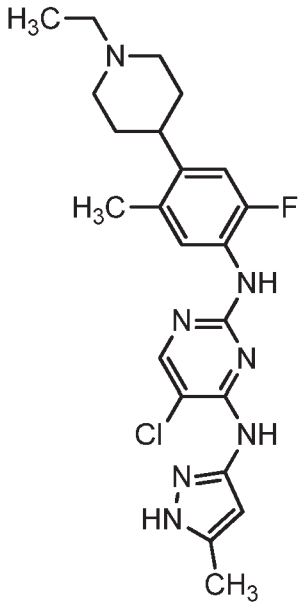
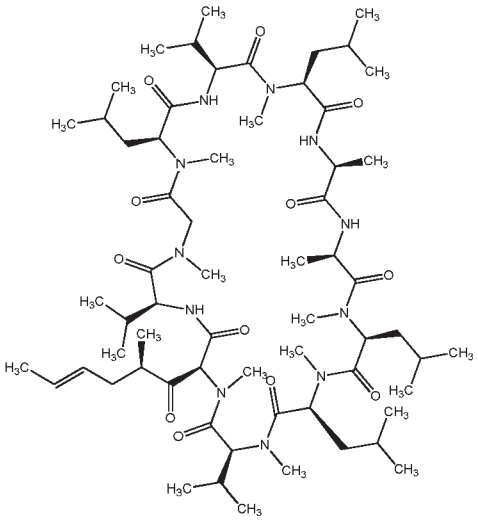
			EP 2606070 US 8,735,551
A32		Antibody Drug Conjugate (ADC)	WO 2014/160160 Ab: 12425 (see Table 1, paragraph [00191]) Linker: SMCC (see paragraph [00117] Payload: DM1 (see paragraph [00111] See also Claim 29
A33		Monoclonal antibody or Fab to M-CSF	WO 2004/045532
A34	Binimetinib		WO 2003/077914
A35	Midostaurin		WO 2003/037347 EP 1441737 US 2012/252785

A36	Everolimus AFINITOR®		WO 2014/085318
A37			WO 2007/030377 US 7,482,367

A38	Pasireotide diaspartate SIGNIFOR®		WO2002/010192 US 7,473,761
A39	Dovitinib		WO 2009/115562 US 8,563,556
A40			WO 2013/184757

A41			WO 2006/122806
A42			WO 2008/073687 US 8,372,858

A43			WO 2010/002655 US 8,519,129
A44			WO 2010/002655 US 8,519,129

A45			WO 2010/002655
A46	Valspodar AMDRAY™		EP 296122

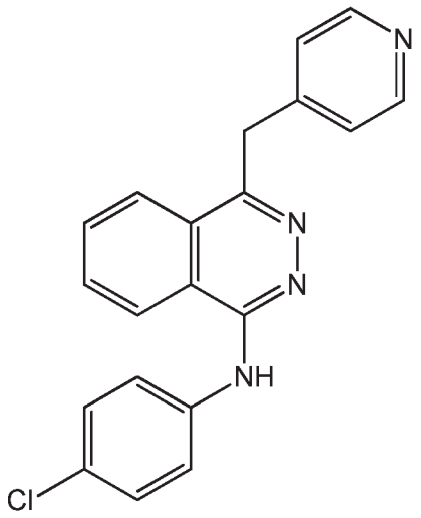
A47	Vatalanib succinate	 succinate	WO 98/35958
A48		IDH inhibitor	WO2014/141104
A49		BCR-ABL inhibitor	WO2013/171639 WO2013/171640 WO2013/171641 WO2013/171642
A50		cRAF inhibitor	WO2014/151616
A51		ERK1/2 ATP competitive inhibitor	PCT/US2014/062913

Table 7. See Examples.

Table 8. See Examples.

Table 9. See Examples.

Table 10. See Examples.

Table 11. See Examples.

Table 12. See Examples.

Table 13. See Examples.

Table 14. See Examples.

Table 15. See Examples.

Table 16. See Examples.

EXAMPLES

Example 1. Characterization of ABTIM3 and other anti-TIM-3 antibodies.

Panels of anti-TIM-3 antibodies were assayed for binding to TIM-3 expressing cells. The dissociation constants (K_D) of two such antibodies, ABTIM3 and anti-TIM-3 #2, as measured by surface plasmon resonance, is summarized in Figure 2A. In Figures 2B and 2C, the binding of various anti-TIM-3 antibodies, including ABTIM3, to cells transfected with human TIM-3 was measured using flow cytometry. Next, three antibodies, ABTIM3, anti-TIM-3 #2, and anti-TIM-3 #3, and a control antibody were assayed for the ability to bind cynomolgus TIM-3 in cells transfected with cynoTIM-3. Figure 2D shows that ABTIM3 has the strongest affinity for cynomolgus TIM-3 out of the three antibodies tested. Figure 2E tests seven anti-human-TIM-3 antibodies for the ability to bind cynomolgus TIM-3, and shows that ABTIM3 binds with the highest affinity. Overall, the experiments indicate that ABTIM3 has strong (sub-nanomolar) affinity for both human and cynomolgus TIM-3.

The ability of three anti-TIM-3 antibodies, including ABTIM3, to bind to human TIM-4 expressed in CHO cells and murine TIM-3 expressed in cells was also measured by flow cytometry. Human TIM-3 has about 23% sequence identity with human TIM-4. Murine TIM-3 has about 66% sequence identity with human TIM-3 and 64% sequence identity with cynomolgus TIM-3. The results from these assays show that ABTIM3 does not bind to human TIM-4. ABTIM3 is also not cross-reactive with murine TIM-3. Taken together with the binding assay results described above, ABTIM3 antibody is specific for human and cynomolgus TIM-3.

In a cross-blocking experiment, ABTIM3 was shown to cross-block anti-TIM-3 #2, suggesting that these antibodies bind to epitopes that are near each other, and possibly overlap, although the two epitopes are not necessarily identical.

The ability of TIM-3 antibodies, *e.g.*, ABTIM3, to bind to activated PBMCs expressing TIM-3 was also assessed. Whole human PBMCs from a donor were stimulated for 10 days with platebound CD3/CD28 (1μg/ml each), in the presence of 10 ng/ml recombinant human IL-12. Cells were ficolled to remove dead cells and reactivated for three days with the same stimulus. Antibodies that bind to TIM-3, *e.g.*, ABTIM3 and anti-TIM-3 #2, were compared, and anti-PD-1, anti-PD-L1, and anti-LAG-3 antibodies, and mouse IgG1 were used as control antibodies. Cells

were incubated with the antibodies at various concentrations from 0.001 to 100 μg/ml, and the antibody binding to the cells was analyzed by flow cytometry. Cells were gated for CD4 or CD8 positive populations, and mean fluorescence intensity (MFI) for each antibody and concentration was plotted on a graph. Dissociation constant (K_D) values were then calculated. The results from the assays are shown in Table 7 below.

Table 7. K_D values for anti-TIM-3 binding to activated PBMCs

Antibody	CD4 gated PBMCs K_D	CD8 gated PBMCs K_D
ABTIM3	0.29 nM	0.30 nM
Anti-TIM-3 #2	2.84 nM	3.14 nM
Anti-PD-L1 control	0.20 nM	0.30 nM
Anti-LAG-3 control		2.33 nM
Anti-PD-1 control	22.8 nM	85.9 nM

These results demonstrate that ABTIM3 was able to bind to TIM-3 expressed on activated PBMCs.

Example 2. Domain analysis of anti-TIM-3 antibody binding to TIM-3.

TIM-3 has an extracellular IgV domain and a mucin domain. The regions of TIM-3 bound by each of five antibodies was determined using a recombinant construct that replaced the IgV domain of TIM-3 with the IgV domain of PD-1, and this construct is depicted in Figure 3A. Figure 3B shows that the anti-TIM-3 monoclonal antibody (anti-TIM-3 #3), and two anti-PD-L1 control monoclonal antibodies (anti-PD-L1 #1 and #2), bind to the chimeric protein of Figure 3A, while anti-TIM-3 #2 and ABTIM3 do not substantially bind. This result suggests that the anti-TIM-3 monoclonal antibodies anti-TIM-3 #2 and ABTIM3 bind to the IgV domain of TIM-3, while anti-TIM-3 #3 binds to the mucin domain of TIM-3. The dissociation constant (K_D) values were calculated for each tested antibody for the recombinant construct are shown in Table 8.

Table 8. K_D values for binding to PD-L1 IgV/TIM-3 mucin construct

Antibody	Antigen	K_D
Anti-PD-L1 #1	PD-L1 IgV domain	0.52 nM
Anti-PD-L1 #2	PD-L1 IgV domain	0.38 nM

Anti-TIM-3 #3	TIM-3 mucin domain	2.71 nM
Anti-TIM-3 #2	TIM-3	No binding to the chimeric protein
ABTIM3	TIM-3	No binding to the chimeric protein

Example 3. TIM-3 binding to PtdSer is blocked by anti-TIM-3 antibodies.

TIM-3 binds to PtdSer (phosphatidylserine), a lipid that is typically present on the surface of apoptotic cells and not normal cells. Anti-CD95-treated WR19L(Fas) cells were cultured under conditions that promote PtdSer accumulation on the cell surface (flipping of PtdSer from the inner membrane to external exposure upon induction of apoptosis). TIM-3-Ig (huTIM-3 extracellular domain fused to an Ig Fc region) was added to the cells, and binding of TIM-3-Ig to the cells was assayed in the presence of various antibodies. As shown in Figure 4, several anti-TIM-3 mAbs, including ABTIM3, anti-TIM-3#5, and anti-TIM-3 #2, inhibit the binding of TIM-3 to PtdSer.

Example 4. IFN-gamma secretion of CD4+ cells is enhanced by anti-TIM-3 antibodies.

The ability of four antibodies to enhance IFN-gamma secretion and proliferation of IL-12 stimulated CD4+ cells was assayed. This assay used the observation that a high dose of IL-12 induces expression of TIM-3 and yields an exhausted phenotype in T cells (see Yang et al., J. Clin. Invest. 122:4 p1271 2012). Figure 5A shows four panels, each of which indicates the results of an experiment where cells were exposed to an antibody selected from ABTIM3, anti-TIM-3 #2, mIgG1, and anti-PD-L1 antibody (anti-PD-L1 control). After PMA/ionomycin restimulation and fixation and permeabilization of cells, the resulting IFN-gamma levels were measured by flow cytometry (y axis) and proliferation was measured by CFSE fluorescence (x axis). Figure 5B quantifies IFN-gamma expression in cells exposed to these four antibodies. From left to right, the bars in Figure 5B correspond to antibodies ABTIM3, anti-TIM-3 #2, anti-PD-L1 control, and mIgG1.

Example 5. TIM-3 blockade enhances *in vitro* functional activity.

5.1 TIM-3 blockade enhances in vitro cytotoxic activity of purified NK cells

TIM-3 is highly expressed endogenously on NK (natural killer) cells; its expression is further induced on activated NK cells. TIM-3 may act to restrain NK cell function, as do other inhibitory receptors. See Ndhlovu et al., Blood 119:3734, 2012, and Silva et al., Cancer Immunol Res 2:410, 2014. Accordingly, the ability of ABTIM3 and other anti-TIM-3 antibodies to enhance NK cell cytotoxic activity was assayed.

