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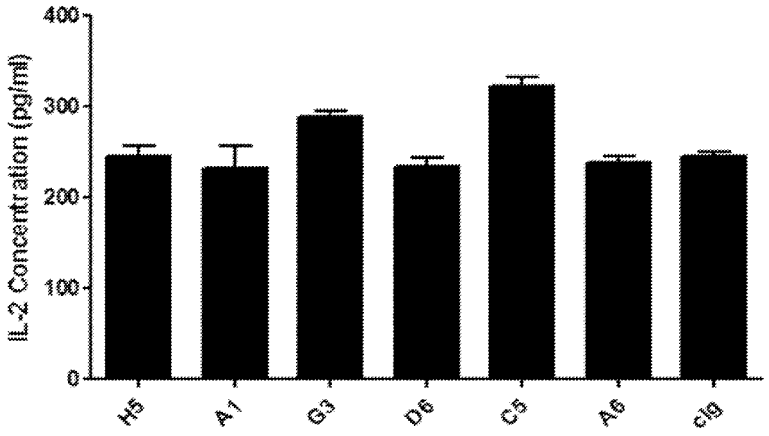
**Declarations under Rule 4.17**:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

*[Continued on next page]*

(54) Title: ANTIBODY THERAPEUTICS THAT BIND TIM3

Figure 1




(57) Abstract: There is disclosed compositions and methods relating to or derived from anti-TIM3 antibodies. More specifically, there is disclosed fully human antibodies that bind TIM3, TEVI3-antibody binding fragments and derivatives of such antibodies, and TIM3 -binding polypeptides comprising such fragments. Further still, there is disclosed nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating a disease.

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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# Antibody Therapeutics That Bind TIM3

## Related Applications

This application claims priority to United States Provisional Application No. 62/129,321, filed on March 6, 2015, the entire contents of which are incorporated by reference in their entirety herein.

## 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 February 29, 2016, is named 126036-05120_SL.txt and is 79,385 bytes in size.

## Technical Field

The present disclosure provides compositions and methods relating to or derived from anti-TIM3 (T-cell immunoglobulin and mucin-domain containing-3) antibodies. More specifically, the present disclosure provides fully human antibodies that bind TIM3, TIM3-antibody binding fragments and derivatives of such antibodies, and TIM3-binding polypeptides comprising such fragments. Further still, the present disclosure provides nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating a disease.

## Background

The TIM-3 gene family consists of eight genes in mouse and three genes in human, and each of these genes are located at chromosome 11 and at chromosome 5q33. These gene regions are known to be related with autoimmune diseases and allergic diseases. TIM protein is a type I transmembrane protein having a structurally conserved immunoglobulin variable (IgV) domain and a mucin domain.

TIM protein was considered to be specifically expressed on T cells and directly regulated the T cell activity, but there are also reports on expression of TIM3 protein in antigen-presenting cells and on their functions. According to the crystal structure analysis, the TIM protein has a conserved protein structure and has a ligand binding site in an IgV domain.

TIM3 was identified as a molecule specifically expressed on mouse Th1 cells but not on Th2 cells. The DNA sequence, the amino acid sequence and the three-dimensional

structure of TIM3 is available in the public data base such as the GenBank accession number NM_032782 and NM_134250. TIM-3 is also known as HAVCR2.

In humans, as similar to mice, TIM3 is expressed on T-cells as well as phagocytic cells such as macrophages and dendritic cells. Binding of TIM3 to a protein ligand (*e.g.*, galectin-9) can inhibit the Th1 response via mechanism of apoptosis induction, and therefore lead to such as induction of peripheral tolerance.

The reduction in expression of human TIM3 with siRNA or the inhibition of human TIM3 by blocking-antibody increased the secretion of interferon γ (IFN-γ) from CD4 positive T-cells, supporting the inhibitory role of TIM-3 in human T cells. In phagocytes, TIM3 also functions as a receptor for recognizing the apoptosis cells.

Analysis of clinical samples from autoimmune disease patients showed no expression of TIM3 in CD4 positive cells. In particular, in T cell clones derived from the cerebrospinal fluid of patients with multiple sclerosis, the expression level of TIM3 was lower and the secretion level of IFN-γ was higher than those of clones derived from normal healthy persons.

According to the microarray analysis of hematopoietic stem cells from acute myeloid leukemia (hereinafter referred to as "AML") patients and normal hematopoietic stem cells, TIM3 is expressed on AML stem cells and therefore the analysis suggested involvement of TIM3 in hematological malignancy. Examples of the anti-TIM3 monoclonal antibodies which were established up to now include anti-human TIM-3 rat monoclonal antibody (Clone 344823, manufactured by R&D Systems) and anti-human TIM-3 mouse monoclonal antibody (Clone F38-2E2, manufactured by R&D Systems). Therefore, there is a need in the art for fully human anti-TIM3 antibodies.

**Summary of the Invention**

This invention pertains to binding proteins capable of binding to TIM3, *e.g.,* human TIM3, including anti-TIM3 antibodies, and antigen-binding fragments thereof.

In one aspect, the present disclosure provides an isolated fully human antibody of an IgG class that binds to a TIM3 epitope, wherein said antibody comprises a heavy chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39,

SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69, and a light chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

In another aspect, the present disclosure provides a fully human antibody of an IgG class that binds to a TIM3 epitope with a binding affinity of at least $10^{-6}$M, which has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70. In one embodiment, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting SEQ ID NO. 1/SEQ ID NO. 2 (called TIA1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called TIA5 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called TIA6 herein), SEQ ID NO. 7/SEQ ID NO. 8

(called TIA7 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called TIA9 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called TIA10 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called TIA11 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called TIB1 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called TIB2 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called TIC1 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called TIC2 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called TIC4 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called TIC5 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called TIC8 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called TIC10 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called TIC11 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called TID1 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called TID6 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called TID10 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called TID12 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called TIE2 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called TIE3 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called TIE7 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called TIE9 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called TIF3 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called TIF7 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called TIF8 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called TIG1 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called TIG3 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called TIG6 herein), SEQ ID NO. 7/SEQ ID NO. 62 (called TIG9 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called TIG10 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called TIH1 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called TIH5 herein), and SEQ ID NO. 69/SEQ ID NO. 70 (called TIH11 herein).

In another aspect, the present disclosure provides an anti-TIM3 Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ

ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70. In one embodiment, the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 7/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, and SEQ ID NO. 69/SEQ ID NO. 70.

In another aspect, the present disclosure provides an anti-TIM3 single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connecting the heavy chain and light chain variable domain regions, wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4,

SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70. In one embodiment, the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 7/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, and SEQ ID NO. 69/SEQ ID NO. 70.

Also included in the invention, is an isolated anti-TIM3 antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain comprising complementarity determining regions (CDRs) as set forth in a heavy chain variable region amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69, and comprising a light chain variable region comprising CDRs as set forth in a light chain

variable region amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

The present disclosure further provides a method for treating a broad spectrum of mammalian cancers or a broad-spectrum of inflammatory diseases and autoimmune diseases, comprising administering an anti-TIM3 polypeptide, wherein the anti-TIM3 polypeptide is selected from the group consisting of an isolated fully human antibody of an IgG class that binds to TIM3 and comprises a heavy chain variable domain and a light chain variable domain; an anti-TIM3 fully human antibody Fab fragment comprising a heavy chain variable domain and a light chain variable domain; and a single chain human antibody comprising a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain and the light chain variable domain are connected via a peptide linker; wherein the fully human antibody has a heavy chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO.

58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

In certain embodiments, the fully human antibody, or antibody fragment, has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called TIA1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called TIA5 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called TIA6 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called TIA7 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called TIA9 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called TIA10 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called TIA11 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called TIB1 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called TIB2 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called TIC1 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called TIC2 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called TIC4 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called TIC5 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called TIC8 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called TIC10 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called TIC11 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called TID1 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called TID6 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called TID10 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called TID12 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called TIE2 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called TIE3 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called TIE7 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called TIE9 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called TIF3 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called TIF7 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called TIF8 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called TIG1 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called TIG3 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called TIG6 herein), SEQ ID NO. 7/SEQ ID NO. 62 (called TIG9 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called TIG10 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called TIH1 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called TIH5 herein), and SEQ ID NO. 69/SEQ ID NO. 70 (called TIH11 herein).

In certain embodiments, the antibody, or antigen-binding fragment thereof, of the invention has a binding affinity ($K_D$) of at least 1 x $10^{-6}$ M. In other embodiments, the antibody, or antigen-binding fragment thereof, of the invention has a $K_D$ of at least 1 x $10^{-7}$ M. In other embodiments, the antibody, or antigen-binding fragment thereof, of the invention has a $K_D$ of at least 1 x $10^{-8}$ M.

In certain embodiments, the antibody is an IgG1 isotype. In other embodiments, the antibody is an IgG4 isotype.

In certain embodiments, the antibody, or antigen-binding fragment, described herein is recombinant. In certain embodiments, the antibody, or antigen-binding fragment, described herein is a human antibody, or antigen binding fragment of an antibody.

The invention also provides pharmaceutical compositions comprising an effective amount of an anti-TIM3 antibodies or fragments disclosed herein, and a pharmaceutically acceptable carrier.

In certain embodiments, the broad spectrum of mammalian cancers to be treated is selected from the group consisting of ovarian, colon, breast, lung cancers, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, and mast cell derived tumors. In other embodiments, the autoimmune disease or inflammatory disease is selected from the group consisting of intestinal mucosal inflammation, wasting disease associated with colitis, multiple sclerosis, systemic lupus erythematosus, viral infections, rheumatoid arthritis, osteoarthritis, psoriasis, Cohn's disease, and inflammatory bowel disease.

**Description of the Drawings**

Figure 1 graphically depicts functional activity of the listed anti-TIM3 antibodies by their ability to augment IL-2 production. cIg is the control immunoglobulin and is a non-specific isotype matched irrelevant (*i.e.,* does not bind to TIM3) antibody.

Figure 2A graphically depicts functional activity of the listed anti-TIM3 antibodies by their ability to augment cell activation. cIg is the control immunoglobulin and is a non-specific isotype matched irrelevant (*i.e.,* does not bind to TIM3) antibody

Figure 2B graphically depicts normalization of the results described in Figure 2A. As a measure of the magnitude of the cell activation enhancement shown in Figure 2A, cell activation was normalized relative to the cultures receiving that of the medium control (Figure 2B).

Figure 3A graphically depicts the ability of TIM3 ligation to modulate T cell activation by stimulating T cells with immobilized antibodies in the absence of monocytes. cIg is the control immunoglobulin and is a non-specific isotype matched irrelevant (*i.e.,* does not bind to TIM3) antibody

Figure 3B graphically depicts results of Figure 3A normalized with respect to the medium control. The data shown in Figure 3B reveal that antibody TIA1 exhibited significant TIM3 agonistic activity whereas antibody TIG3 did not.

## Detailed Description

Definitions

The terms "peptide," "polypeptide" and "protein" each refers to a molecule comprising two or more amino acid residues joined to each other by peptide bonds. These terms encompass, *e.g.*, native and artificial proteins, protein fragments and polypeptide analogs (such as muteins, variants, and fusion proteins) of a protein sequence as well as post-translationally, or otherwise covalently or non-covalently, modified proteins. A peptide, polypeptide, or protein may be monomeric or polymeric.

A "variant" of a polypeptide (for example, a variant of an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Disclosed variants include, for example, fusion proteins.

A "derivative" of a polypeptide is a polypeptide (*e.g.*, an antibody) that has been chemically modified, *e.g.*, via conjugation to another chemical moiety (such as, for example, polyethylene glycol or albumin, *e.g.*, human serum albumin), phosphorylation, and glycosylation. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below.

An "antigen binding protein" is a protein comprising a portion that binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a conformation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins include antibodies, antibody fragments (*e.g.*, an antigen binding portion of an antibody), antibody derivatives, and antibody analogs. The antigen binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. See, for example, Korndorfer et al., 2003, *Proteins: Structure, Function, and Bioinformatics*, Volume 53, Issue 1:121-129; Roque et al., 2004, *Biotechnol. Prog.* 20:639-654. In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronection components as a scaffold.

An antigen binding protein can have, for example, the structure of an immunoglobulin. An "immunoglobulin" is a tetrameric molecule composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa or lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Preferably, the anti-EGFR antibodies disclosed herein are characterized by their variable domain region sequences in the heavy $V_H$ and light $V_L$ amino acid sequences. The preferred antibody is A6 which is a kappa IgG antibody. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

The variable regions of immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat et al. in Sequences of Proteins of Immunological Interest, 5$^{th}$ Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. Other numbering systems for the amino acids in immunoglobulin chains include IMGT.RTM. (international ImMunoGeneTics information system; Lefranc et al, *Dev. Comp. Immunol.* 29:185-203; 2005) and AHo (Honegger and Pluckthun, *J. Mol. Biol.* 309(3):657-670; 2001).

An "antibody" refers to an intact immunoglobulin or to an antigen binding portion thereof that competes with the intact antibody for specific binding, unless otherwise specified. In one embodiment, an antibody comprises a heavy chain comprising a heavy chain variable domain and heavy chain constant regions $C_{H1}$, $C_{H2}$ and $C_{H3}$, and comprises a light chain comprising a light chain variable domain and a light chain constant region ($C_L$). The heavy and light chain variable domain sequences may be selected from those described herein in SEQ ID Nos: 1 to 70.