In this assay, NK cells were purified from whole blood by negative bead selection and then incubated with antibody (10 μg/mL) at 37 °C. After 1 hour, target K562 cells were added. After a 4-hour incubation at 37 °C, the percent of K562 cell killing was measured. Antibody ABTIM3 resulted in elevated levels of K523 cell killing relative to anti-TIM-3 #2 or the isotype control.

5.2 TIM-3 blockade increases proliferation from autologous T-DC co-cultures

TIM-3 can be expressed on dendritic cells (DCs) and T cells. Naïve T cells and dendritic cells were isolated from donor samples. Naïve T cells and conventional DCs were cocultured for four days in the presence of anti-CD3/CD28. ABTIM3 was added at varying doses, 0.01 μg/mL, 0.1 μg/mL, 1 μg/mL, 5 μg/mL, and 25 μg/mL, to the co-culture. Cell proliferation was detected by a CFSE proliferation assay, which relies on dilution of CFSE staining to detect proliferating cells.

As shown in Figure 22, the presence of ABTIM3 at every tested dosage resulted in an increase in proliferating cells, as represented by CFSE-diluted cells, compared to no antibody and the mouse isotype (IgG1) control.

Example 6. Characterization of humanized anti-TIM-3 antibody.

6.1 Generation of humanized anti-TIM-3 antibodies

The murine anti-TIM-3 antibody ABTIM3 was humanized by grafting the CDRs, *e.g.*, provided in Table 3, to human IgG4 constant region, with a stabilized hinge region containing the S228P mutation. Additional modifications were made to the CDR2 of the heavy chain by

mutating the putative deamidation site from N at position 6 of HCDR (Kabat), or position 4 of the HCDR2 (Chothia) to S or Q to remove the deamidation site. Other modifications included using alternative frameworks. The unique heavy chains and light chains combined in various combinations to generate a small library of unique humanized mAbs.

5

6.2 Binding assays

The binding capability of the humanized mAbs generated were tested by competition binding with the parent murine anti-TIM-3 antibody in a fluorescence-activated sorting assay. A representative graph depicting the results from the FACs-based competition assay comparing the
10 binding between the parent murine anti-TIM-3 antibody and 4 humanized anti-TIM-3 antibodies (ABTIM3-hum01, ABTIM3-hum04, ABTIM3-hum07, and ABTIM3-hum08), and hIgG4 control is shown in Figure 7.

The results from multiple surface plasmon resonance Biacore binding assays for a panel of humanized anti-TIM-3 antibodies are summarized in Table 9.

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Table 9. Biacore K_D values for a panel of anti-TIM-3 antibodies

Clone	KD (nM) 4.7.14	KD (nM) 4.29.14	KD (nM) 5.1.14	KD (nM) 5.30.14
ABTIM3-hum02		0.308	0.269	0.174
ABTIM3-hum03		0.351	0.16	0.314
ABTIM3-hum05		0.313	0.279	0.332
ABTIM3-hum06		0.498	0.214	0.364
ABTIM3-hum09				0.161
ABTIM3-hum10				0.107
ABTIM3-hum11				0.194
ABTIM3-hum12				0.355
ABTIM-hum01				0.23
ABTIM-hum04				0.172
ABTIM3-hum01	0.103		0.114	0.193
ABTIM3-hum07	0.135		0.199	0.196
ABTIM3-hum08	0.123		0.309	0.175
ABTIM3-hum04	0.216			

All of the tested humanized mAbs were demonstrated to have relatively the same affinity as each other and the parent murine anti-TIM-3 antibody, within 0.1-0.5 nM K_D.

6.3 Binding to TIM-3 expressing cells

The humanized anti-TIM-3 antibodies were assayed for binding to TIM-3 expressing cells using fluorescence activated cell sorting and Biacore assays, described in Example 1. In Figure 8A, the binding of various humanized anti-TIM-3 antibodies to cells transfected with human TIM-3 was measured using flow cytometry. ABTIM3 was used as a positive control. Negative controls include hIgG4, goat anti-human, and goat anti- mouse secondary Ab-FITC. The results from the flow cytometry competition assay were used to determine the dissociation constant (K_D) for cells expressing human TIM-3, as shown in Table 10 below.

Table 10. K_D values for binding to cells expressing huTIM-3.

Antibody	**K_D (nM)**
ABTIM3-hum03	0.887
ABTIM3-hum11	0.906
ABTIM3-hum21	0.917
ABTIM3	1.04

A competition binding assay was also performed to assess binding of the humanized anti-TIM-3 antibodies, ABTIM3-hum03 and ABTIM3-hum11, to cells expressing human TIM-3, while in the presence of the parental murine antibody, ABTIM3. As shown in Figure 8B, the humanized anti-TIM-3 antibodies competed with ABTIM3.

The K_D values for two humanized anti-TIM-3 antibodies for recombinant TIM-3-Ig fusion proteins were assayed by surface plasmon resonance in a Biacore assay, as shown in Table 11.

Table 11. Biacore K_D values for TIM-3-Ig

		cynoTIM-3/Fc	**huTIM-3/his**	**mTIM-3/his**	**ratTIM-3/Fc**
ABTIM3-hum03	KD(M)	1.04E-09	1.24E-10		
	KD(M)	3.89E-09	1.84E-10		5.10E-08

	KD(M)	3.08E-09	7.58E-11		
	Mean KD(M)	2.67E-09	1.28E-10		
ABTIM3-hum11	KD(M)	1.24E-09	1.55E-10		
	KD(M)	3.14E-09	2.26E-10		
	KD(M)	5.04E-09	1.09E-10		2.97E-07
	Mean KD(M)	3.14E-09	1.63E-10		

These results show that the humanized TIM-3 antibodies have similar binding affinity with human and cynomolgus proteins. The humanized TIM-3 antibodies showed very weak binding affinity to rat TIM-3/Fc protein, in the order of 1/1000 compared to the binding affinity with huTIM-3/Fc.

Example 7: X-ray crystal structure of the human TIM-3 / ABTIM3-hum21 Fab complex

The crystal structure of a human TIM-3 (IgV domain, SEQ ID NO: 220, Table 12) bound to the Fab fragment of a humanized anti-TIM-3 antibody ABTIM3-hum21 (SEQ ID NO: 221 and 222, Table 12) was determined. As detailed below, TIM-3 was co-expressed with MGB220 Fab in mammalian cells to produce purified complex. Protein crystallography was then employed to generate atomic resolution data for TIM-3 bound to ABTIM3-hum21 Fab to define the epitope. ABTIM3-hum21, a humanized antibody from a parental murine antibody, comprises an IgG1 framework and the variable heavy chain of SEQ ID NO: 84, and the variable light chain of SEQ ID NO: 88. ABTIM3-hum21 differs by only one amino acid in heavy chain CDR2 from other humanized anti-TIM antibodies described herein and this different amino acid (Gln55) is far away (> 6Å) from the epitope and thus would not change antigen binding, which indicates that the crystal structure results obtained are applicable to the other humanized antibodies described herein.

7.1 Protein production

The sequences of TIM-3 and ABTIM3-hum21 Fab produced for crystallography are shown in Table 12. The construct of TIM-3 comprises residues 22 to 130 (underlined) of human TIM-3 (UniProt identifier Q8TDQ0, SEQ ID NO: 129), along with N- and C-terminal residues from recombinant expression vector (shown in lower case letters, SEQ ID NO: 130). The N-

terminal signal sequence from mouse IgG kappa light chain was used for secreted expression of TIM-3 and was cleaved during expression, leaving intact N-terminus of TIM-3. The C-terminus of TIM-3 was fused with a 6x His tag (SEQ ID NO: 133) for purification. For ABTIM3-hum21 Fab, the sequences of heavy (SEQ ID NO: 131) and light (SEQ ID NO: 132) chains are shown.

Table 12: Amino acid sequences used for crystal structure determination

Construct	Amino acid sequence	SEQ ID NO
Human TIM-3 (Q8TDQ0)	MFSHLPFDCVLLLLLLLLTRSSEVEYRAEVGQNAYLPCF YTPAAPGNLVPVCWGKGACPVFECGNVVLRTDERDVNY WTSRYWLNGDFRKGDVSLTIENVTLADSGIYCCRIQIPGI MNDEKFNLKLVIKPAKVTPAPTRQRDFTAAFPRMLTTRG HGPAETQTLGSLPDINLTQISTLANELRDSRLANDLRDSG ATIRIGIYIGAGICAGLALALIFGALIFKWYSHSKEKIQNLS LISLANLPPSGLANAVAEGIRSEENIYTIEENVYEVEEPNE YYCYVSSRQQPSQPLGCRFAMP	129
Human TIM-3 expression construct	metdtlllwvlllwvpgstgSEVEYRAEVGQNAYLPCFYTPAAPGN LVPVCWGKGACPVFECGNVVLRTDERDVNYWTSRYWL NGDFRKGDVSLTIENVTLADSGIYCCRIQIPGIMNDEKFN LKLVIKhhhhhh	130
ABTIM3-hum21 Fab heavy chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWV RQAPGQGLEWIGDIYPGQGDTSYNQKFKGRATMTADKS TSTVYMELSSLRSEDTAVYYCARVGGAFPMDYWGQGTL VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH	131
ABTIM3-hum21 Fab light chain	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQW YQQKPGQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYCQQSRKDPSTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	132

TIM-3 was co-expressed with ABTIM3-hum21 Fab in Expi293® cells to produce complex for crystallography. In detail, 0.3 mg of plasmid encoding TIM-3 was mixed with 0.15 mg of plasmid encoding the heavy chain of ABTIM3-hum21 Fab and 0.15 mg of plasmid encoding the light chain of ABTIM3-hum21 Fab, diluted into 30 mls of Opti-MEM® I medium (Life Technologies), and incubated with 1.5 mgs of Polyethylenimine (Polysciences) in 30 mls of the same medium for 30 min. The mixture was then added into 0.6 L of Expi293® cells

growing in suspension in Expi293® Expression medium (Life Technologies) at 2 million cells/ml at 37 °C with 8% of CO_2 for transfection. After 5 days, the medium containing TIM-3/ABTIM3-HUM21 Fab complex was harvested by centrifugation. Five mls of Ni-NTA resin was added into the medium and kept stirring at 4 °C overnight. The next day the beads were packed into a gravity column and washed with 25 mM Hepes pH 7.4, 150 mM NaCl (HBS) supplemented with 20 mM of imidazole. The complex was eluted with 3 column volumes (CV) of HBS with 500 mM of imidazole, and then dialyzed in HBS at 4 °C overnight. The next day, the complex was incubated with 1/10 (w/w) of PNGaseF (purified in-house) at 37 °C overnight to remove N-linked glycosylation. After deglycosylation, the mixture was bound back to 5 mls of Ni-NTA resin, washed with HBS to remove PNGaseF and eluted with HBS plus 500 mM of imidazole. The eluate was then concentrated and loaded onto HiLoad 16/600 Superdex 75 PG (GE Healthcare) size exclusion column equilibrated in HBS. Peak fractions containing purified TIM-3/ ABTIM3-hum21 Fab complex were analyzed by SDS-PAGE, pooled and concentrated for crystallization.

7.2 Crystallization and structure determination

TIM-3/ABTIM3-hum21 Fab complex was concentrated to 12.5 mg/ml, centrifuged at 20,000 g for 10 min, and screened for crystallization. Crystals for data collection were grown by hanging drop vapor diffusion at 20 °C. In detail, 0.1 µl of the TIM-3/ ABTIM3-hum21 Fab complex was mixed with 0.1 µl of reservoir solution containing 0.04 M potassium phosphate monobasic, 16% (w/v) PEG 8000 and 20% (v/v) Glycerol. The drop was then equilibrated against 45 µl of the same reservoir solution. Before data collection, the crystals were flash cooled in liquid nitrogen.

Diffraction data were collected at beamline 17-ID at the Advanced Photon Source (Argonne National Laboratory, USA), and processed using Autoproc (version 1.1.5, Global Phasing, LTD). The data of TIM-3/ ABTIM3-hum21 Fab was processed to 2.0 Å in space group $P2_1$ with cell dimensions a= 84.3 Å, b= 93.0 Å, c= 85.3 Å, alpha= 90°, beta= 114°, and gamma= 90°. The structure of the complex was solved by molecular replacement using Phaser (version 2.5.5, McCoy *et al.*, (2007) J. Appl. Cryst. 40:658-674) with structures of mouse TIM-3 (PDB ID: 3KAA) and a Fab (in-house structure) as search models. The final model was built in COOT (version 0.6 pre, Emsley & Cowtan (2004) Acta Cryst. D60:2126-2132) and refined using

Phenix (version 1.9, Afonine *et al.*, (2012) Acta Cryst. D68:352-367). The R_{work} and R_{free} values were 17.5 % and 22.1 %, respectively; and the root-mean-square (r.m.s) deviation values of bond lengths and bond angles are 0.007 Å and 1.1 °, respectively.

Epitope was defined as residues of TIM-3 that contain atoms within 5 Å to any atom in ABTIM3-hum21 Fab, identified by CONTACT in CCP4 program suite (version 6.2.0, Winn *et al.*, (2011) Acta. Cryst. D67:235-242) and listed in Table 13. There are 2 copies of TIM-3/ABTIM3-hum21 Fab complexes in the asymmetric unit (the smallest unique unit in the crystal), only those antibody-contacting residues that are common in both copies are listed as epitope residues.

7.3 Epitope of ABTIM3-hum21 on TIM-3

The crystal structure of the TIM-3/ABTIM3-hum21 Fab complex was used to identify the epitope of ABTIM3-hum21 on TIM-3. The interaction surface on TIM-3 by ABTIM3-hum21 was formed by several continuous and discontinuous (*i.e.* noncontiguous) sequences: namely residues Val24, Glu25, Tyr26, Phe39, Tyr40, Thr41, Gly56, Ala57, Cys58, Pro59, Val60, Phe61, Ser105, Gly106, Ile107, Asn119, Asp120, Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, Leu127, and Val128 as detailed in Table 13. These residues form the exemplary three-dimensional conformational epitope that is recognized by ABTIM3-hum21 (Figure 9).

Table 13: Interactions between human TIM-3 and ABTIM3-hum21. TIM-3 residues are numbered as in UniProt entry Q8TDQ0 (SEQ ID NO: 219). The antibody residues are numbered based upon their linear amino acid sequence (SEQ ID NO: 221 and 222) and corresponding chains are labeled ("H" for heavy chain, "L" for light chain). TIM-3 residues shown here have at least one atom within 5 Å to an atom in ABTIM3-hum21, to account for potential water mediated interactions.

TIM-3		ABTIM3-hum21		
Amino acid	**Number**	**Amino acid**	**Number**	**Chain**
Val	24	Ala	102	H
		Asp	98	L
Glu	25	Tyr	31	L
		Arg	96	L
Tyr	26	Tyr	31	L
Phe	39	Ser	31	H

		Tyr	52	H
Tyr	40	Ser	31	H
		Thr	28	H
Thr	41	Thr	28	H
Gly	56	Thr	34	L
Ala	57	Phe	103	H
		Thr	34	L
		Asn	57	L
		Tyr	53	L
		Ala	54	L
Cys	58	Tyr	53	L
		Asn	57	L
Pro	59	Asn	57	L
		Tyr	53	L
Val	60	Asn	57	L
		Tyr	53	L
		Val	58	L
		Ser	60	L
		Glu	59	L
Phe	61	Ser	60	L
Ser	105	Tyr	32	L
Gly	106	Tyr	31	L
		Tyr	32	L
Ile	107	Phe	103	H
		Thr	34	L
		Tyr	31	L
		Leu	36	L
Asn	119	Ser	60	L
Asp	120	Tyr	32	H
Glu	121	Tyr	32	H
		Thr	28	H
Lys	122	Tyr	32	H
		Gly	100	H
		Tyr	53	L
		Glu	59	L
Phe	123	Gly	100	H
		Gly	101	H
		Tyr	32	H
Asn	124	Phe	103	H
		Ala	102	H
		Pro	104	H
		Tyr	53	L
Leu	125	Ala	102	H

Lys	126	Ala	102	H
		Tyr	31	L
		Leu	36	L
		Ser	95	L
		Lys	97	L
Leu	127	Tyr	31	L
Val	128	Tyr	31	L
		Tyr	32	L

7.4 ABTIM3-hum21 *v.s.* TIM-3 ligands

The identification of the epitope of TIM-3 recognized by the anti-TIM-3 antibody indicates that binding of some of the TIM-3 ligands may be disrupted by antibody binding. The known ligands of TIM-3 include CEACAM-1, phosphatidylserine (PtdSer), HMGB1, and Galectin-9 (Gal-9).

With respect to CEACAM-1, a recent study has showed that CEACAM-1 is a ligand for TIM-3 required for its ability to mediate T-cell inhibition, and this interaction has a crucial role in regulating autoimmunity and anti-tumour immunity (Huang *et al.*, (2014) Nature). The same study also identified, both biochemically and structurally, the crucial amino acid residues of TIM-3 mediating its binding to CEACAM-1 (Figure 10A). The ABTIM3-hum21 epitope on TIM-3 overlaps with these CEACAM-1-binding residues (Figure 10A), including C58, N119 and K122. For example, K122 forms hydrogen bond N42 of CEACAM-1, but is complete blocked by ABTIM3-hum21 (Figure 10B). Superimposition of the crystal structures obtained from the TIM-3/ ABTIM3-hum21 Fab and the TIM-3/CEACAM-1 (PDB ID: 4QYC) complexes results in a significant clash between ABTIM3-hum21 and CEACAM-1 (Figure 10C). Altogether, these data suggests that ABTIM3-hum21 disrupts CEACAM-1 binding.

With respect to PtdSer, the FG loop and CC' loop of TIM-3 form a pocket (often referred to as the metal ion-dependent ligand binding site (MILIBS)) that has been shown by crystal structure to bind Ca^{2+} and PtdSer simultaneously (DeKruyff, *et al.*, (2010) J Immunol. 184(4):1918-1930). This binding is thought to help TIM-3-expressing cells engage and penetrate the membrane of apoptotic cells (which displays PtdSer) for engulfment. The crystal structure of TIM-3/ ABTIM3-hum21 Fab indicates that ABTIM3-hum21 binds the PtdSer-binding loops of the human TIM-3 IgV domain; and the attacking angle of the antibody suggests it will prevent PtdSer-mediated membrane penetration of TIM-3 (Figure 11).

With respect to HMGB1, it has been reported to interact with TIM-3 to help tumor-associated dendritic cells suppress nucleic acid-mediated innate immune response (Chiba *et al.*, (2012) Nat. Immunol. 13(9):832-842). The amino acid residue at position 62 of TIM-3 (Q in mouse, E in human TIM-3) has been shown to be important for mouse HMGB1 binding to mouse TIM-3. E62 is not present in the ABTIM3-hum21 epitope, though it is very close to the two epitope residues V60 and F61, thus there is a chance that ABTIM3-hum21 can block HMGB1 binding depending on the attacking angle of HMGB1 to TIM-3.

With respect to Gal-9, it has been shown to bind mouse TIM-3 to negatively regulate Th1-immune response (Zhu *et al.*, (2005) Nat. Immunol. 6(12):1245-1252). However, it has also been reported that human TIM-3 on T cells does not act as a receptor for Gal-9 (Leitner *et al.*, (2013) PLoS Pathog. 9(3):e1003253). From the crystal structure of human TIM-3/ ABTIM3-hum21 Fab, half of the proposed Gal-9 binding site in mouse TIM-3 is not conserved in human TIM-3 (N74 and N90 in mouse TIM-3 become D74 and R89 in human TIM-3), *i.e.* this half-site in human TIM-3 will not be able to bind Gal-9. The left-over half site (N33 and N99 in human TIM-3) is conserved but is far away from the ABTIM3-hum21 epitope on TIM-3 (Figure 9A). Therefore, even if Gal-9 is a ligand of human TIM-3, ABTIM3-hum21 will not disrupt the binding of Gal-9 to human TIM-3.

7.5 Hydrogen-Deuterium Exchange Experimental Setup

HDx/MS experiments were performed using methods similar to those described in the literature (Chalmers *et al.*, (2006) Anal. Chem. 78(4):1005-1014). The experiments were performed on a Waters HDx/MS platform, which includes a LEAP autosampler, nanoACQUITY UPLC and Synapt G2 mass spectrometer. The deuterium buffer used to label the protein backbone of human TIM-3 (aa22-135; SEQ ID NO: 139) was 25mM HEPES, 150 mM NaCl, 5 mM $CaCl_2$ pH7.4 with deterium; the overall percentage of deuterium in the solution was 94.2%. For human TIM-3 (aa22-135) deuterium labeling experiments in the absence of antibody, 300 pmol of human TIM-3 (aa22-135), volume of 7.7 µl, was diluted using 100 µl of the deuterium buffer in a chilled tube and incubated for 15 minutes on a rotator at 4 °C. The labeling reaction was then quenched with 100 µl of chilled quench buffer at 2 °C for five minutes followed by injected onto the LC-MS system for automated pepsin digestion and peptide analysis.

For human TIM-3 (aa22-135) deuterium labeling experiments in the presence of antibodies, 400 pmol of ABTIM3-hum03 or ABTIM3-hum11 was first immobilized on Thermo Protein G Plus beads and cross-linked using disuccinimidyl suberate (DSS). To perform the labeling experiments, the antibody beads (containing 400 pmol antibody) were incubated with 300 pmol human TIM-3 (aa22-135) for 25 minutes at 4 °C. After 25 minutes the beads were washed with 200 µl of HEPES buffer. Then 200 µl of chilled deuterium buffer (87.5% deuterium) was added and the complex was incubated for 15 minutes at 4 °C. After 15 minutes, the deuterium buffer was spun out and the labeling reaction was quenched with 200 µl of chilled quench buffer on ice for 4 minutes. After spinning the sample for 30 seconds in a centrifuge, the quenched solution was injected onto the LC-MS system for automated pepsin digestion and peptide analysis.