Antigen binding portions of an antibody may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen binding portions include, *inter alia*, Fab, Fab', $F(ab')_2$, Fv, domain antibodies (dAbs), and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies, triabodies, tetrabodies, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

In certain embodiments, antibodies can be obtained from sources such as serum or plasma that contain immunoglobulins having varied antigenic specificity. If such antibodies are subjected to affinity purification, they can be enriched for a particular antigenic specificity. Such enriched preparations of antibodies usually are made of less than about 10% antibody having specific binding activity for the particular antigen. Subjecting these preparations to several rounds of affinity purification can increase the proportion of antibody having specific binding activity for the antigen. Antibodies prepared in this manner are often referred to as "monospecific."

The term “monospecific”, as used herein, refers to an antibody that displays an affinity for one particular epitope. Monospecific antibody preparations can be made up of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, or 99.9% antibody having specific binding activity for the particular antigen.

An "antibody fragment" or “antigen binding fragment of an antibody” comprises a portion of an intact antibody, and preferably comprises the antibody antigen binding or variable domains. Examples of an antibody fragment include a Fab, an Fab', an F(ab')2, an Fv fragment, and a linear antibody

A Fab fragment is a monovalent fragment having the $V_L$, $V_H$, $C_L$ and $C_{H1}$ domains; a $F(ab')_2$ fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the $V_H$ and $C_{H1}$ domains; an Fv fragment has the $V_L$ and $V_H$ domains of a single arm of an antibody; and a dAb fragment has a $V_H$ domain, a $V_L$ domain, or an antigen-binding fragment of a $V_H$ or $V_L$ domain (U.S. Patents 6,846,634; 6,696,245, US App. Pub.20/0202512; 2004/0202995; 2004/0038291; 2004/0009507;20 03/0039958, and Ward et al., *Nature* 341:544-546, 1989).

A single-chain antibody (scFv) is an antibody in which a $V_L$ and a $V_H$ region are joined via a linker (*e.g.*, a synthetic sequence of amino acid residues) to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on

itself and form a monovalent antigen binding site (see, e.g., Bird et al., 1988, *Science* 242:423-26 and Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-83).

Diabodies are bivalent antibodies comprising two polypeptide chains, wherein each polypeptide chain comprises $V_H$ and $V_L$ domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, e.g., Holliger et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:6444-48, and Poljak et al., 1994, *Structure* 2:1121-23). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.

An antigen binding protein, such as an antibody, may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a "bispecific" or "bifunctional" antibody has two different binding sites.

The term "human antibody" includes antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and constant domains of the antibody are derived from human immunoglobulin sequences (referred to as a “fully human antibody”). These antibodies may be prepared in a variety of ways, examples of which are described below, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes. In a preferred embodiment, a fully human antibody is made using recombinant methods such that the glycosylation pattern of the antibody is different than an antibody having the same sequence if it were to exist in nature.

A “humanized antibody” has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-

human species antibody are mutated to produce the humanized antibody. In another embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies may be found in U.S. Patents 6,054,297, 5,886,152 and 5,877,293.

The term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In one embodiment, one or more of the CDRs are derived from a human anti-TIM3 antibody. In another embodiment, all of the CDRs are derived from a human anti-TIM3 antibody. In another embodiment, the CDRs from more than one human anti-TIM3 antibodies are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first human anti-PAR-2 antibody, a CDR2 and a CDR3 from the light chain of a second human anti-TIM3 antibody, and the CDRs from the heavy chain from a third anti-TIM3 antibody. Other combinations are possible.

Further, the framework regions may be derived from one of the same anti-TIM3 antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. In one example of a chimeric antibody, a portion of the heavy and/or light chain is identical with, homologous to, or derived from an antibody from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with, homologous to, or derived from an antibody (-ies) from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies that exhibit the desired biological activity (*i.e.*, the ability to specifically bind TIM3).

An “agonist antibody” as used herein, is an antibody that induces or increases the biological activity of an antigen (for example, TIM3) to which the antibody binds. In one embodiment, the antibodies of the invention are agonist anti-TIM3 antibodies.

A "CDR grafted antibody" is an antibody comprising one or more CDRs derived from an antibody of a particular species or isotype and the framework of another antibody of the same or different species or isotype.

A "multi-specific antibody" is an antibody that recognizes more than one epitope on one or more antigens. A subclass of this type of antibody is a "bi-specific antibody" which recognizes two distinct epitopes on the same or different antigens.

An antigen binding protein "specifically binds" to an antigen (*e.g.*, TIM3) if it binds to the antigen with a dissociation constant of 1 nanomolar or less.

An "antigen binding domain, "antigen binding region," or "antigen binding site" is a portion of an antigen binding protein that contains amino acid residues (or other moieties) that interact with an antigen and contribute to the antigen binding protein's specificity and affinity for the antigen. For an antibody that specifically binds to its antigen, this will include at least part of at least one of its CDR domains.

The term "Fc polypeptide" includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

An "epitope" is the portion of a molecule that is bound by an antigen binding protein (*e.g.*, by an antibody). An epitope can comprise non-contiguous portions of the molecule (*e.g.*, in a polypeptide, amino acid residues that are not contiguous in the polypeptide's primary sequence but that, in the context of the polypeptide's tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein).

The “percent identity” or "percent homology" of two polynucleotide or two polypeptide sequences is determined by comparing the sequences using the GAP computer program (a part of the GCG Wisconsin Package, version 10.3 (Accelrys, San Diego, Calif.)) using its default parameters.

The terms "polynucleotide," "oligonucleotide" and "nucleic acid" are used interchangeably throughout and include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs (*e.g.*, peptide nucleic acids and non-naturally occurring nucleotide analogs), and hybrids thereof. The nucleic acid molecule can be single-stranded or double-stranded. In one

embodiment, the nucleic acid molecules of the invention comprise a contiguous open reading frame encoding an antibody, or a fragment, derivative, mutein, or variant thereof.

Two single-stranded polynucleotides are "the complement" of each other if their sequences can be aligned in an anti-parallel orientation such that every nucleotide in one polynucleotide is opposite its complementary nucleotide in the other polynucleotide, without the introduction of gaps, and without unpaired nucleotides at the 5' or the 3' end of either sequence. A polynucleotide is "complementary" to another polynucleotide if the two polynucleotides can hybridize to one another under moderately stringent conditions. Thus, a polynucleotide can be complementary to another polynucleotide without being its complement.

A "vector" is a nucleic acid that can be used to introduce another nucleic acid linked to it into a cell. One type of vector is a "plasmid," which refers to a linear or circular double stranded DNA molecule into which additional nucleic acid segments can be ligated. Another type of vector is a viral vector (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), wherein additional DNA segments can be introduced into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors comprising a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. An "expression vector" is a type of vector that can direct the expression of a chosen polynucleotide.

A nucleotide sequence is "operably linked" to a regulatory sequence if the regulatory sequence affects the expression (*e.g.*, the level, timing, or location of expression) of the nucleotide sequence. A "regulatory sequence" is a nucleic acid that affects the expression (*e.g.*, the level, timing, or location of expression) of a nucleic acid to which it is operably linked. The regulatory sequence can, for example, exert its effects directly on the regulated nucleic acid, or through the action of one or more other molecules (*e.g.*, polypeptides that bind to the regulatory sequence and/or the nucleic acid). Examples of regulatory sequences include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Further examples of regulatory sequences are described in, for example, Goeddel, 1990, Gene Expression Technology: *Methods in Enzymology* 185, Academic Press, San Diego, Calif. and Baron et al., 1995, *Nucleic Acids Res.* 23:3605-06.

A "host cell" is a cell that can be used to express a nucleic acid, *e.g.*, a nucleic acid of the invention. A host cell can be a prokaryote, for example, *E. coli*, or it can be a eukaryote, for example, a single-celled eukaryote (*e.g.*, a yeast or other fungus), a plant cell (*e.g.*, a tobacco or tomato plant cell), an animal cell (*e.g.*, a human cell, a monkey cell, a hamster cell, a rat cell, a mouse cell, or an insect cell) or a hybridoma. Examples of host cells include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (see Gluzman et al., 1981, *Cell* 23:175), L cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells or their derivatives such as Veggie CHO and related cell lines which grow in serum-free media (see Rasmussen et al., 1998, *Cytotechnology* 28:31) or CHO strain DX-B11, which is deficient in DHFR (see Urlaub et al., 1980, *Proc. Natl. Acad. Sci. USA* 77:4216-20), HeLa cells, BHK (ATCC CRL 10) cell lines, the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) (see McMahan et al., 1991, *EMBO J.* 10:2821), human embryonic kidney cells such as 293,293 EBNA or MSR 293, human epidermal A431 cells, human Colo205 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HL-60, U937, HaK or Jurkat cells. In one embodiment, a host cell is a mammalian host cell, but is not a human host cell. Typically, a host cell is a cultured cell that can be transformed or transfected with a polypeptide-encoding nucleic acid, which can then be expressed in the host cell. The phrase "recombinant host cell" can be used to denote a host cell that has been transformed or transfected with a nucleic acid to be expressed. A host cell also can be a cell that comprises the nucleic acid but does not express it at a desired level unless a regulatory sequence is introduced into the host cell such that it becomes operably linked with the nucleic acid. It is understood that the term host cell refers not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to, e.g., mutation or environmental influence, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The term “recombinant antibody” refers to an antibody that is expressed from a cell or cell line transfected with an expression vector (or possibly more than one expression vector) comprising the coding sequence of the antibody (or fragment thereof), where said antibody coding sequence is not naturally associated with the cell. In one embodiment, a recombinant antibody has a glycosylation pattern that is different than the glycosylation pattern of an antibody having the same sequence if it were to exist in nature. In one embodiment, a

recombinant antibody is expressed in a mammalian host cell which is not a human host cell. Notably, individual mammalian host cells have unique glycosylation patterns.

The term "effective amount" as used herein, refers to that amount of an antibody, or an antigen binding portion thereof, that binds TIM3, which is sufficient to effect treatment of a disease when administered to a subject. Therapeutically effective amounts of antibodies provided herein will vary depending upon the relative activity of the antibodies and depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

The term "isolated" refers to a protein (*e.g.*, an antibody) that is substantially free of other cellular material. In one embodiment, an isolated antibody is substantially free of other proteins from the same species. In one embodiment, an isolated antibody is expressed by a cell from a different species and is substantially free of other proteins from the different species. A protein may be rendered substantially free of naturally associated components (or components associated with the cellular expression system used to produce the antibody) by isolation, using protein purification techniques well known in the art. In one embodiment, the antibodies, or antigen binding fragments, of the invention are isolated.

TIM3 Antigen Binding Proteins

The present invention pertains to TIM3 binding proteins, particularly anti-TIM3 antibodies, or antigen-binding portions thereof, that bind TIM3, *e.g.,* human TIM3, and uses thereof. Various aspects of the invention relate to antibodies and antibody fragments, pharmaceutical compositions, nucleic acids, recombinant expression vectors, and host cells for making such antibodies and fragments. Methods of using the antibodies of the invention to detect human TIM3, to increase TIM3 activity or activate TIM3, either *in vitro* or *in vivo*, and to prevent or treat disorders such as cancer are also encompassed by the invention.

As described in Table 1 below, included in the invention are novel antibody heavy and light chain variable domains that are specific to TIM3. In one embodiment, the invention provides an anti-TIM3 antibody, or an antigen-binding fragment thereof, that comprises a heavy chain having a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31,

SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69, and an anti-TIM3 antibody, or an antigen-binding fragment thereof, that comprises a light chain having a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70. In one embodiment, the invention provides an anti-TIM3 antibody, or an antigen-binding fragment thereof, that comprises a light chain having a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70; and a heavy chain having a variable domain comprising an amino acid sequence as set forth in any one of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69.

Complementarity determining regions (CDRs) are known as hypervariable regions both in the light chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework (FR). Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody may be identified using

methods known in the art, including, for example, the system described by Kabat et al. *supra*; Lefranc et al., *supra* and/or Honegger and Pluckthun, *supra*. Also familiar to those in the art is the numbering system described in Kabat *et al.* (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, Va.). In this regard Kabat *et al.* defined a numbering system for variable domain sequences that is applicable to any antibody. One of ordinary skill in the art can unambiguously assign this system of "Kabat numbering" to any variable domain amino acid sequence, without reliance on any experimental data beyond the sequence itself.

In certain embodiments, the present invention provides an anti-TIM3 antibody comprising the CDRs of the heavy and light chain variable domains described in Table 1 (SEQ ID Nos: 1 to 70). For example, the invention provides an anti-TIM3 antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region having the CDRs described in an amino acid sequence as set forth in any one of SEQ ID Nos: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 63, 65, 67 and 69. In one embodiment, the invention provides an anti-TIM3 antibody, or antigen-binding fragment thereof, comprising a light chain variable region having the CDRs described in an amino acid sequence as set forth in any one of SEQ ID Nos:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68 and 70. In one embodiment, the invention provides an anti-TIM3 antibody, or antigen-binding fragment thereof, comprising a light chain variable region having the CDRs described in an amino acid sequence as set forth in any one of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68 and 70; and a heavy chain variable region having the CDRs described in an amino acid sequence as set forth in any one of SEQ ID Nos: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 63, 65, 67 and 69.

One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein.