All deuterium exchange experiments were quenched using 1 M TCEP and 6 M urea (pH 2.6). After quenching, the exchanged antigen was subjected to on-line pepsin digestion using a Poroszyme Immobilized Pepsin column (2.1 x 30 mm) at 12 °C followed by trapping on a Waters Vanguard HSS T3 trapping column. Peptides were eluted from the trapping column and separated on a Waters BEH C18 1 x 100 mm column (maintained at 1 °C) at a flow rate of 40 µl/min using a binary 8.4 minute gradient of 2 to 35% B (mobile phase A was 99.9% water and 0.1% formic acid; mobile phase B was 99.9% acetonitrile and 0.1% formic acid).

7.6 Hydrogen-Deuterium Exchange Results

For human TIM-3 93% of the sequence was monitored by deuterium exchange as shown in Figure 18. In this figure each bar represents a peptide that is monitored in all deuterium exchange experiments. For differential experiments between antibody bound and unbound states it is informative to examine the difference in deuterium uptake between the two states. In Figure 19 a negative value indicates that the TIM-3-antibody complex undergoes less deuterium uptake relative to TIM-3 alone. A decrease in deuterium uptake can be due to protection of the region from exchangeable deuterium or stabilization of the hydrogen bonding network. In contrast, a positive value indicates that the complex undergoes more deuterium uptake relative to TIM-3 alone. An increase in deuterium uptake can be due to destabilization of hydrogen bonding networks (i.e. localized unfolding of the protein).

ABTIM3-hum03 shares identical CDRs with ABTIM3-hum11 except that ABTIM3-hum03 has a glutamine at position 55 in HCDR2 while ABTIM3-hum11 has an asparagine at position 55 in HCDR2. ABTIM3-hum03 shares the same CDR regions with ABTIM3-hum21. One expects these antiboides to have the same epitope on TIM-3. From Figure 19 one observes that ABTIM3-hum03 and ABTIM3-hum11 exhihit the same protection profile which is consistent with the two antibodies sharing the same epitope. Closer examination of Figure 19 reveals that when TIM-3 is complexed with either of the two antibodies that many regions of TIM-3 undero significant protection, typically defined as proection less than or equal to -0.5 Da (Houde *et al.*(2010) J. Pharma. Sci. 100(6): 2071-2086). The observation of broad protection suggests that binding of either of the two antibodies to the TIM-3 antigen cause a broad based stabilization of hydrogen bonding networks in TIM-3. This broad protection is in addition to the protection that results from solvent sheilding of the epitope at the antibody-antigen interface. Given the significant amount of broad protection, it is useful to rank order the most protected regions of TIM-3 upon antibody binding to delineat the regions likely to be involved in the epitope. TIM-3 regions that are the most protected upon ABTIM3-hum03 or ABTIM3-hum 11 binding include the regions 23-25 (EVE), 41-61 (TPAAPGNLVPVCWGKGACPVF, SEQ ID NO: 140), 73-77 (RDVNY, SEQ ID NO: 141), and 121-127 (EKFNLKL, SEQ ID NO: 142). Comparing these protected regions to the X-ray crstyal structure data summarized in Table 13 shows consistent agreement indicating that the epitope determined by X-ray crystal structure is present in solution.

Example 8: TIM-3 expression in cancer

TIM-3 is expressed in various cancers. In this example, several different analysis methods were used to identify cancers with TIM-3 expression in which therapeutic benefit could be achieved by an anti-TIM-3 antibody.

8.1 Immunohistochemical staining of tumors

ABTIM-3 was used to stain various tumor tissues. TIM-3 tumor expression was identified in esophageal squamous cell carcinoma, primary and metastatic renal cell carcinoma, colorectal cancer, and leukemic stem cells in AML.

8.2 Expression analysis in TCGA and ICGC databases

Overall TIM-3 expression was compared in the The Cancer Genome Atlas (TCGA) database and the International Cancer Genome Consortium (ICGC) database. The following cancers were identified as among the highest expressors of TIM-3: diffuse large B cell lymphoma (DLBCL), kidney renal clear cell carcinoma (KIRC), glioblastoma multiforme (GBM), nasopharyngeal carcinoma (NPC), lung adenocarcinoma (LUAD), kidney renal papillary cell carcinoma (KIRP), mesothelioma (MESO), acute myeloid leukemia (AML), and in breast cancer, triple negative (TN) immunomodulatory (IM) subtype (Figure 12).

Next, cancers were identified that were characterized by high TIM-3 expression in conjunction with high expression of other immune cell markers. The other immune cell markers include: T cell marker CD3e, T regulatory cell marker FoxP3, natural killer cell marker NKp30, macrophage marker CD68, and dendritic cell marker CD11c. As shown in Figure 12, cancer indications with high expression of TIM-3 and the other immune cell marker were identified. "High" expression was quantified by 3rd quartile (or top 25%) expressors across more than 34,000 cases. For TIM-3 and CD3e, the top indications were diffuse large B cell lymphoma (DLBCL), nasopharyngeal carcinoma (NPC), and kidney renal clear cell carcinoma (KIRC). For TIM-3 and FoxP3, the top indications were diffuse large B cell lymphoma (DLBCL), nasopharyngeal carcinoma (NPC), and lung adenocarcinoma (LUAD). For TIM-3 and NKp30, the top indications were diffuse large B cell lymphoma (DLBCL), nasopharyngeal carcinoma (NPC), and acute myeloid leukemia (AML). For TIM-3 and CD68, the top indications were diffuse large B cell lymphoma (DLBCL), kidney renal clear cell carcinoma (KIRC), and kidney renal papillary cell carcinoma (KIRP). For TIM-3 and CD11c, the top indications were diffuse large B cell lymphoma (DLBCL), mesothelioma (MESO) (though only a small sample was assessed), and kidney renal papillary cell carcinoma (KIRP).

A comparison was also performed of the correlation between TIM-3 or PD-1 to T cell associated or macrophage associated markers in the TCGA database. The analysis revealed correlation between TIM-3 expression and both T cell associated markers (*e.g.*, ZAP70, CD3D, CD3G, CD8B, GZMH, GZMK, and ITK) and macrophage associated markers (*e.g.*, LILRB4, MRC1, MSR1, SIGLEC1, TREM2, CD163, ITGAX, and ITGAM), however, TIM-3 expression is more associated with macrophage markers, especially inhibitory receptors on macrophages (*e.g.*, LILRB4). Expression of a macrophage signature, *e.g.*, macrophage associated markers

(*e.g.*, LILRB4, MRC1, MSR1, SIGLEC1, TREM2, CD163, ITGAX, and ITGAM) was determined for various cancers and were organized for the highest expressors of the macrophage signature in Figure 13. The cancer indications with high expression of the macrophage signature are also the same indications with high expression of TIM-3.

Example 9: Patient selection based on PDL1/CD8/IFN-γ status

For each of several types of cancer, samples from multiple patients were tested for PDL1/CD8/IFN-γ status. Each sample was classified as: triple-negative for PDL1/CD8/IFN-γ, single or double positive for these markers, or triple-positive for these markers. Figure 14 shows that in this experiment, within a population of patients, the following types of cancer are frequently triple-positive for PDL1/CD8/IFN-γ: Lung cancer (squamous), lung cancer (adenocarcinoma), head and neck cancer, cervical cancer (squamous), stomach cancer, thyroid cancer, melanoma, and nasopharyngeal cancer. Patients having these types of cancer are good candidates for therapy with anti PD-1 antibodies and combination therapies as described herein. The likelihood of successful treatment can be further boosted by determining which patients are triple-positive for PDL1/CD8/IFN-γ, and treating the triple-positive patients with anti-TIM-3 antibodies, alone or in combination with one or more immodulators (*e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor), and/or combination therapies, as described herein.

Figure 15 shows that within a population of patients, the following types of cancer are rarely triple positive for PDL1/CD8/IFN-γ: ER+ breast cancer and pancreatic cancer. Notably, even in cancers that are generally not positive for for PDL1/CD8/IFN-γ, one can increase the likelihood of successful treatment by determining which patients are triple-positive for PDL1/CD8/IFN-γ, and treating the triple-positive patients with anti-TIM-3 antibodies, alone or in combination with one or more immodulators (*e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor), and/or combination therapies, as described herein.

Figure 16 shows the proportion of breast cancer patients that are triple positive for PDL1/CD8/IFN-γ. Considering breast cancer in general, the proportion of triple-positives is somewhat low. However, when one focuses only on IM-TN breast cancer, it can be seen that a much larger percentage of patients is triple positive for PDL1/CD8/IFN-γ. IM-TN breast cancer is particularly difficult to treat with conventional therapies. The discovery that IM-TN breast cancer is often triple-postive for PDL1/CD8/IFN-γ opens up new avenues of therapy for this

cancer with anti-TIM-3 antibodies, alone or in combination with one or more immodulators (*e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor), and/or combination therapies, as described herein.

Figure 17 shows the proportion of colon cancer patients that are triple positive for PDL1/CD8/IFN-γ. Considering colon cancer in general, the proportion of triple-positive is somewhat low. However, when one focuses only on MSI-high (high microsatellite instability) breast cancer, it can be seen that a much larger percentage of patients is triple positive for PDL1/CD8/IFN-γ. MSI levels can be assayed using, *e.g.*, commercially available PCR-based methods.

Gastric cancer samples were tested for levels of PDL1/CD8/IFN-γ (data not shown). It was found that in MSI-high or EBV+ gastric cancers, about 49% were positive for PDL1, and a high proportion of the PDL1-positive cells were triple positive for PDL1/CD8/IFN-γ. It was also found that a proportion of PDL1-positive cells and PDL1/CD8/IFN-γ positive cells were also positive for PIK3CA. This finding suggests that these cancers may be treated with an anti-TIM-3 antibody, alone or in combination with one or more immodulators (*e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor), optionally in combination with a PIK3 therapeutic.

MSI-high CRC samples were tested for a combination of markers (data not shown). It was found that in MSI-high CRC samples, a high proportion of the PDL1/CD8/IFN-γ samples are also positive for LAG-3, PD-1 (also called PDCD1), RNF43, and BRAF. This finding suggests that these cancers may be treated with an anti-TIM-3 antibody, optionally in combination with a therapeutic that targets one or more of LAG-3, PDCD1, RNF43, and BRAF.

Squamous cell lung cancers were tested for a combination of markers (data not shown). It was found that in squamous cell lung cancer samples, a high proportion of the PDL1/CD8/IFN-γ samples are also positive for LAG-3. This finding suggests that these cancers may be treated with an anti-TIM-3antibody, optionally in combination with a therapeutic that targets LAG-3, *e.g.*, a LAG-3 antibody.

Papillary thyroid cancers were tested for a combination of markers including the BRAF V600E mutation (data not shown). It was found that a high proportion of thyroid cancer samples that are positive for PDL1 are also positive for BRAF V600E. This finding suggests that these cancers may be treated with an anti-TIM-3 antibody, alone or in combination with one or more immodulators (*e.g.*, a PD-1 inhibitor or a PD-L1 inhibitor), optionally in combination with a therapeutic that targets BRAF.

Example 10: Patient selection based on PD-L1 status

To enable broad examination of cancer indications for PD-1/PD-L1 based therapies, we evaluated PD-L1 expression at both the protein and mRNA level in human cancers including both lung and hepatic tumors.

PD-L1 protein expression was evaluated in a set of formalin-fixed paraffin-embedded non-small cell lung (NSCLC) adenocarcinoma (ACA), NSCLC squamous cell carcinoma (SCC), and hepatocellular carcinoma (HCC) tumors by immunohistochemistry (IHC). PD-L1 expression was scored semi-quantitatively by a manual histo-score (H-score) methodology based on staining intensity and percentage of positive tumor cells. In our IHC analysis, PD-L1 positivity (PD-L1+) was defined as an H-score ≥ 20. In parallel, PD-L1 mRNA expression data was examined from The Cancer Genome Atlas (TCGA) in these same indications (503 NSCLC ACA, 489 NSCLC SCC, and 191 HCC) and analyzed by comparing the expression in matched normal tissues from TCGA.

With RNAseq analysis, data was calculated as log2 (RPKM+0.1) after RSEM normalization, utilizing OmicSoft RNASeq pipelines across TCGA tumor indications. The expression of PD-L1 is elevated in NSCLC ACA and SCC, relative to that in HCC. By overlaying the distributions and comparing the expression levels across all indications in TCGA, we ranked overexpression profiles for PD-L1 and found the TCGA HCC cohort to have much reduced PD-L1 mRNA levels, with a median level of -0.8 compared to 1.3 for ACA and 1.5 for SCC, which amounts to more than a 2-fold change of median level expression. With RNAseq, our analysis defines 50% of NSCLC adenocarcinoma, 54% of NSCLC squamous cell carcinoma, and 6% of HCC as high expressers for PD-L1.

Tumor cell PD-L1 protein expression was measured in 45 lung adenocarcinoma (ACA) samples, 47 lung squamous cell carcinoma (SCC) samples, and 36 hepatocellular carcinoma (HCC) samples. 16/45 (35.6%) lung ACA, 21/47 (44.7%) lung SCC were PD-L1 positive. In contrast, PD-L1 positivity was seen in only 2/36 (5.6%) HCC samples.

In summary, with IHC and RNAseq analysis in large and independent human NSCLC and HCC sample sets, we have found PD-L1 expression to be more enriched in NSCLC than in HCC. Within NSCLC, there are comparable findings between adenocarcinoma and squamous cell carcinomas. Importantly, amongst the large number of samples (128 for IHC and 1183 for

RNAseq) in the 3 indications, very good concordance is observed between protein- and mRNA-based analyses. Our finding thus establishes the basis for large scale mRNA-based data mining in TCGA for indications and patient segments that may be enriched for responses to PD-1/PD-L1-and/or TIM-3 based immune therapies.

Example 11: Competition assays indicate humanized anti-TIM3 antibodies bind to a similar epitope.

As described above, the epitope of TIM-3 recognized by ABTIM3-hum21 was determined by x-ray crystallography studies. ABTIM3-hum21 differs by only one amino acid in the heavy chain CDR2 from the other humanized anti-TIM3 antibodies described herein, and this different amino acid (Gln55) is far away (>6Å) from the epitope and thus would not be expected to change antigen binding. Two different competition assays were performed to compare epitope binding between ABTIM3-hum21 and two other humanized anti-TIM3 antibodies, ABTIM3-hum03 and ABTIM3-hum11. The results of both competition assays show that both ABTIM3-hum04 and ABTIM3-hum11 effectively compete with ABTIM3-hum03 for binding to TIM3, thus demonstrating that ABTIM3-hum03 and ABTIM3-hum11 also bind to a similar epitope as ABTIM3-hum21, *e.g.*, the epitope as described herein.

11.1 Flow cytometry competition assay

K_D of ABTMI3-hum21 was determined by labeling ABTIM3-hum21 with phycoerythrin, incubated with 300.19 hTIM-3 expressing cells, and a binding curve was established to determine a K_D of 2.15.

Titrated concentrations of unlabelled hIgG1(isotype control), ABTIM3-hum21 (positive control), ABTIM3-hum11 or ABTIM3-hum03 were mixed with ABTIM3-hum21 at its K_D and incubated with 300.19 hTIM-3 expressing cells at 4°C for 3 hours. Cells were washed twice and run on an LSRFortessa flow cytometer. Data was analyzed in FlowJo and MFI (PE) values were plotted and graphed in GraphPad (Prism) software. The experiment was performed twice.

The results of the competition assay demonstrate that ABTIM3-hum11 and ABTIM3-hum03 (but not isotype control) both competed with ABTIM3-hum21 for binding with human TIM3 expressed on the 300.19 cells (Figure 20). K_D for ABTIM3-hum11 and ABTIM3-hum03 was calculated from the binding curves; the calculated K_D for ABTIM3-hum11 was 2.276 nM

and the calculated K_D for ABTIM3-hum03 was 2.413 nM. These results demonstrate that ABTIM3-hum11 and ABTIM3-hum03 bind to a similar or the same epitope as ABTIM3-hum21.

11.2 Biacore competition assay

hTIM-3/his antigen was captured by immobilized anti-His antibody (RU10000) on a CM5 chip. The first antibody was injected to reach saturation (>90%). Then the second antibody was injected to assess whether a second binding event occurs. Occurrence of a second binding event indicates that the two tested antibodies have different epitopes. Lack of a second binding event, indicates that the two antibodies may recognize and bind to the same epitope. Control assays were run where a test antibody was run with human IgG1 isotype control, or where the test antibody was run as the first and second antibody (*e.g.*, self-self cycle) to observe the baseline of a binding event. Table 14 summarizes the Biacore cycles run and indicates which antibodies were used as the first and second antibody in each cycle.

Table 14. Summary of Biacore competition assay cycles

Cycles	1st Antibody	2nd Antibody
1	huIgG1	huIgG1
2	huIgG1	ABTIM3-hum21
3	huIgG1	ABTIM3-hum03
4	huIgG1	ABTIM3-hum11
5	ABTIM3-hum21	huIgG1
6	ABTIM3-hum21	ABTIM3-hum21
7	ABTIM3-hum21	ABTIM3-hum03
8	ABTIM3-hum21	ABTIM3-hum11
9	ABTIM3-hum03	huIgG1
10	ABTIM3-hum03	ABTIM3-hum21
11	ABTIM3-hum03	ABTIM3-hum03
12	ABTIM3-hum03	ABTIM3-hum11
13	ABTIM3-hum11	huIgG1
14	ABTIM3-hum11	ABTIM3-hum21
15	ABTIM3-hum11	ABTIM3-hum03
16	ABTIM3-hum11	ABTIM3-hum11

Detection of the baseline and first and second binding events are recorded as RU (resonance units) and can be presented in a sensogram. A typical sensogram is shown in Figure 21, where a binding event is shown after the 1st antibody injection. After a wash, the second antibody is injected and a second binding may be detected. Significant changes in RU indicate a binding event. A summary of the changes in RU detected from the 1st and 2nd antibody injections from the Biacore competition assay is shown in Table 15.

Table 15. Summary of results from Biacore competition assay

1st Antibody Injection		2nd Antibody Injection			
		huIgG1	ABTIM3-hum21	ABTIM3-hum03	ABTIM3-hum11
huIgG1	0.27	3.6	88.2	86.3	83.2
ABTIM3-hum21	95.85	4.5	6.6	7.6	8.1
ABTIM3-hum03	93.33	4.5	6.9	7.3	8.5
ABTIM3-hum11	93.48	3.8	NA[1]	5.3	7.2

[1] No value was calculated from the sensogram, due to an unknown fluid problem.

The results shown above demonstrate that injection of ABTIM3-hum21, ABTIM3-hum03, and ABTIM3-hum11 during the first antibody injection results in a binding event. Injection of ABTIM3-hum21, ABTIM3-hum03, and ABTIM3-hum11 as the second antibody after injection is human IgG1 control antibody results in a second binding event. However, injection of any of the anti-TIM3 antibodies tested here as the first and second antibodies did not result in a second binding event, demonstrating that for each pair of 1st and 2nd antibodies tested, there was competition for binding to the same TIM3 epitope. These results indicate that ABTIM3-hum21, ABTIM3-hum03, and ABTIM3-hum11 bind to a similar or the same epitope on human TIM3.

Example 12: Pharmacokinetic properties of ABTIM3-hum11

Various pharmacokinetic properties of ABTIM3-hum11 were assessed in mouse and rat models. ABTIM3-hum11 was injected intravenously into mice at varying doses, 1 mg/kg, 3 mg/kg, and 10 mg/kg. Blood samples were obtained at various timepoints between 0 and 672 hours (0-28 days). 10 mg/kg ABTIM3-hum11 was injected intravenously into rats, and blood samples were obtained at various time points from 0-400 hours (0-16 days). The concentration of ABTIM3-hum11 present in the serum was determined (Figures 23A and 23B). The results

showed that ABTIM3-hum11 is stable in both mouse and rat serum. Table 16 shows additional pharmacokinetic properties determined, including halflife (T1/2), peak serum concentration (Cmax), AUC up to the last measurable concentration (AUClast), and AUC as extrapolated to infinity (AUCinf).

Table 16. Summary of pharmacokinetic properties of ABTIM3-hum11

Species	Dose (mg/kg)		T ½ (hr)	Cmax (μg/mL)	AUClast (hr*μg/mL)	AUCinf (hr*μg/mL)
Mouse	1	N	3	3	3	3
		Mean	142.3	17.3	1507.8	1571.4
		STD	96.9	0.7	337.9	439.5
	3	N	3	3	3	3
		Mean	266.1	37.2	4617.9	5369.0
		STD	73.1	2.3	2109.8	2496.1
	10	N	3	3	3	3
		Mean	254.9	147.5	23906.5	28621.7
		STD	39.2	13.2	4369.8	6314.1
Rat	10	N	3	3	3	3
		Mean	400.8	243.4	26032.3	53767.1
		STD	75.9	19.1	895.8	5362.6

In a toxicity study, three naïve mice were administered a single dose by intravenous injection at 1 mg/kg, 3 mg/kg, or 10 mg/kg of ABTIM3-hum11. After 28 days, no adverse events were observed, indicating that ABTIM3 antibody is tolerable in mouse models.

INCORPORATION BY REFERENCE

All publications, patents, and Accession numbers mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

EQUIVALENTS

While specific embodiments of the compositions and methods herein have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

CLAIMS

1. An isolated antibody molecule capable of binding to human T-cell immunoglobulin domain and mucin domain 3 (TIM-3), comprising:

(a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 10; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(b) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 4; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(c) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 25; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(d) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 24; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(e) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 31; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14; or

(f) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 30; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8.

2. The antibody molecule of claim 1, wherein said antibody molecule is a humanized antibody molecule, and/or a monospecific antibody or a bispecific antibody molecule.

3. The antibody molecule of claim 1 or 2, wherein said antibody molecule has a first binding specificity for TIM-3 and a second binding specificity for PD-1, LAG-3, CEACAM-1, CEACAM-5, PD-L1 or PD-L2; and/or

wherein said antibody molecule comprises an antigen binding fragment of an antibody or a half antibody or antigen binding fragment of a half antibody.