An antigen binding protein may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest, *i.e.,* TIM3.

In one embodiment, the present disclosure provides a fully human antibody of an IgG class that binds to a TIM3 epitope with a binding affinity of at least $10^{-6}$M, which has a heavy

chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, and combinations thereof.

In one embodiment, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting SEQ ID NO. 1/SEQ ID NO. 2 (called TIA1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called TIA5 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called TIA6 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called TIA7 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called TIA9 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called TIA10 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called TIA11 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called TIB1 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called TIB2 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called TIC1 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called TIC2 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called TIC4 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called TIC5 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called TIC8 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called TIC10 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called TIC11 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called TID1 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called TID6 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called TID10 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called TID12 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called TIE2 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called TIE3 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called TIE7 herein), SEQ ID NO.

47/SEQ ID NO. 48 (called TIE9 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called TIF3 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called TIF7 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called TIF8 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called TIG1 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called TIG3 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called TIG6 herein), SEQ ID NO. 7/SEQ ID NO. 62 (called TIG9 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called TIG10 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called TIH1 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called TIH5 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called TIH11 herein), and combinations thereof.

In one embodiment, the invention provides an anti-TIM3 antibody, or an antigen-binding fragment thereof, comprising a heavy chain comprising a CDR3 domain as set forth in any one of SEQ ID Nos: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 63, 65, 67 and 69, and comprising a heavy chain variable domain comprising an amino acid sequence that has at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence as set forth in any one of SEQ ID Nos: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 63, 65, 67 and 69. In one embodiment, the invention provides an anti-TIM3 antibody, or an antigen-binding fragment thereof, comprising a light chain comprising a CDR3 domain as set forth in any one of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68 and 70, and having a light chain variable domain comprising an amino acid sequence that has at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence as set forth in any one of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68 and 70. Thus, in certain embodiments, the CDR3 domain is held constant, while variability may be introduced into the remaining CDRs and/or framework regions of the heavy and/or light chains, while the antibody, or antigen binding fragment thereof, retains the ability to bind to TIM3 and retains the functional characteristics, *e.g.,* binding affinity, of the parent.

In one embodiment, the substitutions made within a heavy or light chain that is at least 95% identical (or at least 96% identical, or at least 97% identical, or at least 98% identical, or at least 99% identical) are conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not

substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, e.g., Pearson (1994) Methods Mol. Biol. 24: 307-331, herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate, and (7) sulfur-containing side chains are cysteine and methionine.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having the antigen binding regions of any of the antibodies described in Table 1.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIA1. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 1, and a light chain variable domain sequence as set forth in SEQ ID NO: 2. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 1, and a light chain variable domain comprising the CDRs of SEQ ID NO:2. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 1, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 2. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIA5. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 3, and a light

chain variable domain sequence as set forth in SEQ ID NO: 4. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 3, and a light chain variable domain comprising the CDRs of SEQ ID NO: 4. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 3, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 4. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIA6. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 5, and a light chain variable domain sequence as set forth in SEQ ID NO: 6. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 5, and a light chain variable domain comprising the CDRs of SEQ ID NO: 6. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 5, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 6. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIA7. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 7, and a light chain variable domain sequence as set forth in SEQ ID NO: 8. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 7, and a light chain variable domain comprising the CDRs of SEQ ID

NO: 8. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 7, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 8. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIA9. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 9, and a light chain variable domain sequence as set forth in SEQ ID NO: 10. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 9, and a light chain variable domain comprising the CDRs of SEQ ID NO: 10. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 9, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 10. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIA10. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 11, and a light chain variable domain sequence as set forth in SEQ ID NO: 12. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 11, and a light chain variable domain comprising the CDRs of SEQ ID NO: 12. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least

98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 11, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO:12. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIA11. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 13, and a light chain variable domain sequence as set forth in SEQ ID NO: 14. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 13, and a light chain variable domain comprising the CDRs of SEQ ID NO: 14. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 13, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 14. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIB1. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 15, and a light chain variable domain sequence as set forth in SEQ ID NO: 16. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 15, and a light chain variable domain comprising the CDRs of SEQ ID NO: 16. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 15, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99%

identical to the sequence set forth in SEQ ID NO: 16. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIB2. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 17, and a light chain variable domain sequence as set forth in SEQ ID NO: 18. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 17, and a light chain variable domain comprising the CDRs of SEQ ID NO: 18. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 17, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 18. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIC1. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 19, and a light chain variable domain sequence as set forth in SEQ ID NO: 20. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 19, and a light chain variable domain comprising the CDRs of SEQ ID NO: 20. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 19, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 20. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIC2. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 21, and a light chain variable domain sequence as set forth in SEQ ID NO: 22. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 21, and a light chain variable domain comprising the CDRs of SEQ ID NO: 22. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 21, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 22. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIC4. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 23, and a light chain variable domain sequence as set forth in SEQ ID NO: 24. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 23, and a light chain variable domain comprising the CDRs of SEQ ID NO: 24. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 23, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 24. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIC5. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof,

comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 25, and a light chain variable domain sequence as set forth in SEQ ID NO: 26. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 25, and a light chain variable domain comprising the CDRs of SEQ ID NO: 26. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 25, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 26. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIC8. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 27, and a light chain variable domain sequence as set forth in SEQ ID NO: 28. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 27, and a light chain variable domain comprising the CDRs of SEQ ID NO: 28. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 27, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 28. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIC10. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 29, and a light chain variable domain sequence as set forth in SEQ ID NO: 30. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the

CDRs of SEQ ID NO: 29, and a light chain variable domain comprising the CDRs of SEQ ID NO: 30. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 29, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 30. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIC11. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 31, and a light chain variable domain sequence as set forth in SEQ ID NO: 32. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 31, and a light chain variable domain comprising the CDRs of SEQ ID NO: 32. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 31, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 32. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TID1. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 33, and a light chain variable domain sequence as set forth in SEQ ID NO: 34. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 33, and a light chain variable domain comprising the CDRs of SEQ ID NO: 34. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid

sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 33, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 34. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TID6. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 35, and a light chain variable domain sequence as set forth in SEQ ID NO: 36. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 35, and a light chain variable domain comprising the CDRs of SEQ ID NO: 36. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 35, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 36. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TID10. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 37, and a light chain variable domain sequence as set forth in SEQ ID NO: 38. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 37, and a light chain variable domain comprising the CDRs of SEQ ID NO: 38. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 37, and comprises a light chain variable region having an amino acid sequence that is at least 95%

identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 38. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TID12. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 39, and a light chain variable domain sequence as set forth in SEQ ID NO: 40. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 39, and a light chain variable domain comprising the CDRs of SEQ ID NO: 40. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 39, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 40. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIE2. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 41, and a light chain variable domain sequence as set forth in SEQ ID NO: 42. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 41, and a light chain variable domain comprising the CDRs of SEQ ID NO: 42. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 41, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 42. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIE3. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 43, and a light chain variable domain sequence as set forth in SEQ ID NO: 44. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 43, and a light chain variable domain comprising the CDRs of SEQ ID NO: 44. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 43, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 44. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIE7. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 45, and a light chain variable domain sequence as set forth in SEQ ID NO: 46. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 45, and a light chain variable domain comprising the CDRs of SEQ ID NO: 46. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 45, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 46. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIE9. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof,

comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 47, and a light chain variable domain sequence as set forth in SEQ ID NO: 48. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 47, and a light chain variable domain comprising the CDRs of SEQ ID NO: 48. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 47, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 48. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIF3. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 49, and a light chain variable domain sequence as set forth in SEQ ID NO: 50. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 49, and a light chain variable domain comprising the CDRs of SEQ ID NO: 50. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 49, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 50. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIF7. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 51, and a light chain variable domain sequence as set forth in SEQ ID NO: 52. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the

CDRs of SEQ ID NO: 51, and a light chain variable domain comprising the CDRs of SEQ ID NO: 52. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 51, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 52. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIF8. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 53, and a light chain variable domain sequence as set forth in SEQ ID NO: 54. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 53, and a light chain variable domain comprising the CDRs of SEQ ID NO: 54. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 53, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 54. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIG1. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 55, and a light chain variable domain sequence as set forth in SEQ ID NO: 56. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 55, and a light chain variable domain comprising the CDRs of SEQ ID NO: 56. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid

sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 55, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 56. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIG3. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 57, and a light chain variable domain sequence as set forth in SEQ ID NO: 58. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 57, and a light chain variable domain comprising the CDRs of SEQ ID NO: 58. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 57, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 58. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIG6. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 59, and a light chain variable domain sequence as set forth in SEQ ID NO: 60. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 59, and a light chain variable domain comprising the CDRs of SEQ ID NO: 60. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 59, and comprises a light chain variable region having an amino acid sequence that is at least 95%

identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 60. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIG9. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 7, and a light chain variable domain sequence as set forth in SEQ ID NO: 62. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 7, and a light chain variable domain comprising the CDRs of SEQ ID NO: 62. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 7, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 62. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIG10. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 63, and a light chain variable domain sequence as set forth in SEQ ID NO: 64. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 63, and a light chain variable domain comprising the CDRs of SEQ ID NO: 64. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 63, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 64. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIH11. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 65, and a light chain variable domain sequence as set forth in SEQ ID NO: 66. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 65, and a light chain variable domain comprising the CDRs of SEQ ID NO: 66. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 65, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 66. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIH5. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 67, and a light chain variable domain sequence as set forth in SEQ ID NO: 68. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 67, and a light chain variable domain comprising the CDRs of SEQ ID NO: 68. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 67, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 68. The antibody may further be an IgG1 or an IgG4 isotype.

In one embodiment, the present invention is directed to an antibody, or an antigen binding fragment thereof, having antigen binding regions of antibody TIH11. In one embodiment, the invention provides an antibody, or antigen-binding fragment thereof,

comprising a heavy chain variable domain sequence as set forth in SEQ ID NO: 69, and a light chain variable domain sequence as set forth in SEQ ID NO: 70. In one embodiment, the invention is directed to an antibody having a heavy chain variable domain comprising the CDRs of SEQ ID NO: 69, and a light chain variable domain comprising the CDRs of SEQ ID NO: 70. In one embodiment, the invention features an isolated human antibody, or antigen-binding fragment thereof, that comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 69, and comprises a light chain variable region having an amino acid sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical to the sequence set forth in SEQ ID NO: 70. The antibody may further be an IgG1 or an IgG4 isotype.

As described in Table 1, the heavy chain sequences SEQ ID NO: 29 and SEQ ID NO: 41 share at least 95% identity to each other.

As described in Table 1, the light chain sequences SEQ ID NO: 38 and SEQ ID NO: 46 share at least 95% identity to each other.

Antigen binding proteins (*e.g.*, antibodies, antibody fragments, antibody derivatives, antibody muteins, and antibody variants) are polypeptides that bind to TIM3.

Antigen-binding fragments of antigen binding proteins of the invention may be produced by conventional techniques. Examples of such fragments include, but are not limited to, Fab and $F(ab')_2$ fragments.

Single chain antibodies may be formed by linking heavy and light chain variable domain (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) have been prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides ($V_L$ and $V_H$). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (*e.g.*, dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt et al., 1997, *Prot. Eng.* 10:423; Kortt et al., 2001, *Biomol. Eng.* 18:95-108). By combining different $V_L$ and $V_H$-comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum et al., 2001, *Biomol. Eng.* 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Patent 4,946,778; Bird, 1988, *Science*

242:423; Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879; Ward et al., 1989, *Nature* 334:544, de Graaf et al., 2002, *Methods Mol. Biol.* 178:379-87.

In certain embodiments, the present disclosure provides a fully human antibody Fab fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, wherein the heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, and combinations thereof. Preferably, the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO.

42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 7/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, and combinations thereof.

In one embodiment, the present disclosure provides a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, wherein the heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, SEQ ID NO. 69, and that has a light chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to the amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, SEQ ID NO. 70, and combinations thereof. Preferably, the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO.

15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 7/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, and combinations thereof.

Techniques are known for deriving an antibody of a different subclass or isotype from an antibody of interest, *i.e.*, subclass switching. Thus, IgG antibodies may be derived from an IgM antibody, for example, and vice versa. Such techniques allow the preparation of new antibodies that possess the antigen-binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques may be employed. Cloned DNA encoding particular antibody polypeptides may be employed in such procedures, *e.g.*, DNA encoding the constant domain of an antibody of the desired isotype (Lantto et al., 2002, *Methods Mol. Biol.* 178:303-16). Moreover, if an IgG4 is desired, it may also be desired to introduce a point mutation (CPSC->CPPC) (SEQ ID Nos. 71 and 72, respectively) in the hinge region (Bloom et al., 1997, *Protein Science* 6:407) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies. In one embodiment, the antibody of the invention is a human IgG1 antibody. In one embodiment, the antibody of the invention is a human IgG4 antibody.

The present disclosure provides a number of antibodies structurally characterized by the amino acid sequences of their variable domain regions. However, the amino acid sequences can undergo some changes while retaining their high degree of binding to their specific targets. More specifically, many amino acids in the variable domain region can be changed with conservative substitutions and it is predictable that the binding characteristics of the resulting antibody will not differ from the binding characteristics of the wild type antibody sequence. There are many amino acids in an antibody variable domain that do not directly interact with the antigen or impact antigen binding and are not critical for

determining antibody structure. For example, a predicted nonessential amino acid residue in any of the disclosed antibodies is preferably replaced with another amino acid residue from the same class. Methods of identifying amino acid conservative substitutions which do not eliminate antigen binding are well- known in the art (see, e.g., Brummell et al., *Biochem.* 32: 1180-1187 (1993); Kobayashi et al. *Protein Eng.* 12(10):879-884 (1999); and Burks et al. *Proc. Natl. Acad. Sci. USA* 94:412-417 (1997)). Near et al. *Mol. Immunol.* 30:369-377, 1993 explains how to impact or not impact binding through site-directed mutagenesis. Near et al. only mutated residues that they thought had a high probability of changing antigen binding. Most had a modest or negative effect on binding affinity (Near et al. Table 3) and binding to different forms of digoxin (Near et al. Table 2). Thus, the invention also includes, in certain embodiments, variable amino acid sequences having at least 95% identity to those sequences disclosed herein.

In certain embodiments, an antibody, or antigen-binding fragment thereof, provided herein has a dissociation constant ($K_D$) of 1 x $10^{-6}$ M or less; 5 x $10^{-7}$ M or less' 1 x $10^{-7}$ M or less; 5 x $10^{-8}$ M or less; 1 x $10^{-8}$ M or less; 5 x $10^{-9}$ M or less; or 1 x $10^{-9}$ M or less. In one embodiment, the antibody, or antigen-binding fragment thereof, of the invention as a $K_D$ from 1 x $10^{-7}$ M to 1 x $10^{-10}$ M. In one embodiment, the antibody, or antigen-binding fragment thereof, of the invention as a $K_D$ from 1 x $10^{-8}$ M to 1 x $10^{-10}$ M. In one embodiment, the affinity of the antibody is determined using Octet methods.

Those of ordinary skill in the art will appreciate standard methods known for determining the $K_D$ of an antibody, or fragment thereof. For example, in one embodiment, $K_D$ is measured by a radiolabeled antigen binding assay (RIA). In one embodiment, an RIA is performed with the Fab version of an antibody of interest and its antigen, *e.g.,* human TIM3. For example, solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of ($^{125}$I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, e.g., Chen *et al.*, J. Mol. Biol. 293:865-881(1999)). According to another embodiment, $K_D$ is measured using a BIACORE surface plasmon resonance assay. The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE system (Biacore Life Sciences division of GE Healthcare, Piscataway, NJ).

In particular embodiments, antigen binding proteins of the present invention have a binding affinity ($K_a$) for TIM3 of at least $10^6$ $M^{-1}$. In other embodiments, the antigen binding proteins exhibit a $K_a$ of at least $10^7$ $M^{-1}$, at least $10^8$ $M^{-1}$, at least $10^9$ $M^{-1}$, or at least $10^{10}$ $M^{-1}$. In another embodiment, the antigen binding protein exhibits a $K_a$ substantially the same as that of an antibody described herein in the Examples.

In another embodiment, the present disclosure provides an antigen binding protein that has a low dissociation rate from TIM3. In one embodiment, the antigen binding protein has a $K_{off}$ of 1 X $10^{-4}$ to $^{-1}$ $sec^{-1}$ or lower. In another embodiment, the $K_{off}$ is 5 X $10^{-5}$ to $^{-1}$ $sec^{-1}$ or lower. In another embodiment, the $K_{off}$ is substantially the same as an antibody described herein. In another embodiment, the antigen binding protein binds to TIM3 with substantially the same $K_{off}$ as an antibody described herein.

In another aspect, the present disclosure provides an antigen binding protein that induces or increases activity of TIM3.

In another aspect, the present disclosure provides an antigen binding protein that binds to TIM3 expressed on the surface of a cell and, when so bound, induces or increases TIM3 signaling activity in the cell without causing a significant reduction in the amount of TIM3 on the surface of the cell. Any method for determining or estimating the amount of TIM3 on the surface and/or in the interior of the cell can be used. In other embodiments, binding of the antigen binding protein to the TIM3-expressing cell causes less than about 75%, 50%, 40%, 30%, 20%, 15%, 10%, 5%, 1%, or 0.1% of the cell-surface TIM3 to be internalized.

In another aspect, the present disclosure provides an antigen binding protein having a half-life of at least one day *in vitro* or *in vivo* (*e.g.*, when administered to a human subject). In one embodiment, the antigen binding protein has a half-life of at least three days. In another embodiment, the antigen binding protein has a half-life of four days or longer. In another embodiment, the antigen binding protein has a half-life of eight days or longer. In another embodiment, the antigen binding protein is derivatized or modified such that it has a longer half-life as compared to the underivatized or unmodified antigen binding protein. In another embodiment, the antigen binding protein contains one or more point mutations to increase serum half life, such as described in WO00/09560, incorporated by reference herein.

The present disclosure further provides multi-specific antigen binding proteins, for example, bispecific antigen binding protein, *e.g.*, antigen binding protein that bind to two different epitopes of TIM3, or to an epitope of TIM3 and an epitope of another molecule, via

two different antigen binding sites or regions. Moreover, bispecific antigen binding protein as disclosed herein can comprise a TIM3 binding site from one of the herein-described antibodies and a second TIM3 binding region from another of the herein-described antibodies, including those described herein by reference to other publications. Alternatively, a bispecific antigen binding protein may comprise an antigen binding site from one of the herein described antibodies and a second antigen binding site from another TIM3 antibody that is known in the art, or from an antibody that is prepared by known methods or the methods described herein.

Numerous methods of preparing bispecific antibodies are known in the art. Such methods include the use of hybrid-hybridomas as described by Milstein et al., 1983, *Nature* 305:537, and chemical coupling of antibody fragments (Brennan et al., 1985, *Science* 229:81; Glennie et al., 1987, *J. Immunol.* 139:2367; U.S. Patent 6,010,902). Moreover, bispecific antibodies can be produced via recombinant means, for example by using leucine zipper moieties (*i.e.*, from the *Fos* and *Jun* proteins, which preferentially form heterodimers; Kostelny et al., 1992, *J. Immunol.* 148:1547) or other lock and key interactive domain structures as described in U.S. Patent 5,582,996. Additional useful techniques include those described in U.S. Patents 5,959,083; and 5,807,706.

In another aspect, the antigen binding protein comprises a derivative of an antibody. The derivatized antibody can comprise any molecule or substance that imparts a desired property to the antibody, such as increased half-life in a particular use. The derivatized antibody can comprise, for example, a detectable (or labeling) moiety (*e.g.*, a radioactive, colorimetric, antigenic or enzymatic molecule, a detectable bead (such as a magnetic or electrodense (*e.g.*, gold) bead), or a molecule that binds to another molecule (*e.g.*, biotin or streptavidin), a therapeutic or diagnostic moiety (*e.g.*, a radioactive, cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antibody for a particular use (*e.g.*, administration to a subject, such as a human subject, or other *in vivo* or *in vitro* uses). Examples of molecules that can be used to derivatize an antibody include albumin (*e.g.*, human serum albumin) and polyethylene glycol (PEG). Albumin-linked and PEGylated derivatives of antibodies can be prepared using techniques well known in the art. In one embodiment, the antibody is conjugated or otherwise linked to transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyrrolidone),

polyethylene glycols, propropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols.

Oligomers that contain one or more antigen binding proteins may be employed as TIM3 agonists. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers, or higher oligomers. Oligomers comprising two or more antigen binding protein are contemplated for use, with one example being a homodimer. Other oligomers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, etc.

One embodiment is directed to oligomers comprising multiple antigen binding proteins joined via covalent or non-covalent interactions between peptide moieties fused to the antigen binding proteins. Such peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of antigen binding proteins attached thereto, as described in more detail below.

In particular embodiments, the oligomers comprise from two to four antigen binding proteins. The antigen binding proteins of the oligomer may be in any form, such as any of the forms described above, *e.g.*, variants or fragments. Preferably, the oligomers comprise antigen binding proteins that have TIM3 binding activity.

In one embodiment, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of Fusion Proteins Comprising Certain Heterologous Polypeptides Fused to Various Portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:10535; Byrn et al., 1990, *Nature* 344:677; and Hollenbaugh et al., 1992 "Construction of Immunoglobulin Fusion Proteins", in *Current Protocols in Immunology*, Suppl. 4, pages 10.19.1-10.19.11.

One embodiment is directed to a dimer comprising two fusion proteins created by fusing a TIM3 binding fragment of an anti-TIM3 antibody to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer.

Another method for preparing oligomeric antigen binding proteins involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the

proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., 1988, *Science* 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe et al., 1994, *FEBS Letters* 344:191. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow et al., 1994, *Semin. Immunol.* 6:267-78. In one approach, recombinant fusion proteins comprising an anti-TIM3 antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric anti-TIM3 antibody fragments or derivatives that form are recovered from the culture supernatant.

Antigen binding proteins directed against TIM3 can be used, for example, in assays to detect the presence of TIM3 polypeptides, either *in vitro* or *in vivo*. The antigen binding proteins also may be employed in purifying TIM3 proteins by immunoaffinity chromatography. Antigen binding proteins can be used in the methods disclosed herein. Such antigen binding proteins that function as TIM3 agonists may be employed in treating any TIM3-induced condition, including but not limited to various cancers.

Antigen binding proteins may be employed in an *in vitro* procedure, or administered *in vivo* to enhance TIM3-induced biological activity. Disorders that would benefit (directly or indirectly) from the activation of TIM3, examples of which are provided herein, thus may be treated. In one embodiment, the present invention provides a therapeutic method comprising *in vivo* administration of a TIM3 antigen binding protein to a mammal in need thereof in an amount effective for increasing TIM3 biological activity.

In certain embodiments of the invention, antigen binding proteins include fully human monoclonal antibodies that enhance a biological activity of TIM3.

Antigen binding proteins, including antibodies and antibody fragments described herein, may be prepared by any of a number of conventional techniques. For example, they may be purified from cells that naturally express them (*e.g.*, an antibody can be purified from a hybridoma that produces it), or produced in recombinant expression systems, using any technique known in the art. See, for example, Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses, Kennet et al. (eds.), Plenum Press, New York (1980); and

Antibodies: A Laboratory Manual, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1988).

Any expression system known in the art can be used to make the recombinant polypeptides, including antibodies and antibody fragments described herein, of the invention. In general, host cells are transformed with a recombinant expression vector that comprises DNA encoding a desired polypeptide, including DNA encoding the amino acid sequences set forth in Table 1. Among the host cells that may be employed are prokaryotes, yeast or higher eukaryotic cells. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or *bacilli*. Higher eukaryotic cells include insect cells and established cell lines of mammalian origin. Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (Gluzman et al., 1981, *Cell* 23:175), L cells, 293 cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells, HeLa cells, BHK (ATCC CRL 10) cell lines, and the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) as described by McMahan et al., 1991, *EMBO J.* 10: 2821. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., 1985).

The transformed cells can be cultured under conditions that promote expression of the polypeptide, and the polypeptide recovered by conventional protein purification procedures. One such purification procedure includes the use of affinity chromatography, *e.g.*, over a matrix having all or a portion (*e.g.*, the extracellular domain) of TIM3 bound thereto. Polypeptides contemplated for use herein include substantially homogeneous recombinant mammalian anti-TIM3 antibody polypeptides substantially free of contaminating endogenous materials.

Antigen binding proteins may be prepared, and screened for desired properties, by any of a number of known techniques. Certain of the techniques involve isolating a nucleic acid encoding a polypeptide chain (or portion thereof) of an antigen binding protein of interest (*e.g.*, an anti-TIM3 antibody), and manipulating the nucleic acid through recombinant DNA technology. The nucleic acid may be fused to another nucleic acid of interest, or altered (*e.g.*, by mutagenesis or other conventional techniques) to add, delete, or substitute one or more amino acid residues, for example.

Polypeptides of the present disclosure can be produced using any standard methods known in the art. In one example, the polypeptides are produced by recombinant DNA

methods by inserting a nucleic acid sequence (*e.g.*, a cDNA) encoding the polypeptide into a recombinant expression vector and expressing the DNA sequence under conditions promoting expression.

Nucleic acids encoding any of the various polypeptides disclosed herein may be synthesized chemically. Codon usage may be selected so as to improve expression in a cell. Such codon usage will depend on the cell type selected. Specialized codon usage patterns have been developed for E. coli and other bacteria, as well as mammalian cells, plant cells, yeast cells and insect cells. See for example: Mayfield et al., *Proc. Natl. Acad. Sci. USA.* 2003 100(2):438-42; Sinclair et al. *Protein Expr. Purif.* 2002 (1):96-105; Connell N D. *Curr. Opin. Biotechnol.* 2001 12(5):446-9; Makrides et al. *Microbiol. Rev.* 1996 60(3):512-38; and Sharp et al. *Yeast.* 1991 7(7):657-78.

General techniques for nucleic acid manipulation are described for example in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Vols. 1-3, Cold Spring Harbor Laboratory Press, 2 ed., 1989, or F. Ausubel et al., *Current Protocols in Molecular Biology* (Green Publishing and Wiley-Interscience: New York, 1987) and periodic updates, herein incorporated by reference. The DNA encoding the polypeptide is operably linked to suitable transcriptional or translational regulatory elements derived from mammalian, viral, or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants is additionally incorporated.