4. The antibody molecule of any of claims 1-3, which is a Fab, F(ab')2, Fv, or a single chain Fv fragment (scFv); or comprises

a heavy chain constant region selected from IgG1, IgG2, IgG3, and IgG4, and/or

a light chain constant region chosen from the light chain constant regions of kappa or lambda.

5. The antibody molecule of any of claims 1-4, which comprises:

a VH comprising an amino acid sequence chosen from SEQ ID NO: 1, 16, 26, 32, 36, 44, 48, 52, 60, 68, 72, 76, 80, 84, 92, or 100, or an amino acid sequence at least 85% identical to any of SEQ ID NOs: 1, 16, 26, 32, 36, 44, 48, 52, 60, 68, 72, 76, 80, 84, 92, or 100; and/or

a VL comprising an amino acid sequence chosen from SEQ ID NO: 2, 20, 40, 56, 64, 88, 96, or 104, or an amino acid sequence at least 85% identical to any of SEQ ID NOs: 2, 20, 40, 56, 64, 88, 96, or 104.

6. The antibody molecule of any one of claims 1-5, which comprises:

a VH comprising an amino acid sequence chosen from SEQ ID NO: 1, 16, 26, 32, 36, 44, 48, 52, 60, 68, 72, 76, 80, 84, 92, or 100; and/or

a VL comprising an amino acid sequence chosen from SEQ ID NO: 2, 20, 40, 56, 64, 88, 96, or 104.

7. The antibody molecule of any of claims 1-6, which comprises:

a heavy chain comprising an amino acid sequence chosen from SEQ ID NO: 18, 121,_28, 34, 38, 116, 46, 50, 54, 62, 70, 74, 78, 82, 86, 94, or 102; and/or

a light chain comprising an amino acid sequence chosen from SEQ ID NO: 22, 42, 58, 66, 90, 98, or 106.

8. The antibody molecule of any of claims 1-6, which comprises:

(a) a VH comprising the amino acid sequence of SEQ ID NO: 1 and a VL comprising the amino acid sequence of SEQ ID NO: 2;

(b) a VH comprising the amino acid sequence of SEQ ID NO: 16 and a VL comprising the amino acid sequence of SEQ ID NO: 20;

(c) a VH comprising the amino acid sequence of SEQ ID NO: 26 and a VL comprising the amino acid sequence of SEQ ID NO: 20;

(d) a VH comprising the amino acid sequence of SEQ ID NO: 32 and a VL comprising the amino acid sequence of SEQ ID NO: 20;

(e) a VH comprising the amino acid sequence of SEQ ID NO: 36 and a VL comprising the amino acid sequence of SEQ ID NO: 40;

(f) a VH comprising the amino acid sequence of SEQ ID NO: 44 and a VL comprising the amino acid sequence of SEQ ID NO: 40;

(g) a VH comprising the amino acid sequence of SEQ ID NO: 48 and a VL comprising the amino acid sequence of SEQ ID NO: 40;

(h) a VH comprising the amino acid sequence of SEQ ID NO: 36 and a VL comprising the amino acid sequence of SEQ ID NO: 20;

(i) a VH comprising the amino acid sequence of SEQ ID NO: 16 and a VL comprising the amino acid sequence of SEQ ID NO: 40;

(j) a VH comprising the amino acid sequence of SEQ ID NO: 52 and a VL comprising the amino acid sequence of SEQ ID NO: 56;

(k) a VH comprising the amino acid sequence of SEQ ID NO: 60 and a VL comprising the amino acid sequence of SEQ ID NO: 56;

(l) a VH comprising the amino acid sequence of SEQ ID NO: 52 and a VL comprising the amino acid sequence of SEQ ID NO: 64;

(m) a VH comprising the amino acid sequence of SEQ ID NO: 60 and a VL comprising the amino acid sequence of SEQ ID NO: 64;

(n) a VH comprising the amino acid sequence of SEQ ID NO: 68 and a VL comprising the amino acid sequence of SEQ ID NO: 64;

(o) a VH comprising the amino acid sequence of SEQ ID NO: 72 and a VL comprising the amino acid sequence of SEQ ID NO: 64;

(p) a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 56;

(q) a VH comprising the amino acid sequence of SEQ ID NO: 80 and a VL comprising the amino acid sequence of SEQ ID NO: 56;

(r) a VH comprising the amino acid sequence of SEQ ID NO: 68 and a VL comprising the amino acid sequence of SEQ ID NO: 56;

(s) a VH comprising the amino acid sequence of SEQ ID NO: 72 and a VL comprising the amino acid sequence of SEQ ID NO: 56;

(t) a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 64;

(u) a VH comprising the amino acid sequence of SEQ ID NO: 80 and a VL comprising the amino acid sequence of SEQ ID NO: 64;

(v) a VH comprising the amino acid sequence of SEQ ID NO: 84 and a VL comprising the amino acid sequence of SEQ ID NO: 88;

(w) a VH comprising the amino acid sequence of SEQ ID NO: 92 and a VL comprising the amino acid sequence of SEQ ID NO: 96; or

(x) a VH comprising the amino acid sequence of SEQ ID NO: 100 and a VL comprising the amino acid sequence of SEQ ID NO: 104.

9. The antibody molecule of any of claims 1-5, which comprises:

(a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain comprising the amino acid sequence of SEQ ID NO: 22;

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 28 and a light chain comprising the amino acid sequence of SEQ ID NO: 22;

(c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 34 and a light chain comprising the amino acid sequence of SEQ ID NO: 22;

(d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain comprising the amino acid sequence of SEQ ID NO: 42;

(e) a heavy chain comprising the amino acid sequence of SEQ ID NO: 46 and a light chain comprising the amino acid sequence of SEQ ID NO: 42;

(f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50 and a light chain comprising the amino acid sequence of SEQ ID NO: 42;

(g) a heavy chain comprising the amino acid sequence of SEQ ID NO: 116 and a light chain comprising the amino acid sequence of SEQ ID NO: 22;

(h) a heavy chain comprising the amino acid sequence of SEQ ID NO: 121 and a light chain comprising the amino acid sequence of SEQ ID NO: 42;

(i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 54 and a light chain comprising the amino acid sequence of SEQ ID NO: 58;

(j) a heavy chain comprising the amino acid sequence of SEQ ID NO: 62 and a light chain comprising the amino acid sequence of SEQ ID NO: 58;

(k) a heavy chain comprising the amino acid sequence of SEQ ID NO: 54 and a light chain comprising the amino acid sequence of SEQ ID NO: 66;

(l) a heavy chain comprising the amino acid sequence of SEQ ID NO: 62 and a light chain comprising the amino acid sequence of SEQ ID NO: 66;

(m) a heavy chain comprising the amino acid sequence of SEQ ID NO: 70 and a light chain comprising the amino acid sequence of SEQ ID NO: 66;

(n) a heavy chain comprising the amino acid sequence of SEQ ID NO: 74 and a light chain comprising the amino acid sequence of SEQ ID NO: 66;

(o) a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and a light chain comprising the amino acid sequence of SEQ ID NO: 58;

(p) a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and a light chain comprising the amino acid sequence of SEQ ID NO: 58;

(q) a heavy chain comprising the amino acid sequence of SEQ ID NO: 70 and a light chain comprising the amino acid sequence of SEQ ID NO: 58;

(r) a heavy chain comprising the amino acid sequence of SEQ ID NO: 74 and a light chain comprising the amino acid sequence of SEQ ID NO: 58;

(s) a heavy chain comprising the amino acid sequence of SEQ ID NO: 78 and a light chain comprising the amino acid sequence of SEQ ID NO: 66;

(t) a heavy chain comprising the amino acid sequence of SEQ ID NO: 82 and a light chain comprising the amino acid sequence of SEQ ID NO: 66;

(u) a heavy chain comprising the amino acid sequence of SEQ ID NO: 86 and a light chain comprising the amino acid sequence of SEQ ID NO: 90;

(v) a heavy chain comprising the amino acid sequence of SEQ ID NO: 94 and a light chain comprising the amino acid sequence of SEQ ID NO: 98; or

(w) a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 and a light chain comprising the amino acid sequence of SEQ ID NO: 106.

10. The antibody molecule of any of claims 1-9, which comprises:

(a) a human IgG4 heavy chain constant region with a mutation at position 228 according to EU numbering or position 108 of SEQ ID NO: 108 or 110 and a kappa light chain constant region;

(b) a human IgG4 heavy chain constant region with a Serine to Proline mutation at position 228 according to EU numbering or position 108 of SEQ ID NO: 108 or 110 and a kappa light chain constant region;

(c) a human IgG1 heavy chain constant region with an Asparagine to Alanine mutation at position 297 according to EU numbering or position 180 of SEQ ID NO: 112 and a kappa light chain constant region;

(d) a human IgG1 heavy chain constant region with an Aspartate to Alanine mutation at position 265 according to EU numbering or position 148 of SEQ ID NO: 113 and Proline to Alanine mutation at position 329 according to EU numbering or position 212 of SEQ ID NO: 113, and a kappa light chain constant region; or

(e) a human IgG1 heavy chain constant region with a Leucine to Alanine mutation at position 234 according to EU numbering or position 117 of SEQ ID NO: 114 and Leucine to Alanine mutation at position 235 according to EU numbering or position 118 of SEQ ID NO: 114, and a kappa light chain constant region.

11. The antibody molecule of any of claims 1-10, which has one, two, three, or all of the following properties:

(a) is capable of binding to human TIM-3 with a dissociation constant (K_D) of less than about 0.5 nM;

(b) is capable of reducing:

(i) binding of TIM-3 to phosphatidylserine (PtdSer), HMGB1, CEACAM-1, Semaphorin 4-A, or a combination thereof, or a cell that expresses PtdSer, HMGB1, CEACAM-1, Semaphorin 4-A, or a combination thereof; or

(ii) PtdSer-mediated membrane penetration of TIM-3.

(c) is capable of enhancing an antigen-specific T cell response; or

(d) binds an IgV domain of TIM-3.

12. An isolated antibody molecule that binds to the same epitope as, or an epitope that overlaps with, the epitope of a monoclonal antibody to human T-cell immunoglobulin domain and mucin domain 3 (TIM-3), wherein the monoclonal antibody comprises:

(a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 10; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(b) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 4; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(c) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 25; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14;

(d) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 24; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8;

(e) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 9; a VHCDR2 amino acid sequence of SEQ ID NO: 31; and a VHCDR3 amino acid sequence of SEQ ID NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 12, a VLCDR2 amino acid sequence of SEQ ID NO: 13, and a VLCDR3 amino acid sequence of SEQ ID NO: 14; or

(f) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 3; a VHCDR2 amino acid sequence of SEQ ID NO: 30; and a VHCDR3 amino acid sequence of SEQ ID

NO: 5; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 6, a VLCDR2 amino acid sequence of SEQ ID NO: 7, and a VLCDR3 amino acid sequence of SEQ ID NO: 8, wherein

(1) the antibody molecule binds to one, two, three, or all of: the two residues adjacent to the N-terminus of the A strand or Val24 and Glu25 in human TIM-3, the BC loop, the CC' loop, or the G strand of human TIM-3; and

(2) the antibody molecule has one, two, three, four, five, six, seven or all of the following properties:

(i) reduces PtdSer-dependent membrane penetration of TIM-3;

(ii) reduces binding of TIM-3 to one, two, or all of PtdSer, HMGB1, or CEACAM-1;

(iii) does not inhibit binding of TIM-3 to Galectin-9;

(iv) competes with CEACAM-1 for binding to one, two, or all of Cys58, Asn119 and Lys122 of TIM-3;

(v) reduces the formation of a hydrogen bond between Lys122 of TIM-3 and Asn42 of CEACAM-1;

(vi) competes with PtdSer for binding to the FG loop and the CC' loop of TIM-3;

(vii) competes with HMGB1 for binding to Glu62 of TIM-3; or

(viii) does not compete with Galectin-9 for binding to TIM-3.