The recombinant DNA can also include any type of protein tag sequence that may be useful for purifying the protein. Examples of protein tags include but are not limited to a histidine tag, a FLAG tag, a myc tag, an HA tag, or a GST tag. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts can be found in *Cloning Vectors: A Laboratory Manual*, (Elsevier, N.Y., 1985).

The expression construct is introduced into the host cell using a method appropriate to the host cell. A variety of methods for introducing nucleic acids into host cells are known in the art, including, but not limited to, electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (where the vector is an infectious agent). Suitable host cells include prokaryotes, yeast, mammalian cells, or bacterial cells.

Suitable bacteria include gram negative or gram positive organisms, for example, *E. coli* or *Bacillus spp*. Yeast, preferably from the *Saccharomyces* species, such as *S. cerevisiae*, may also be used for production of polypeptides. Various mammalian or insect cell culture systems can also be employed to express recombinant proteins. *Baculovirus* systems for production of heterologous proteins in insect cells are reviewed by Luckow and Summers, (*Bio/Technology*, 6:47, 1988). Examples of suitable mammalian host cell lines include endothelial cells, COS-7 monkey kidney cells, CV-1, L cells, C127, 3T3, Chinese hamster ovary (CHO), human embryonic kidney cells, HeLa, 293, 293T, and BHK cell lines. Purified polypeptides are prepared by culturing suitable host/vector systems to express the recombinant proteins. For many applications, the small size of many of the polypeptides disclosed herein would make expression in *E. coli* as the preferred method for expression. The protein is then purified from culture media or cell extracts.

Proteins disclosed herein can also be produced using cell-translation systems. For such purposes the nucleic acids encoding the polypeptide must be modified to allow in vitro transcription to produce mRNA and to allow cell-free translation of the mRNA in the particular cell-free system being utilized (eukaryotic such as a mammalian or yeast cell-free translation system or prokaryotic such as a bacterial cell-free translation system. TIM3-binding polypeptides can also be produced by chemical synthesis (*e.g.*, by the methods described in Solid Phase Peptide Synthesis, 2nd ed., 1984, The Pierce Chemical Co., Rockford, Ill.). Modifications to the protein can also be produced by chemical synthesis.

The polypeptides of the present disclosure can be purified by isolation/purification methods for proteins generally known in the field of protein chemistry. Non-limiting examples include extraction, recrystallization, salting out (*e.g.*, with ammonium sulfate or sodium sulfate), centrifugation, dialysis, ultrafiltration, adsorption chromatography, ion exchange chromatography, hydrophobic chromatography, normal phase chromatography, reversed-phase chromatography, gel filtration, gel permeation chromatography, affinity chromatography, electrophoresis, countercurrent distribution or any combinations of these. After purification, polypeptides may be exchanged into different buffers and/or concentrated by any of a variety of methods known to the art, including, but not limited to, filtration and dialysis. The purified polypeptide is preferably at least 85% pure, more preferably at least 95% pure, and most preferably at least 98% pure. Regardless of the exact numerical value of the purity, the polypeptide is sufficiently pure for use as a pharmaceutical product.

In certain embodiments, the present disclosure provides monoclonal antibodies that bind to TIM3. Monoclonal antibodies may be produced using any technique known in the art, *e.g.*, by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, *e.g.*, by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0 Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 48210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

Fragments or analogs of antibodies can be readily prepared by those of ordinary skill in the art following the teachings of this specification and using techniques known in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Computerized comparison methods can be used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. See, Bowie et al., 1991, *Science* 253:164.

Post-Translational Modifications of Polypeptides

In certain embodiments, the binding polypeptides of the invention may further comprise post-translational modifications. Exemplary post-translational protein modifications include phosphorylation, acetylation, methylation, ADP-ribosylation, ubiquitination, glycosylation, carbonylation, sumoylation, biotinylation or addition of a polypeptide side chain or of a hydrophobic group. As a result, the modified soluble polypeptides may contain non-amino acid elements, such as lipids, poly- or mono-saccharide, and phosphates. A preferred form of glycosylation is sialylation, which conjugates one or more sialic acid moieties to the polypeptide. Sialic acid moieties improve solubility and serum half-life while

also reducing the possible immunogeneticity of the protein. See Raju et al. *Biochemistry.* 2001 31; 40(30):8868-76.

In one embodiment, modified forms of the subject soluble polypeptides comprise linking the subject soluble polypeptides to nonproteinaceous polymers. In one embodiment, the polymer is polyethylene glycol ("PEG"), polypropylene glycol, or polyoxyalkylenes, in the manner as set forth in U.S. Patents 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

PEG is a water soluble polymer that is commercially available or can be prepared by ring-opening polymerization of ethylene glycol according to methods well known in the art (Sandler and Karo, Polymer Synthesis, Academic Press, New York, Vol. 3, pages 138-161). The term "PEG" is used broadly to encompass any polyethylene glycol molecule, without regard to size or to modification at an end of the PEG, and can be represented by the formula: $X\text{--}O(CH_2CH_2O)_n\text{-}CH_2CH_2OH$ (1), where n is 20 to 2300 and X is H or a terminal modification, *e.g.*, a $C_{1\text{-}4}$ alkyl. In one embodiment, the PEG of the invention terminates on one end with hydroxy or methoxy, *i.e.*, X is H or $CH_3$ ("methoxy PEG"). A PEG can contain further chemical groups which are necessary for binding reactions; which results from the chemical synthesis of the molecule; or which is a spacer for optimal distance of parts of the molecule. In addition, such a PEG can consist of one or more PEG side-chains which are linked together. PEGs with more than one PEG chain are called multiarmed or branched PEGs. Branched PEGs can be prepared, for example, by the addition of polyethylene oxide to various polyols, including glycerol, pentaerythriol, and sorbitol. For example, a four-armed branched PEG can be prepared from pentaerythriol and ethylene oxide. Branched PEG are described in, for example, EP-A 0 473 084 and U.S. Patent. 5,932,462. One form of PEGs includes two PEG side-chains (PEG2) linked via the primary amino groups of a lysine (Monfardini et al., *Bioconjugate Chem.* 6 (1995) 62-69).

The serum clearance rate of PEG-modified polypeptide may be decreased by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or even 90%, relative to the clearance rate of the unmodified binding polypeptide. The PEG-modified polypeptide may have a half-life ($t_{1/2}$) which is enhanced relative to the half-life of the unmodified protein. The half-life of PEG-binding polypeptide may be enhanced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400% or 500%, or even by 1000% relative to the half-life of the unmodified binding polypeptide. In some embodiments, the protein half-life is determined *in vitro*, such as in a buffered saline solution or in serum. In

other embodiments, the protein half-life is an *in vivo* half life, such as the half-life of the protein in the serum or other bodily fluid of an animal.

Therapeutic Methods, Formulations and Modes of Administration

The present disclosure further provides a method for treating a broad spectrum of mammalian cancer, or a broad-spectrum of inflammatory disease or autoimmune disease, comprising administering an anti-TIM3 polypeptide. Any of the antibodies disclosed herein may be used in such methods. For example, the methods may be performed using an anti-TIM3 polypeptide selected from the group consisting of a fully human antibody of an IgG class that binds to a TIM3 epitope with a binding affinity of at least $10^{-6}$M, a Fab fully human antibody fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, including the heavy and light chain variable regions (and CDRs within said sequences) described in SEQ ID Nos. 1-70 (Table 1).

For example, in one embodiment, the methods disclosed herein include the use of a fully human antibody having a heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69, and that has a light chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44,

SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

In one embodiment, the methods described herein include the use of a fully human Fab antibody fragment comprising a heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to an amino acid sequence consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

In one embodiment, the methods described herein include the use of a single chain human antibody comprising a heavy chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to an amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and

SEQ ID NO. 69, and comprising a light chain variable domain sequence that is at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, or at least 99% identical, to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

In one embodiment, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called TIA1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called TIA5 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called TIA6 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called TIA7 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called TIA9 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called TIA10 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called TIA11 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called TIB1 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called TIB2 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called TIC1 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called TIC2 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called TIC4 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called TIC5 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called TIC8 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called TIC10 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called TIC11 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called TID1 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called TID6 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called TID10 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called TID12 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called TIE2 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called TIE3 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called TIE7 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called TIE9 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called TIF3 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called TIF7 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called TIF8 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called TIG1 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called TIG3 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called TIG6 herein), SEQ ID NO. 7/SEQ ID NO. 62 (called TIG9 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called TIG10 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called TIH1 herein), SEQ ID NO.

67/SEQ ID NO. 68 (called TIH5 herein), and SEQ ID NO. 69/SEQ ID NO. 70 (called TIH11 herein).

In one embodiment, the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called TIA1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called TIA5 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called TIA6 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called TIA7 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called TIA9 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called TIA10 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called TIA11 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called TIB1 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called TIB2 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called TIC1 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called TIC2 herein), SEQ ID NO. 23/SEQ ID NO. 24 (called TIC4 herein), SEQ ID NO. 25/SEQ ID NO. 26 (called TIC5 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called TIC8 herein), SEQ ID NO. 29/SEQ ID NO. 30 (called TIC10 herein), SEQ ID NO. 31/SEQ ID NO. 32 (called TIC11 herein), SEQ ID NO. 33/SEQ ID NO. 34 (called TID1 herein), SEQ ID NO. 35/SEQ ID NO. 36 (called TID6 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called TID10 herein), SEQ ID NO. 39/SEQ ID NO. 40 (called TID12 herein), SEQ ID NO. 41/SEQ ID NO. 42 (called TIE2 herein), SEQ ID NO. 43/SEQ ID NO. 44 (called TIE3 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called TIE7 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called TIE9 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called TIF3 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called TIF7 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called TIF8 herein), SEQ ID NO. 55/SEQ ID NO. 56 (called TIG1 herein), SEQ ID NO. 57/SEQ ID NO. 58 (called TIG3 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called TIG6 herein), SEQ ID NO. 7/SEQ ID NO. 62 (called TIG9 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called TIG10 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called TIH1 herein), SEQ ID NO. 67/SEQ ID NO. 68 (called TIH5 herein), and SEQ ID NO. 69/SEQ ID NO. 70 (called TIH11 herein).

In one embodiment, the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO.

21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 7/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, and SEQ ID NO. 69/SEQ ID NO. 70.

In one embodiment, the anti-TIM3 antibodies and antibody fragments of the invention are used to treat cancer in a mammalian subject. In one embodiment, the cancer to be treated is selected from the group consisting of ovarian cancer, colon cancer, breast cancer, lung cancers, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas and mast cell derived tumors, and combinations thereof. In one embodiment, the anti-TIM3 antibodies and antibody fragments of the invention are used to treat an autoimmune disease or an inflammatory disease. In one embodiment, the autoimmune disease or inflammatory disease is selected from the group consisting of intestinal mucosal inflammation, wasting disease associated with colitis, multiple sclerosis, systemic lupus erythematosus, viral infections, rheumatoid arthritis, osteoarthritis, psoriasis, Crohn's disease, and inflammatory bowel disease.

In one embodiment, the TIM3 antibodies and antibody fragments described herein are useful in treating, delaying the progression of, preventing relapse of or alleviating a symptom of a cancer or other neoplastic condition, including, hematological malignancies and/or TIM3+ tumors. In one embodiment, the TIM3 antibodies and antibody fragments described herein are useful in treating a cancer selected from the group consisting of non-Hodgkin's lymphoma (NHL), acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), multiple myeloma (MM), breast cancer, ovarian cancer, head and neck cancer, bladder cancer, melanoma, colorectal cancer, pancreatic cancer, lung cancer, leiomyoma, leiomyosarcoma, glioma, glioblastoma, and solid tumors, wherein solid tumors are selected from the group consisting of breast tumors, ovarian tumors, lung tumors, pancreatic tumors, prostate tumors,

melanoma tumors, colorectal tumors, lung tumors, head and neck tumors, bladder tumors, esophageal tumors, liver tumors, and kidney tumors.

As used herein, "hematological cancer" refers to a cancer of the blood, and includes leukemia, lymphoma and myeloma among others. "Leukemia" refers to a cancer of the blood in which too many white blood cells that are ineffective in fighting infection are made, thus crowding out the other parts that make up the blood, such as platelets and red blood cells. It is understood that cases of leukemia are classified as acute or chronic.

Certain forms of leukemia include, acute lymphocytic leukemia (ALL); acute myeloid leukemia (AML); chronic lymphocytic leukemia (CLL); chronic myelogenous leukemia (CML); Myeloproliferative disorder/neoplasm (MPDS); and myelodysplasia syndrome. "Lymphoma" may refer to a Hodgkin' s lymphoma, both indolent and aggressive non-Hodgkin's lymphoma, Burkitt's lymphoma, and follicular lymphoma (small cell and large cell), among others. Myeloma may refer to multiple myeloma (MM), giant cell myeloma, heavy-chain myeloma, and light chain or Bence-Jones myeloma.

The present disclosure features methods for treating or preventing the *S. aureus* infection comprising administering an anti-TIM3 polypeptide. Techniques and dosages for administration vary depending on the type of specific polypeptide and the specific condition being treated but can be readily determined by the skilled artisan. In general, regulatory agencies require that a protein reagent to be used as a therapeutic is formulated so as to have acceptably low levels of pyrogens. Accordingly, therapeutic formulations will generally be distinguished from other formulations in that they are substantially pyrogen free, or at least contain no more than acceptable levels of pyrogen as determined by the appropriate regulatory agency (*e.g.*, FDA).

Therapeutic compositions of the present disclosure may be administered with a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Administration may be parenteral (*e.g.*, intravenous, subcutaneous), oral, or topical, as non-limiting examples. In addition, any gene therapy technique, using nucleic acids encoding the polypeptides of the invention, may be employed, such as naked DNA delivery, recombinant genes and vectors, cell-based delivery, including ex vivo manipulation of patients' cells, and the like.

The composition can be in the form of a pill, tablet, capsule, liquid, or sustained release tablet for oral administration; or a liquid for intravenous, subcutaneous or parenteral

administration; gel, lotion, ointment, cream, or a polymer or other sustained release vehicle for local administration.

In certain embodiments, the disclosed antibodies are administered by inhalation, but aerosolization of full IgG antibodies may prove limiting due to their molecular size (~150kDa). To maximize available commercial aerosolization devices, smaller Fab fragments may be required. In this case, we may also need to generate Fab fragments from the parental IgG molecules. Therefore, we will perform initial studies using standard enzyme-based digestion methodologies for the generation of Fab fragments, which will then be characterized in parallel with full IgG molecules.

Methods well known in the art for making formulations are found, for example, in "Remington: The Science and Practice of Pharmacy" (20th ed., ed. A. R. Gennaro A R., 2000, Lippincott Williams & Wilkins, Philadelphia, Pa.). Formulations for parenteral administration may, for example, contain excipients, sterile water, saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated napthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Nanoparticulate formulations (*e.g.*, biodegradable nanoparticles, solid lipid nanoparticles, liposomes) may be used to control the biodistribution of the compounds. Other potentially useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. The concentration of the compound in the formulation varies depending upon a number of factors, including the dosage of the drug to be administered, and the route of administration.

The polypeptide may be optionally administered as a pharmaceutically acceptable salt, such as non-toxic acid addition salts or metal complexes that are commonly used in the pharmaceutical industry. Examples of acid addition salts include organic acids such as acetic, lactic, pamoic, maleic, citric, malic, ascorbic, succinic, benzoic, palmitic, suberic, salicylic, tartaric, methanesulfonic, toluenesulfonic, or trifluoroacetic acids or the like; polymeric acids such as tannic acid, carboxymethyl cellulose, or the like; and inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid phosphoric acid, or the like. Metal complexes include zinc, iron, and the like. In one example, the polypeptide is formulated in the presence of sodium acetate to increase thermal stability.

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for

example, inert diluents or fillers (*e.g.*, sucrose and sorbitol), lubricating agents, glidants, and anti-adhesives (*e.g.*, magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc).

Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium.

A therapeutically effective dose refers to a dose that produces the therapeutic effects for which it is administered. The exact dose will depend on the disorder to be treated, and may be ascertained by one skilled in the art using known techniques. In general, the polypeptide is administered at about 0.01 μg/kg to about 50 mg/kg per day, preferably 0.01 mg/kg to about 30 mg/kg per day, most preferably 0.1 mg/kg to about 20 mg/kg per day. The polypeptide may be given daily (*e.g.*, once, twice, three times, or four times daily) or preferably less frequently (*e.g.*, weekly, every two weeks, every three weeks, monthly, or quarterly). In addition, as is known in the art, adjustments for age as well as the body weight, general health, sex, diet, time of administration, drug interaction, and the severity of the disease may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

A TIM3 binding polypeptide, as disclosed herein, can be administered alone or in combination with one or more additional therapies such as chemotherapy radiotherapy, immunotherapy, surgical intervention, or any combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above.

In certain embodiments of such methods, one or more polypeptide therapeutic agents can be administered, together (simultaneously) or at different times (sequentially). In addition, polypeptide therapeutic agents can be administered with another type of compounds for treating cancer or for inhibiting angiogenesis.

In certain embodiments, the subject anti-TIM3 antibodies agents of the invention can be used alone.

In certain embodiments, the binding polypeptides of fragments thereof can be labeled or unlabeled for diagnostic purposes. Typically, diagnostic assays entail detecting the formation of a complex resulting from the binding of a binding polypeptide to TIM3. The binding polypeptides or fragments can be directly labeled, similar to antibodies. A variety of labels can be employed, including, but not limited to, radionuclides, fluorescers, enzymes,

enzyme substrates, enzyme cofactors, enzyme inhibitors and ligands (*e.g.*, biotin, haptens). Numerous appropriate immunoassays are known to the skilled artisan (see, for example, U.S. Patents. 3,817,827; 3,850,752; 3,901,654; and 4,098,876). When unlabeled, the binding polypeptides can be used in assays, such as agglutination assays. Unlabeled binding polypeptides can also be used in combination with another (one or more) suitable reagent which can be used to detect the binding polypeptide, such as a labeled antibody reactive with the binding polypeptide or other suitable reagent (*e.g.*, labeled protein A).

In one embodiment, the binding polypeptides of the present invention can be utilized in enzyme immunoassays, wherein the subject polypeptides are conjugated to an enzyme. When a biological sample comprising a TIM3 protein is combined with the subject binding polypeptides, binding occurs between the binding polypeptides and the TIM3 protein. In one embodiment, a sample containing cells expressing a TIM3 protein (*e.g.*, endothelial cells) is combined with the subject antibodies, and binding occurs between the binding polypeptides and cells bearing a TIM3 protein recognized by the binding polypeptide. These bound cells can be separated from unbound reagents and the presence of the binding polypeptide-enzyme conjugate specifically bound to the cells can be determined, for example, by contacting the sample with a substrate of the enzyme which produces a color or other detectable change when acted on by the enzyme. In another embodiment, the subject binding polypeptides can be unlabeled, and a second, labeled polypeptide (*e.g.*, an antibody) can be added which recognizes the subject binding polypeptide.

In certain aspects, kits for use in detecting the presence of a TIM3 protein in a biological sample can also be prepared. Such kits will include a TIM3 binding polypeptide which binds to a TIM3 protein or portion of said receptor, as well as one or more ancillary reagents suitable for detecting the presence of a complex between the binding polypeptide and the receptor protein or portions thereof. The polypeptide compositions of the present invention can be provided in lyophilized form, either alone or in combination with additional antibodies specific for other epitopes. The binding polypeptides and/or antibodies, which can be labeled or unlabeled, can be included in the kits with adjunct ingredients (*e.g.*, buffers, such as Tris, phosphate and carbonate, stabilizers, excipients, biocides and/or inert proteins, e.g., bovine serum albumin). For example, the binding polypeptides and/or antibodies can be provided as a lyophilized mixture with the adjunct ingredients, or the adjunct ingredients can be separately provided for combination by the user. Generally these adjunct materials will be present in less than about 5% weight based on the amount of active binding polypeptide or

antibody, and usually will be present in a total amount of at least about 0.001% weight based on polypeptide or antibody concentration. Where a second antibody capable of binding to the binding polypeptide is employed, such antibody can be provided in the kit, for instance in a separate vial or container. The second antibody, if present, is typically labeled, and can be formulated in an analogous manner with the antibody formulations described above.

Polypeptide sequences are indicated using standard one- or three-letter abbreviations. Unless otherwise indicated, each polypeptide sequence has amino termini at the left and a carboxy termini at the right; each single-stranded nucleic acid sequence, and the top strand of each double-stranded nucleic acid sequence, has a 5' termini at the left and a 3' termini at the right. A particular polypeptide sequence also can be described by explaining how it differs from a reference sequence.

Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included for purposes of illustration only and are not intended to be limiting of the invention.

## Example 1

Human antibodies specific for human TIM3 were identified and selected for therapeutic characteristics, including specificity for TIM3 and a high degree of affinity for TIM3 (*e.g.*, at least $10^{-6}$ M). The identified antibodies are described in Table 1.

The functional activity of the anti-TIM3 antibodies was evaluated by determining if they could augment a lymphocyte response to allogeneic stimulation in a mixed leukoocyte reaction (MLR). Purified CD4 positive lymphocytes ($1x10^5$) from one donor were cultured with monocyte derived dendritic cells ($1x10^4$) from a second donor in the presence or absence of test antibodies (10 microgram/ml). Parallel plates were set up to allow the harvest of cell supernatants on day 2 of culture to allow measurement of interleukin-2 (IL-2), and the harvest of cells on day 5 for assessment of cell activation, as determined by CD25 expression. Anti-TIM3 antibodies capable of augmenting IL-2 production are shown in Figure 1. Anti-TIM3 antibodies capable of augmenting cell activation as assessed by CD25 expression are shown in Figure 2A. The level of CD25 expression was higher in the cultures where anti-TIM3 antibodies had been added (Figure 2A). The control antibody (cIg) was an isotype matched control that does not bind to TIM3 or to any other molecule on the cell, *i.e.*, a nonspecific isotype matched irrelevant antibody. As a measure of the magnitude of the cell activation enhancement shown in Figure 2A, cell activation was normalized to that of the

medium control (Figure 2B). By normalizing the data with respect to the medium control (nil), a notable level of augmentation was detected in the cultures which received anti-TIM3 antibodies (Figure 2B), with the exception of the D6 antibody, which did not augment CD25 activation above control levels.

The ability of TIM3 ligation to modulate T cell activation was determined by stimulating T cells with immobilized antibodies in the absence of monocytes. Lymphocytes were added to wells pre-coated with immobilized anti-CD3 (5 microgram per well) with or without the test antibodies immobilized at 10 microgram per ml. After three days of culture, the cells were evaluated for CD25 expression as a measure of T cell activation. The level of CD25 expression was higher in the cultures where anti-TIM3 antibody TIA1 had been added (Figure 3A). The control antibody was an isotype matched, nonspecific (*i.e.*, does not bind to TIM3) antibody. By normalizing the data with respect to the medium control, antibody TIA1 exhibited significant TIM3 agonistic activity whereas antibody TIG3 did not (Figure 3B).

**Table 1. Amino acid sequences of heavy and light chain variable domains**

| | Heavy chain variable domain | Light chain variable domain |
|---|---|---|
| TIA1 | QMQLVQSGGEVKKPGASVKVSCK TSGYRFTSYGISWVRQAPGQGLE WMGWISGYNGETNYAETLQGRLT LTTDTSTSTAYMELGSLRPDDTAV YYCTRDGHSPYFDYWGQGTLVTV SS SEQ ID NO. 1 | QAVLTQPASVSGSPGQSVTISCTGTSSD VGGYNYVSWYQQHPGKAPKLMIYEVS KRPSGIPERFSGSNSGNTATLTISRVEA GDEADYYCQVWDSSSDHWVFGRGTK LTVL SEQ ID NO. 2 |
| TIA5 | QVQLVQSGGGLVQPGGSLRLSCA ASGFTFSSYAMSWVRQAPGKGLE WVSAISGSGGSTYYADSVKGRFTI SRDNSKNTLLLQMNSLRVEDTAV YYCARDFSGWGGFDIWGQGTMV TVSS SEQ ID NO. 3 | NFMLTQPPSASGTPGQRVTISCSGSSSN IGSNTVNWYQQLPGTAPKLLIYSNNQR PSGVPARFSGSKSGTSASLAISGLQSEQ EADYYCAAWDDSLNNYVFGTGTKVT VL SEQ ID NO. 4 |
| TIA6 | QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYGISWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRV TMTTDTSTSTAYMELRSLRSDDTA VYYCAKGDYFDYWGQGTLVTVSS SEQ ID NO. 5 | SYELMQPASVSGSPGQSITISCTGTSYD VGRYNYVSWYQQHPGKAPKLIIYGVS SRPAGASNRFSGSKSGNTASLTISGLQT EDEADYYCSSYTSSDAYVFGTGTKLTV L SEQ ID NO. 6 |
| TIA7 | EVQLVQSGAEVKKPGASVKVSCK ASGYTFTDYYIHWVRQAPGQGLE WMGWINANSGATNYAQNFQGRV TMTRDTSIRSAYMELSNLTSDDTA VYYCARDRATTPSFDYWGQGTLV TVSS SEQ ID NO. 7 | AIQLTQSPSSLSASVGDRVTITCRASQSI SSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSASGTDFTLTISSLQPEDSAT YYCQQSYSTPYTFGQGTKLEIK SEQ ID NO. 8 |