13. The antibody molecule of claim 12, wherein the antibody molecule binds to one, two, three, four, five, six, seven, or all of the following:

(a) one, two, three, or all of: the A strand, the EF loop, the F strand, or the FG loop;

(b) one, two, three, or all of: the third residue N-terminal to the A strand or Glu23 in human TIM-3, the C strand, the C'C'' loop, or the C'' strand;

(c) one or both of residues Val24 and Glu25 adjacent to the N-terminus of the A strand; residue Thr41 within the BC loop; four, five, six, seven, or all of residues Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, Leu127, and Val128 within the G strand; and three, four, five, or all of residues Gly56, Ala57, Cys58, Pro59, Val60, and Phe61 within the CC' loop;

(d) residues Val24 and Glu25 adjacent to the N-terminus of the A strand; residue Thr41 within the BC loop; residues Glu121, Lys122, Phe123, Asn124, Leu125, Lys126, Leu127, and Val128 within the G strand; and residues Gly56, Ala57, Cys58, Pro59, Val60, and Phe61 within the CC' loop;

(e) one or more residues chosen from: residue Tyr26 within the A strand, residues Phe39 and Tyr40 within the BC loop; residue Ser105 within the EF loop; residues Gly106 and Ile107 within the F strand; and residues Asn119 and Asp120 within the FG loop;

(f) residue Tyr26 within the A strand, residues Phe39 and Tyr40 within the BC loop; residue Ser105 within the EF loop; residues Gly106 and Ile107 within the F strand; and residues Asn119 and Asp120 within the FG loop;

(g) one or more residues chosen from: residue Glu23 N-terminal to the A strand; residues Pro42, Ala43, Ala44, Pro45, Gly46, Asn47, Leu48, Val49, and Pro50 within the BC loop; residues Val51, Cys52, Trp53, Gly54, and Lys55 within the C strand; residues Arg73 and Asp74 with the C'C'' loop; and residues Val75, Asn76, and Tyr77 in the C" strand; and/or

(h) residue Glu23 N-terminal to the A strand; residues Pro42, Ala43, Ala44, Pro45, Gly46, Asn47, Leu48, Val49, and Pro50 within the BC loop; residues Val51, Cys52, Trp53, Gly54, and Lys55 within the C loop; residues Arg73 and Asp74 with the C'C'' strand; and residues Val75, Asn76, and Tyr77 in the C" strand.

14. A pharmaceutical composition comprising the isolated antibody molecule of any of claims 1-13 and a pharmaceutically acceptable carrier, excipient or stabilizer.

15. An isolated nucleic acid encoding the antibody heavy and light chain variable regions of the antibody molecule of any of claims 1-13.

16. An isolated nucleic acid encoding heavy chain CDRs 1-3 and light chain CDRs 1-3 of claim 1, wherein said nucleic acid comprises a nucleotide sequence encoding SEQ ID NOs: 3-10, 12-14, 24, 25, 30, or 31.

17. The nucleic acid of claim 16, further comprising:

a nucleotide sequence encoding a VH, wherein said nucleotide sequence comprises any of SEQ ID NO: 11, 17, 29, 33, 37, 45, 49, 53, 61, 69, 73, 77, 81, 85, 93, 101, 115, or 120, or is at least 85% identical to any of SEQ ID NO: 11, 17, 29, 33, 37, 45, 49, 53, 61, 69, 73, 77, 81, 85, 93, 101, 115, or 120; and

a nucleotide sequence encoding a VL, wherein said nucleotide sequence comprises any of SEQ ID NO: 15, 21, 41, 57, 65, 89, 97, 105, 118, 123, 125, or 127, or is at least 85% identical to any of SEQ ID NO: 15, 21, 41, 57, 65, 89, 97, 105, 118, 123, 125, or 127.

18. The nucleic acid of claim 16, further comprising:

a nucleotide sequence encoding a heavy chain, wherein said nucleotide sequence comprises any of SEQ ID NO: 19, 29, 35, 39, 47, 51, 55, 63, 71, 75, 79, 83, 87, 95, 103, 117, or 122, or is at least 85% identical to any of SEQ ID NO: 19, 29, 35, 39, 47, 51, 55, 63, 71, 75, 79, 83, 87, 95, 103, 117, or 122; and

a nucleotide sequence encoding a light chain, wherein said nucleotide sequence comprises any of SEQ ID NO: 23, 43, 59, 67, 91, 99, 107, 119, 124, 126, 128, or is at least 85% identical to any of SEQ ID NO: 23, 43, 59, 67, 91, 99, 107, 119, 124, 126, 128.

19. An expression vector comprising the nucleic acid of any of claims 15-18.

20. A host cell comprising the nucleic acid of any of claims 15-18.

21. A method of producing an antibody molecule or fragment thereof, comprising culturing the host cell of claim 20 under conditions suitable for gene expression.

22. A method of detecting TIM-3 in a biological sample from a subject, comprising (i) contacting the sample and/or a reference sample with an isolated antibody molecule of any of claims 1-13 under conditions that allow interaction of the antibody molecule and a polypeptide of TIM-3 to occur, and (ii) detecting formation of a complex between the antibody molecule and the sample and/or the reference sample.

23. An antibody molecule of any of claims 1-13, or a pharmaceutical composition of claim 14, for use in the stimulation of an immune response or the treatment of a cancer or an infectious disease in a subject.

24. The antibody molecule, or pharmaceutical composition, for use as claimed in claim 23, wherein the cancer is chosen from a lung cancer, a melanoma, a renal cancer, a liver cancer, a prostate cancer, a breast cancer, a head and neck cancer, a colorectal cancer, a pancreatic cancer, a brain cancer, a hematological cancer, or a metastatic lesion of the cancer.

25. The antibody molecule, or pharmaceutical composition, as claimed in claim 24, wherein:

(a) the lung cancer is chosen from a non-small cell lung cancer (NSCLC), a lung adenocarcinoma, a squamous cell lung carcinoma, or a small cell lung cancer;

(b) the melanoma is chosen from an advanced melanoma, an unresectable melanoma, a metastatic melanoma, a melanoma with a BRAF mutation, a melanoma with an NRAS mutation, a cutaneous melanoma, or an intraocular melanoma;

(c) the renal cancer is chosen from a renal cell carcinoma (RCC), a metastatic renal cell carcinoma, a clear cell renal cell carcinoma (CCRCC), a kidney clear cell carcinoma, or a kidney papillary cell carcinoma; or

(d) the hematologic cancer is chosen from a lymphoma, a non-Hodgkin lymphoma, a myeloma, or a leukemia.

26. The antibody molecule, or pharmaceutical composition, for use as claimed in any of claims 23-25, wherein the antibody molecule or pharmaceutical composition is to be used in combination with a second therapeutic agent or procedure.

27. The antibody molecule, or pharmaceutical composition, for use as claimed in claim 26, wherein the second therapeutic agent or procedure is chosen from one or more of a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy; or

wherein the antibody molecule is to be used in combination with:

(a) an agonist of a costimulatory molecule chosen from one or more of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand; or

(b) an inhibitor of an immune checkpoint molecule chosen from one or more of PD-1, PD-L1, PD-L2, CTLA-4, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGFR.

28. The antibody molecule, or pharmaceutical composition, for use as claimed in any of claims 23-27, wherein the antibody molecule or pharmaceutical composition is to be used in combination with one or more of the following:

(a) an inhibitor of PD-1;

(b) an inhibitor of PD-L1;

(c) an inhibitor of LAG-3;

(d) an agonist of GITR;

(e) a chemotherapy for the treatment of a lung cancer,;

(f) an indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor for the treatment of a lung cancer;

(g) an inhibitor of CTLA-4 for the treatment of a lung cancer or a melanoma;

(h) a MEK inhibitor for the treatment of a lung cancer, a melanoma, or a renal cancer;

(i) a cancer vaccine;

(j) one or more of:

(i) an immune-based therapy;

(ii) a targeting agent;

(iii) a VEGF tyrosine kinase inhibitor;

(iv) an RNAi inhibitor; or

(v) an inhibitor of a downstream mediator of VEGF signaling for the treatment of a renal cancer;

(k) one, two or all of oxaliplatin, leucovorin or 5-FU, for the treatment of a lung cancer, a melanoma, or a renal cancer; or

(l) a tyrosine kinase inhibitor for the treatment of a renal cancer.

29. The antibody molecule, or pharmaceutical composition, for use as claimed in claim 28, wherein:

(a) the inhibitor of PD-1 is an anti-PD-1 antibody molecule or a fusion protein or chosen from MDX-1106, Merck 3475, CT-011, AMP-224, or AMP-514;

(b) the inhibitor of PD-L1 is an anti-PD-L1 antibody molecule or a fusion protein or chosen from YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, or MDX-1105;

(c) the inhibitor of LAG-3 is an anti-LAG-3 antibody molecule or a fusion protein;

(d) the agonist of GITR is an anti-GITR antibody molecule or a fusion protein;

(e) the chemotherapy is a platinum doublet therapy;

(f) the IDO inhibitor is INCB24360;

(g) the inhibitor of CTLA-4 is an anti-CTLA-4 antibody, ipilimumab, or a soluble ligand of CTLA-4;

(h) the inhibitor of CTLA-4 is used further in combination with a BRAF inhibitor, vemurafenib, or dabrafenib;

(i) the cancer vaccine is a dendritic cell renal carcinoma (DC-RCC) vaccine;

(j) the immune-based therapy comprises interleukin-2 or interferon-α;

(k) the targeting agent is a VEGF inhibitor or an anti-VEGF antibody;

(l) the VEGF tyrosine kinase inhibitor is chosen from sunitinib, sorafenib, axitinib, or pazopanib;

(m) the inhibitor of a downstream mediator of VEGF signaling is an inhibitor of the mammalian target of rapamycin (mTOR), everolimus, or temsirolimus; or

(n) the tyrosine kinase inhibitor is axitinib.

30. The antibody molecule, or a pharmaceutical composition, for use as claimed in any of claims 23-29, wherein the subject has, or is identified as having, one or more of:

(a) a cancer that expresses TIM-3;

(b) a cancer that is positive for one, two, or all of PD-L1, CD8, or IFN-γ;

(c) a cancer that is triple positive for PD-L1, CD8, and IFN-γ; or

(d) a cancer that is Tumor Infiltrating Lymphocyte (TIL) positive.