| | Heavy chain variable domain | Light chain variable domain |
|---|---|---|
| TIA9 | QVQLVQSGSELKKPGASVKVSCK ASGYTFNNYAMTWVRQAPGQGL EWMGLINTKTGDTIYAQGFTGRFV LSLDTSVSTAYLQISSLKAEDTAIY YCARPTYGMDVWGQGTTVTVSS SEQ ID NO. 9 | QSVLTQPPSVSVALGQTARITCGGNNI GSKNVHWYQQKPGQAPVLVIYRDSNR PSGIPERFSGSNSGNTATLTISRAQAGD EADYYCQVWDSSTGVFGGGTKLTVL SEQ ID NO. 10 |
| TIA10 | EVQLVQSGAEVKKPGASVKVSCK ASGYTFTGHYMHWVRQVPGQGL EWMGWIKPNSGGTKYAQKFQGR VTMTRDTSISTAYMEMTGLRSDDT AVYYCARESWTGIGNGEDVWGQ GTTVTVSS SEQ ID NO. 11 | DIVMTQSPSTLSASVGDRVTITCRASQS ISSWLAWYQQKPGKAPKLLIYKASSLE SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPYTFGQGTKLEIK SEQ ID NO. 12 |
| TIA11 | EVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVT MTRDTSTSTVYMELSSLRSEQTAV YYCARDSGYDLGYGMDVWGQGT TVTVSS SEQ ID NO. 13 | DIVMTQSPSSLSASVGDRVTITCRASQS IRDYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFTGSGSGTDFTLTISSLQPEDFA VYSCQQSFSKSYTFGQGTRLEIK SEQ ID NO. 14 |
| TIB1 | QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYGISWVRQAPGQGLE WMGWISPYNGNTNYVQKLQDRV TMTTDTSTSTAYMELRSLRSDDTA VYYCAKSDRYSGPGQLAFDYWGQ GTLVTVSS SEQ ID NO. 15 | QPVLTQPASVSGSPGQSITISCTGTSSDV GGYNSVSWYQQHPGKAPKLMIYDVN KWPSGVSNRFSGSKSGNTASLTISGLQ AEDEADYYCSSYTRTNTLVFGGGTKLT VL SEQ ID NO. 16 |
| TIB2 | EVQLVESGGGLVKPGGSLRLSCAA SGFTFSRADMNWVRQAPGKGLEW VSSISRGSYIYYGDSVKGRFTISRD NAKNSLYLQMNSLRPEDTAVYYC ARNLAGYSYGYAFDYWGPGTLVT VSS SEQ ID NO. 17 | QAGLTQPASVSGSPGQSITISCTGTSSD YVSWYQQHPGKAPKLMIYDVSNRPSG VSNRFSGSKSGNTASLTISGLQAEDEA DYYCSSYTSSSLVVFGGGTKLTVL SEQ ID NO. 18 |
| TIC1 | EVQLVQSGAEVKKPGASVKVSCK ASGYTFTGYYMHWVRQAPGQGL EWMGWINPNSGGTNYAQKFQGR VTMTRDTSISTAYMELSRLRSDDT AVYYCAREDQLDYYYYGMDVWG QGTTVTVSS SEQ ID NO. 19 | AIRMTQSPSSLSASVGDRVTITCRASQS ISSDLNWYQKKPGKAPKLLIYAASSLL TGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPRTFGQGTKLEIK SEQ ID NO. 20 |
| TIC2 | QVQLQQSGAEVKKPGSSVKVSCK ASGGTFSSHVISWVRQAPGQGLE WMGGIIPLLGTPNYAENFQGRVTII VDESTNTAFMELSSLRSEQTAVYY CARGGVPNYYHMDVWGKGTTVT VSS SEQ ID NO. 21 | SYELMQPPSASGTPGQRVTISCSGSSSN IGSNTVNWYGLLPGTAPKLLIYSDNQR PSGVPDRFSGSKSGTSASLAISGLQSEQ ETHYYCAAWDDSLNGWVFGGGTKLT VL SEQ ID NO. 22 |
| TIC4 | QVQLVQSGGGLVQPGGSLRLSCA ASGFSFSTYAMSWVRQAPGKGLE WVSGISGSGRTPYYADSVKGRFTI SRDNDKNSLYLQITSLRAEDTAVY YCARNDIFTGSLPDWGQGTLVTVS S SEQ ID NO. 23 | SYVLTQPRSVSGSPGQSVTLSCTGTSSD VGGYNYVSWYQQHPGKAPKLMISDVS ARPSGISNRFSGSKSGNTASLTISGLQA EDEADYYCSSFTSSSTYVFGAGTKVTV L SEQ ID NO. 24 |

| | Heavy chain variable domain | Light chain variable domain |
|---|---|---|
| TIC5 | EVQLVESGGGLVKPGGSLRLSCTG SGFSLSNYYMTWIRQTPERGLEW MSYLSGSGNLISYADSIKGRFTISR DSAENSLSLQMDSLRVEDTAVYY CAREYYGTFDYWGQGTLVTVSS SEQ ID NO. 25 | AIQLTQSPSTLSASVGDRVTITCRASQTI STWLAWYQQKPGKAPKLLIYKASTLE TGVPSRFSGSGSGTEFTLTISSLQPEDFA TYFCQQSYSTPYTFGQGTKLEIK SEQ ID NO. 26 |
| TIC8 | QVQLVQSGAEVKKPGASVKVSCK ASGYTFSNYEINWVRQATGQGLE WMGWMNPNSGKIGYEQKFQGRV TMTRNTSISSAYMELSSLRSDDTA VYYCARGNGDLGAADYWGQGTL VTVSS SEQ ID NO. 27 | VIWMTQSPSSLSASVGDRVTITCRASQS IGRYLNWYQQKPGKAPKLLIYAASNL QSGVPSRFSGSGSGTDFSVTISSLQPEDF ATYYCQQSYSTPRTFGQGTKLEIK SEQ ID NO. 28 |
| TIC10 | QVQLVQSEAEVKKPGASVKVSCK ASGYTFGGHYMHWLRQAPGQGPE WMGWINPNSGGTNFAQKFEGRVT MTRDSSINTVYMELSSLKSDDTAV YYCARDRYDVSTTFSNYYFDLWG RGTLVTVSS SEQ ID NO. 29 | DIQMTQSPSSLSASVGDRVTMTCRASQ SISSYLNWYQQKPGKAPKLLISAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPITFGQGTKVEIK SEQ ID NO. 30 |
| TIC11 | EVQLVESGGGLIQPGESLRLSCAVS GFTVRGNYVAWVRQAPGKGLEW VATINGGGSPYYADSVKGRFTISR DDSKNTVDLQMNILRVEDTAIYYC ARDTYCTAGICPSSPVWGQGTTVT VSS SEQ ID NO. 31 | QAVLTQPPSVSGAPGQRVTISCTGSSSN IGAGYDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQA EDEAVYFCQSHDTSVTGVVFGGGTKV TVL SEQ ID NO. 32 |
| TID1 | QVQLVESGGGLVKPGGSLRLSCA ASGFTFSSYSMNWVRQAPGKGLE WVSSISSSSSYIYYADSVKGRFTISR DNAKNSLYLQMNSLRAEDTAVYY CASGDHMDVWGQGTTVTVSS SEQ ID NO. 33 | QPVLTQPPSASGTPGQRVTISCSGSSSN VGTNYVYWYQQLPGTAPKLLTHINNQ RPSGVPDRFSGSKSGTSASLAISGLRSE QEADYYCAAWDATLSAWVFGGGTKL TVL SEQ ID NO. 34 |
| TID6 | EVQLLESGGGVVQPGRSLRLSCAA PGFSFSSYGMHWVRQAPGKGLEW VALISYDGSNKYYADSVKGRFTIS RDNSMSTLYLQMNSLRAEDTAVY YCAKPRGYTGYGDYYYGLDVWG QGTTVTVSS SEQ ID NO. 35 | QSALTQPPSVSKGLRQTATLTCTGNSN NVGNQGAAWLQQHQGHPPKLLSYRN NNRPSGISERFSASRSGNTASLTITGLQS EQEADYYCSAWDRSLSALVFGGGTKL TVL SEQ ID NO. 36 |
| TID10 | QVQLVESGGGLVQPGGSLRLSCA ASGFPFNTYWMNWVRQAPGKGL EWVANINPDGSEKYYLDSVKGRF TISRDNAKNSLFLQMNSLRAEDTA VYYCGVVVWGRGTTVTVSS SEQ ID NO. 37 | DIVMTQSPLSLPVTLGQPASISCRSSQSL VHSDGNTYLNWFQQRPGQSPRRLIYR VSNRDSGVPDRFSGSGSGTDFTLKISRV EAEDVGIYYCMQSTHWPLTFGQGTKV EIK SEQ ID NO. 38 |
| TID12 | QMQLVQSGAEVKKPGASVKVSCK ASGYTFTSYGISWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRV TMTTDTSTSTAYMELRSLRSDDTA VYYCARETGYNWNGLDFDYWGQ GTLVTVSS SEQ ID NO. 39 | QAGLTQPPSVSAAPGQKVTISCSGSSSN IGNNYVSWYQQLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQTG DEADYYCGTWDSSLSAGEFGGGTKLT VL SEQ ID NO. 40 |

| | Heavy chain variable domain | Light chain variable domain |
|---|---|---|
| TIE2 | QMQLVQSEAEVKKPGASVKVSCK ASGYTFGGHYMHWLRQAPGQGPE WMGWINPNSGGTNFAQKFEGRVT MTRDSSINTVYMELSSLKSDDTAV YYCARDRYDVSTTFSNYYFDLWG RGTLVTVSS SEQ ID NO. 41 | VIWMTQSPSSLSASVGDRVTITCRASQS ISSYLNWYQQKPGKAPKLLIYTASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPYTFGQGTKVEIK SEQ ID NO. 42 |
| TIE3 | QMQLVQSGAEVKKPGASVKVSCK ASGYTFTNYYMHWVRQAPGQGL EWMGWINPNSDNTAYAQKFQGR VTMTRNTSISTVYMELSSLRSEQT AVYYCARGDSTFGYMDVWGKGT TVTVSS SEQ ID NO. 43 | QSVLTQPPSVSGAPGQRVTISCTGSSSN IAAHYVHWYQQLPGTAPKLLIFGNNN RPSGVPDRFSGSKSGTSASLAISGLRSE QEADYYCAAWDDSLSGWVFGGGTQL TVL SEQ ID NO. 44 |
| TIE7 | EVQLVESGGGLAEDGGSLTLSCAA SGFTFGNHAMRWVRQAPGKGLE WISSISENSRNTFYSDSVKGRFTISR DNSRNTLYLQMNSLRAEDTAVYY CARERGHSYGYGYWGQGTLVTVS S SEQ ID NO. 45 | DVVMTQSPLSLPVTLGQPASISCRSSQS LVHSDGNTYLNWFHQRPGQSPRRLIYK VSNRDSGVPDRFSGSGSGTDFTLKISRV EAEDVGVYYCMQSTQWPLTFGQGTK VEIK SEQ ID NO. 46 |
| TIE9 | QVQLQQSGPGLVKPSQSLSLACAI SGDSVSSNSAAWNWIRQSPSRGLE WLGRTYYRSKWYTDYAVSLKSRI TVSVDTSKNQFSLQLNSVTPEDTA VYYCATGGLNYGYFDSWGRGTLV TVSS SEQ ID NO. 47 | QSALTQPPSASGSPGQSVTISCTGTSSD VGGYKYVSWYQQHPGKAPKLMIYDV SNRPSGVSNRFSGSKSGNTASLTISGLQ AEDEADYYCSSYTSSSAYVFGTGTKVT VL SEQ ID NO. 48 |
| TIF3 | QVQLVQSGSEVKTPGASVKVSCK ASGYALSSYDINWVRQAPGQGLE WIGWMNPNSDRRGYAQKFQGRV TMTTDTSISTAYMELSSLTSEQTA MYYCAREKTRGRFDYWGQGTLV TVSS SEQ ID NO. 49 | VIWMTQSPSSLSASVGDRVTITCRASQ TMNNYLNWYQQKPGKAPKLLIYAAST LQSGVPSRFSGSRSGTEFTLTISGLQPED FATYYCQQSYSTPTFGQGTKVEIK SEQ ID NO. 50 |
| TIF7 | EVQLVESGGGLVQPGGSLRLSCAA SGFTVSRNYMYWVRQAPGKGLE WVSVIYRGGSTYYADSVKGRFTIS RDNSKNKVYLQMNSLRAEDTAVY FCARDGEVLSAFDVWGQGTMVTV SS SEQ ID NO. 51 | EIVLTQSPSSLSASVGDRVTITCRASQSI SSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQSYSTSRTFGQGTKVEIK SEQ ID NO. 52 |
| TIF8 | EVQLVESGAEVKKPGASVKVSCK ASGYTFSSYYIHWVRQAPGQGLE WMGVINPTGGSTHYAEKFQGRVT MTRDTSTSTVYMQLSSLRSEQTAV YYCARDQYGWGNYYYYGMDVW GQGTTVTVSS SEQ ID NO. 53 | DIQLTQSPGTLSVSPGERVTLSCRASQS VGDTYLAWYQQKPGQAPRLLIYGAST RATGVPARFSGSGSGTEFTLTISSLQSE QFAVYYCQQYGSSPLTFGGGTKVEIK SEQ ID NO. 54 |
| TIG1 | QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYIHWVRQAPGQGLE WMGVINPTGGSTHYAEKFQGRVT MTRDTSTSTVYMELSSLRSDDTAV YYCARDHYGWGNYYYYGMDVW GQGTTVTVSS SEQ ID NO. 55 | AIQMTQSPGTLSLSPGERATLSCRASQS VSSSYLAWYQQKPGQAPRLLIYGASSR ATGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQYENSPLTFGGGTKVEIK SEQ ID NO. 56 |