31. The antibody molecule, or a pharmaceutical composition, for use as claimed in any of claims 23-30, wherein the antibody molecule or pharmaceutical composition is to be administered at a dose of about 0.1 to 30 mg/kg, 1 to 30 mg/kg or 1 to 5 mg/kg, or, wherein the antibody molecule or

pharmaceutical composition is to be administered once a week to once every 2, 3, or 4 weeks or the antibody molecule or pharmaceutical composition is to be administered at a dose from about 10 to 20 mg/kg every other week.

32. The antibody molecule, or pharmaceutical composition, for use as claimed in any of claims 23-31, wherein the antibody molecule or pharmaceutical composition is to be used in combination with one or more of: 1) a protein kinase C (PKC) inhibitor; 2) a heat shock protein 90 (HSP90) inhibitor; 3) an inhibitor of a phosphoinositide 3-kinase (PI3K) and/or target of rapamycin (mTOR); 4) an inhibitor of cytochrome P450, a CYP17 inhibitor, or a 17alpha-Hydroxylase/C17-20 Lyase inhibitor; 5) an iron chelating agent; 6) an aromatase inhibitor; 7) an inhibitor of p53 or an inhibitor of a p53/Mdm2 interaction; 8) an apoptosis inducer; 9) an angiogenesis inhibitor; 10) an aldosterone synthase inhibitor; 11) a smoothened (SMO) receptor inhibitor; 12) a prolactin receptor (PRLR) inhibitor; 13) a Wnt signaling inhibitor; 14) a CDK4/6 inhibitor; 15) a fibroblast growth factor receptor 2 (FGFR2)/fibroblast growth factor receptor 4 (FGFR4) inhibitor; 16) an inhibitor of macrophage colony-stimulating factor (M-CSF); 17) an inhibitor of one or more of c-KIT, histamine release, Flt3, or PKC; 18) an inhibitor of one or more of VEGFR-2, PDGFRbeta, c-KIT or Raf kinase C; 19) a somatostatin agonist and/or a growth hormone release inhibitor; 20) an anaplastic lymphoma kinase (ALK) inhibitor; 21) an insulin-like growth factor 1 receptor (IGF-1R) inhibitor; 22) a P-Glycoprotein 1 inhibitor; 23) a vascular endothelial growth factor receptor (VEGFR) inhibitor; 24) a BCR-ABL kinase inhibitor; 25) an FGFR inhibitor; 26) an inhibitor of CYP11B2; 27) a HDM2 inhibitor, *e.g.*, an inhibitor of the HDM2-p53 interaction; 28) an inhibitor of a tyrosine kinase; 29) an inhibitor of c-MET; 30) an inhibitor of JAK; 31) an inhibitor of DAC; 32) an inhibitor of 11β-hydroxylase; 33) an inhibitor of IAP; 34) an inhibitor of PIM kinase; 35) an inhibitor of Porcupine; 36) an inhibitor of BRAF, BRAF V600E, or wild-type BRAF; 37) an inhibitor of HER3; 38) an inhibitor of MEK; or 39) an inhibitor of a lipid kinase.

33. The antibody molecule, or a pharmaceutical composition, for use as claimed in any of claims 23-32, wherein the antibody molecule or pharmaceutical composition is to be used in combination with one or more of Compounds A1 to A51 as described in Table 6.

34. Use of an antibody molecule of any of claims 1-13, or a pharmaceutical composition of claim 14, in the manufacture of a medicament for the stimulation of an immune response or the treatment of a cancer or an infectious disease in a subject.

35. The use according to claim 34, wherein the cancer is chosen from a lung cancer, a melanoma, a renal cancer, a liver cancer, a prostate cancer, a breast cancer, a head and neck cancer, a

colorectal cancer, a pancreatic cancer, a brain cancer, a hematological cancer, or a metastatic lesion of the cancer.

36. The use according to claim 35, wherein:

(a) the lung cancer is chosen from a non-small cell lung cancer (NSCLC), a lung adenocarcinoma, a squamous cell lung carcinoma, or a small cell lung cancer;

(b) the melanoma is chosen from an advanced melanoma, an unresectable melanoma, a metastatic melanoma, a melanoma with a BRAF mutation, a melanoma with an NRAS mutation, a cutaneous melanoma, or an intraocular melanoma;

(c) the renal cancer is chosen from a renal cell carcinoma (RCC), a metastatic renal cell carcinoma, a clear cell renal cell carcinoma (CCRCC), a kidney clear cell carcinoma, or a kidney papillary cell carcinoma; or

(d) the hematologic cancer is chosen from a lymphoma, a non-Hodgkin lymphoma, a myeloma, or a leukemia.

37. The use according to any of claims 34-36, wherein the medicament is to be used in combination with a second therapeutic agent or procedure.

38. The use according to claim 37 wherein the second therapeutic agent or procedure is chosen from one or more of a chemotherapy, a targeted anti-cancer therapy, an oncolytic drug, a cytotoxic agent, an immune-based therapy, a cytokine, surgical procedure, a radiation procedure, an activator of a costimulatory molecule, an inhibitor of an inhibitory molecule, a vaccine, or a cellular immunotherapy; or

wherein the medicament is to be used in combination with:

(a) an agonist of a costimulatory molecule chosen from one or more of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3 or CD83 ligand; or

(b) an inhibitor of an immune checkpoint molecule chosen from one or more of PD-1, PD-L1, PD-L2, CTLA-4, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGFR.

39. The use according to any of claims 34-38, wherein the medicament is to be used in combination with one or more of the following:

(a) an inhibitor of PD-1;

(b) an inhibitor of PD-L1;

(c) an inhibitor of LAG-3;

(d) an agonist of GITR;

(e) a chemotherapy for the treatment of a lung cancer,;

(f) an indoleamine-pyrrole 2,3-dioxygenase (IDO) inhibitor for the treatment of a lung cancer;

(g) an inhibitor of CTLA-4 for the treatment of a lung cancer or a melanoma;

(h) a MEK inhibitor for the treatment of a lung cancer, a melanoma, or a renal cancer;

(i) a cancer vaccine;

(j) one or more of:

(i) an immune-based therapy;

(ii) a targeting agent;

(iii) a VEGF tyrosine kinase inhibitor;

(iv) an RNAi inhibitor; or

(v) an inhibitor of a downstream mediator of VEGF signaling for the treatment of a renal cancer;

(k) one, two or all of oxaliplatin, leucovorin or 5-FU, for the treatment of a lung cancer, a melanoma, or a renal cancer; or

(l) a tyrosine kinase inhibitor for the treatment of a renal cancer.

40. The use according to claim 39, wherein:

(a) the inhibitor of PD-1 is an anti-PD-1 antibody molecule or a fusion protein or chosen from MDX-1106, Merck 3475, CT-011, AMP-224, or AMP-514;

(b) the inhibitor of PD-L1 is an anti-PD-L1 antibody molecule or a fusion protein or chosen from YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, or MDX-1105;

(c) the inhibitor of LAG-3 is an anti-LAG-3 antibody molecule or a fusion protein;

(d) the agonist of GITR is an anti-GITR antibody molecule or a fusion protein;

(e) the chemotherapy is a platinum doublet therapy;

(f) the IDO inhibitor is INCB24360;

(g) the inhibitor of CTLA-4 is an anti-CTLA-4 antibody, ipilimumab, or a soluble ligand of CTLA-4;

(h) the inhibitor of CTLA-4 is used further in combination with a BRAF inhibitor, vemurafenib, or dabrafenib;

(i) the cancer vaccine is a dendritic cell renal carcinoma (DC-RCC) vaccine;

(j) the immune-based therapy comprises interleukin-2 or interferon-α;

(k) the targeting agent is a VEGF inhibitor or an anti-VEGF antibody;

(l) the VEGF tyrosine kinase inhibitor is chosen from sunitinib, sorafenib, axitinib, or pazopanib;

(m) the inhibitor of a downstream mediator of VEGF signaling is an inhibitor of the mammalian target of rapamycin (mTOR), everolimus, or temsirolimus; or

(n) the tyrosine kinase inhibitor is axitinib.

41. The use according to any of claims 34-40, wherein the subject has, or is identified as having, one or more of:

(a) a cancer that expresses TIM-3;

(b) a cancer that is positive for one, two, or all of PD-L1, CD8, or IFN-γ;

(c) a cancer that is triple positive for PD-L1, CD8, and IFN-γ; or

(d) a cancer that is Tumor Infiltrating Lymphocyte (TIL) positive.

42. The use according to any of claims 34-41, wherein the medicament is to be administered at a dose of about 0.1 to 30 mg/kg, 1 to 30 mg/kg or 1 to 5 mg/kg, or, wherein the medicament is to be administered once a week to once every 2, 3, or 4 weeks or the medicament is to be administered at a dose from about 10 to 20 mg/kg every other week.

43. The use according to any of claims 34-42, wherein the medicament is to be used in combination with one or more of: 1) a protein kinase C (PKC) inhibitor; 2) a heat shock protein 90 (HSP90) inhibitor; 3) an inhibitor of a phosphoinositide 3-kinase (PI3K) and/or target of rapamycin (mTOR); 4) an inhibitor of cytochrome P450, a CYP17 inhibitor, or a 17alpha-Hydroxylase/C17-20 Lyase inhibitor; 5) an iron chelating agent; 6) an aromatase inhibitor; 7) an inhibitor of p53 or an inhibitor of a p53/Mdm2 interaction; 8) an apoptosis inducer; 9) an angiogenesis inhibitor; 10) an aldosterone synthase inhibitor; 11) a smoothened (SMO) receptor inhibitor; 12) a prolactin receptor (PRLR) inhibitor; 13) a Wnt signaling inhibitor; 14) a CDK4/6 inhibitor; 15) a fibroblast growth factor receptor 2 (FGFR2)/fibroblast growth factor receptor 4 (FGFR4) inhibitor; 16) an inhibitor of macrophage colony-stimulating factor (M-CSF); 17) an inhibitor of one or more of c-KIT, histamine release, Flt3, or PKC; 18) an inhibitor of one or more of VEGFR-2, PDGFRbeta, c-KIT or Raf kinase C; 19) a somatostatin agonist and/or a growth hormone release inhibitor; 20) an anaplastic lymphoma kinase (ALK) inhibitor; 21) an insulin-like growth factor 1 receptor (IGF-1R) inhibitor; 22) a P-Glycoprotein 1 inhibitor; 23) a vascular endothelial growth factor receptor (VEGFR) inhibitor; 24) a BCR-ABL kinase inhibitor; 25) an FGFR inhibitor; 26) an inhibitor of CYP11B2; 27) a HDM2 inhibitor, *e.g.*, an inhibitor of the HDM2-p53 interaction; 28) an inhibitor of a tyrosine kinase; 29) an inhibitor of c-MET; 30) an inhibitor of JAK; 31) an inhibitor of DAC; 32) an inhibitor of 11β-hydroxylase; 33) an inhibitor of IAP; 34) an inhibitor of PIM kinase; 35) an inhibitor of Porcupine; 36) an inhibitor of BRAF, BRAF V600E, or wild-type BRAF; 37) an inhibitor of HER3; 38) an inhibitor of MEK; or 39) an inhibitor of a lipid kinase.

44. The use according to any of claims 34-43, wherein the medicament is to be used in combination with one or more of Compounds A1 to A51 as described in Table 6.