| | Heavy chain variable domain | Light chain variable domain |
|---|---|---|
| TIG3 | QVQLQQWGAGLLKPSETLSLTCA VSGGSFSGYYWSWIRQTPGKGLE WMAEINHSGDTDYNPSLKSRVTIS VDTSKNQFSLNLTSVTAADTAVYF CARGSRRGRYFPQPFDFWGQGTL VTVSS SEQ ID NO. 57 | SSELTQDPAVSVALGQTVRITCQGDSL RSYYASWYQQKPGQAPVLVIYGKNNR PSGIPDRFSGSSSGNTASLTITGAQAED EADYYCNSRDSSGNHVVFGGGTKLTV L SEQ ID NO. 58 |
| TIG6 | QVQLVESGGALVQPGGSLRLSCA ASGFTFSNDWMSWVRQAPGKGLE WVANINQDGSEKNYVDSVKGRFT ISRDNAKNSLYLQMNSLRGDDTA VYYCARGSGSSWFIWGQGTLVTV SS SEQ ID NO. 59 | EIVLTQSPLSLPVTLGQPASISCRSSQSL VHGSGNTYLNWFQQRPGQSPRRLIYEV SNRDSGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCMQSSFWPLTFGGGTKVE IK SEQ ID NO. 60 |
| TIG9 | EVQLVQSGAEVKKPGASVKVSCK ASGYTFTDYYIHWVRQAPGQGLE WMGWINANSGATNYAQNFQGRV TMTRDTSIRSAYMELSNLTSDDTA VYYCARDRATTPSFDYWGQGTLV TVSS SEQ ID NO. 7 | AIQLTQSPSSLSAPVGDRVTIACRASQTI GHYLNWYQQKSGKAPKLLIYTATSLQ SGVPSRFSGSGYGTDFTLTIGNLQPEDS ATYYCQQSFGIPYTFGQGTKVDIK SEQ ID NO. 62 |
| TIG10 | EVQLVESGAEVRKPGASVKISCKT PGYSFTERSIHWVRQAPGQGLEWI GRTIPTLEMASYAQKFQGRVTISA DKSTRTGYMELRDLRSEQTAVYY CSTQTPSYTDHWGQGTLVTVSS SEQ ID NO. 63 | EIVLTQSPSSLSVTLGQPASISCRSSQSL VHRDGNTYLNWFQQRPGQSPRRLIYR VSNRDSGVPDRFSGSGSGTDFTLKISRV EAEDVGVYYCMQSTQPPLTFGGGTKV EIK SEQ ID NO. 64 |
| TIH1 | QVQLVESGGGLVQPGGSLRLSCA ASGFIFSDYFMTWMRQAPGKGLE WVAYIGDRATPIRYADSVKGRFTI SRDNANNSVYLQMNSLGVEDTAV YYCARGGLSTDYWGQGTLVTVSS SEQ ID NO. 65 | LPVLTQPPSASGTPGQRVTISCSGSSSNI GSNTVNWYQRLPGTAPKLLIYGNSNRP SGVPDRFSGSKSGTSASLAITGLQAEDE ADYYCQSYDSSLSGSTVFGGGTKLTVL SEQ ID NO. 66 |
| TIH5 | QVQLVESGGGLVKPGGSLRLSCA ASGFTFSDYYMSWIRQAPGKGLE WVSSISNSGSTIYYADSVKGRFTIS RDNAKNSLYLQLNSLRDDDTAVY YCARNWQGADYGMDVWGQGTT VTVSS SEQ ID NO. 67 | DIVMTQSPSSLSASVGDRVTITCRASQN ISSYLNWYQQKPGRAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGGGTKVEIK SEQ ID NO. 68 |
| TIH11 | EVQLLESGGGLVQPGGSLRLSCAA SGFTVSSNYMSWVRQAPGKGLEW VAAISFDGSNKYYANSVKGRFTIS RDNSKNTLYLQMNSLKTEDTAVY YCVRVRDGGSFDLWGRGTLVTVS S SEQ ID NO. 69 | DIVMTQSPSTLSASVGDRVTITCRASES ISSWLAWYQQKPGKAPKLLIYTASSLQ SGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQHYANLPLTFGQGTKVEIK SEQ ID NO. 70 |

Incorporation by Reference

The contents of all references, patents, pending patent applications and published patents, cited throughout this application are hereby expressly incorporated by reference.

We claim:

1. An isolated fully human antibody of an IgG class that binds to a TIM3 epitope, wherein said antibody comprises

a heavy chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69; and

a light chain variable domain sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

2. The fully human antibody of claim 1, wherein the antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (TIA1), SEQ ID NO. 3/SEQ ID NO. 4 (TIA5), SEQ ID NO. 5/SEQ ID NO. 6 (TIA6), SEQ ID NO. 7/SEQ ID NO. 8 (TIA7), SEQ ID NO. 9/SEQ ID NO. 10 (TIA9), SEQ ID NO. 11/SEQ ID NO. 12 (TIA10), SEQ ID NO. 13/SEQ ID NO. 14 (TIA11), SEQ ID NO. 15/SEQ ID NO. 16 (TIB1), SEQ ID NO. 17/SEQ ID NO. 18 (TIB2), SEQ ID NO. 19/SEQ ID NO. 20 (TIC1), SEQ ID NO. 21/SEQ ID NO. 22 (TIC2), SEQ ID NO. 23/SEQ ID NO. 24 (TIC4), SEQ ID NO. 25/SEQ ID NO. 26 (TIC5), SEQ ID NO. 27/SEQ ID NO. 28 (TIC8), SEQ ID NO. 29/SEQ ID NO. 30 (TIC10), SEQ ID NO. 31/SEQ ID NO. 32 (TIC11), SEQ ID NO. 33/SEQ ID NO. 34 (TID1), SEQ ID NO. 35/SEQ ID NO. 36 (TID6), SEQ ID NO. 37/SEQ ID NO. 38 (TID10), SEQ ID NO. 39/SEQ ID NO. 40 (TID12), SEQ ID NO. 41/SEQ ID NO. 42 (TIE2), SEQ ID NO. 43/SEQ ID NO. 44 (TIE3), SEQ ID NO. 45/SEQ ID NO. 46 ( TIE7), SEQ ID NO. 47/SEQ ID NO. 48 (TIE9), SEQ ID NO. 49/SEQ ID NO. 50 (TIF3), SEQ ID NO. 51/SEQ ID NO. 52 (TIF7), SEQ ID NO. 53/SEQ ID NO. 54 (TIF8),

SEQ ID NO. 55/SEQ ID NO. 56 (TIG1), SEQ ID NO. 57/SEQ ID NO. 58 (TIG3), SEQ ID NO. 59/SEQ ID NO. 60 (TIG6), SEQ ID NO. 7/SEQ ID NO. 62 (TIG9), SEQ ID NO. 63/SEQ ID NO. 64 (TIG10), SEQ ID NO. 65/SEQ ID NO. 66 (TIH1), SEQ ID NO. 67/SEQ ID NO. 68 (TIH5), and SEQ ID NO. 69/SEQ ID NO. 70 (TIH11 ).

3. The fully human antibody of claim 1 or 2, wherein the antibody has a binding affinity ($K_D$) of at least 1 x $10^{-6}$ M.

4. An anti-TIM3 fully human antibody Fab fragment comprising a heavy chain variable domain comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69; and

a light chain variable domain comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

5. The fully human antibody Fab fragment of claim 4, wherein the antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of: SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO.

38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 7/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, and SEQ ID NO. 69/SEQ ID NO. 70.

6. The fully human antibody Fab fragment of claim 5, wherein the antibody has a $K_D$ of at least 1 x $10^{-6}$ M.

7. An anti-TIM3 single chain human antibody comprising a heavy chain variable domain and a light chain variable domain which are connected by a peptide linker, wherein the heavy chain variable domain comprises an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69 and;

the light chain variable domain comprises an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

8. The fully human single chain antibody of claim 7, wherein the single chain fully human antibody comprises a heavy chain/light chain variable domain sequence selected from the group consisting of: SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ

ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 7/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, and SEQ ID NO. 69/SEQ ID NO. 70.

9. The fully human single chain antibody of claim 7 or 8, wherein the antibody has a $K_D$ of at least 1 x $10^{-6}$ M.

10. A method for treating cancer, or an inflammatory or autoimmune disease, said method comprising administering an effective amount of an anti-TIM3 antibody or antibody fragment of any one of claims 1 to 9, to a subject in need thereof.

11. The method of claim 10, wherein the cancer is selected from the group consisting of ovarian cancer, colon cancer, breast cancer, lung cancer, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, and mast cell derived tumors.

12. The method of claim 10, wherein the autoimmune or inflammatory disease is selected from the group consisting of intestinal mucosal inflammation, wasting disease associated with colitis, multiple sclerosis, systemic lupus erythematosus, viral infections, rheumatoid arthritis, osteoarthritis, psoriasis, Crohn's disease, and inflammatory bowel disease.

13. A method for treating cancer, or an inflammatory or autoimmune disease, comprising administering an effective amount of an anti-TIM3 polypeptide, wherein the anti-TIM3 polypeptide is selected from the group consisting of

an isolated anti-TIM3 fully human antibody of an IgG class comprising a heavy chain variable domain and a light chain variable domain,

an anti-TIM3 fully human antibody Fab fragment comprising a heavy chain variable domain and a light chain variable domain, and

a single chain human antibody, comprising a heavy chain variable domain, a light chain variable domain, and a peptide linker connecting the heavy chain and the light chain;

wherein the heavy chain variable domain comprises an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69; and

wherein the light chain variable domain comprises an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

14. The method of claim 13, wherein the antibody or antibody fragment comprises a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 23/SEQ ID NO. 24, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 32, SEQ ID NO. 33/SEQ ID NO. 34, SEQ ID NO. 35/SEQ ID NO. 36, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 39/SEQ ID NO. 40, SEQ ID NO. 41/SEQ ID NO. 42, SEQ ID NO. 43/SEQ ID NO. 44, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 55/SEQ ID NO. 56, SEQ ID NO. 57/SEQ ID NO. 58, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 7/SEQ

ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 67/SEQ ID NO. 68, and SEQ ID NO. 69/SEQ ID NO. 70.

15. An isolated anti-TIM3 antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain comprising complementarity determining regions (CDRs) as set forth in a heavy chain variable domain amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 23, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 33, SEQ ID NO. 35, SEQ ID NO. 37, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 59, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 67, and SEQ ID NO. 69; and

comprising a light chain variable domain comprising CDRs as set forth in a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 24, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 32, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 38, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 68, and SEQ ID NO. 70.

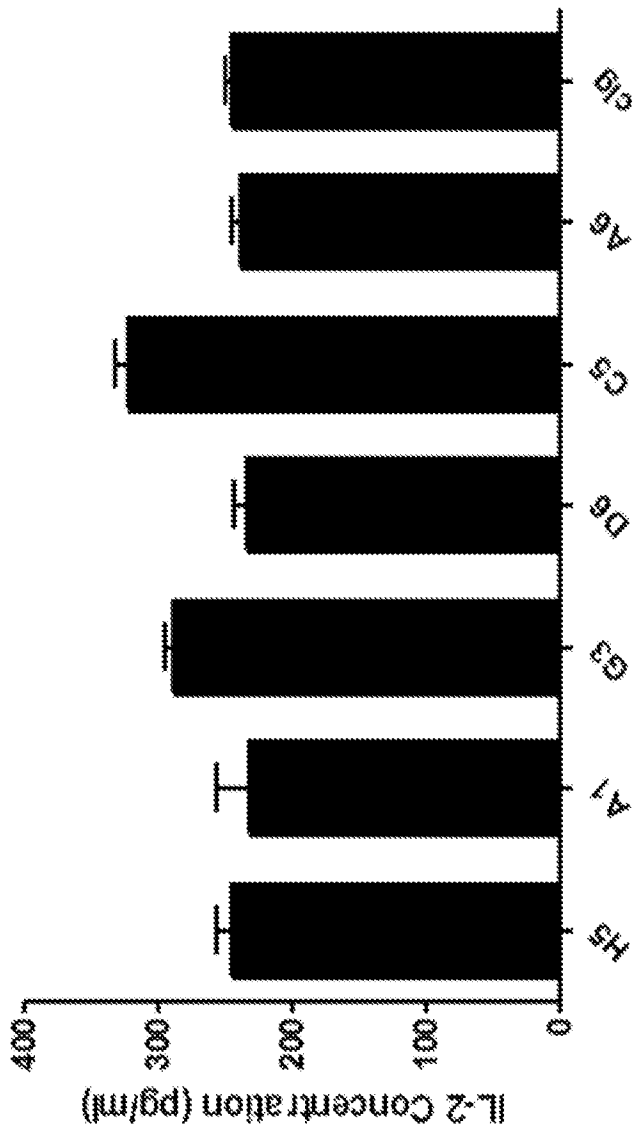
16. A pharmaceutical composition comprising the anti-TIM3 antibody, or antibody fragment of any one of claims 1 to 9 or 15, and a pharmaceutically acceptable carrier.

17. A method of treating cancer, or an inflammatory or autoimmune disease, in a human subject in need thereof, comprising administering an effective amount of the anti-TIM3 antibody, or antigen-binding fragment thereof, of claim 15 to the subject, such that cancer is treated.

18. The method of claim 17, wherein the cancer is selected from the group consisting of: ovarian cancer, colon cancer, breast cancer, lung cancer, myelomas, neuroblastic-derived CNS tumors, monocytic leukemias, B-cell derived leukemias, T-cell derived leukemias, B-cell derived lymphomas, T-cell derived lymphomas, and mast cell derived tumors.

19. The method of claim 17, wherein the autoimmune or inflammatory disease is selected from the group consisting of: intestinal mucosal inflammation, wasting disease associated with colitis, multiple sclerosis, systemic lupus erythematosus, viral infections, rheumatoid arthritis, osteoarthritis, psoriasis, Crohn's disease, and inflammatory bowel disease.

Figure 1



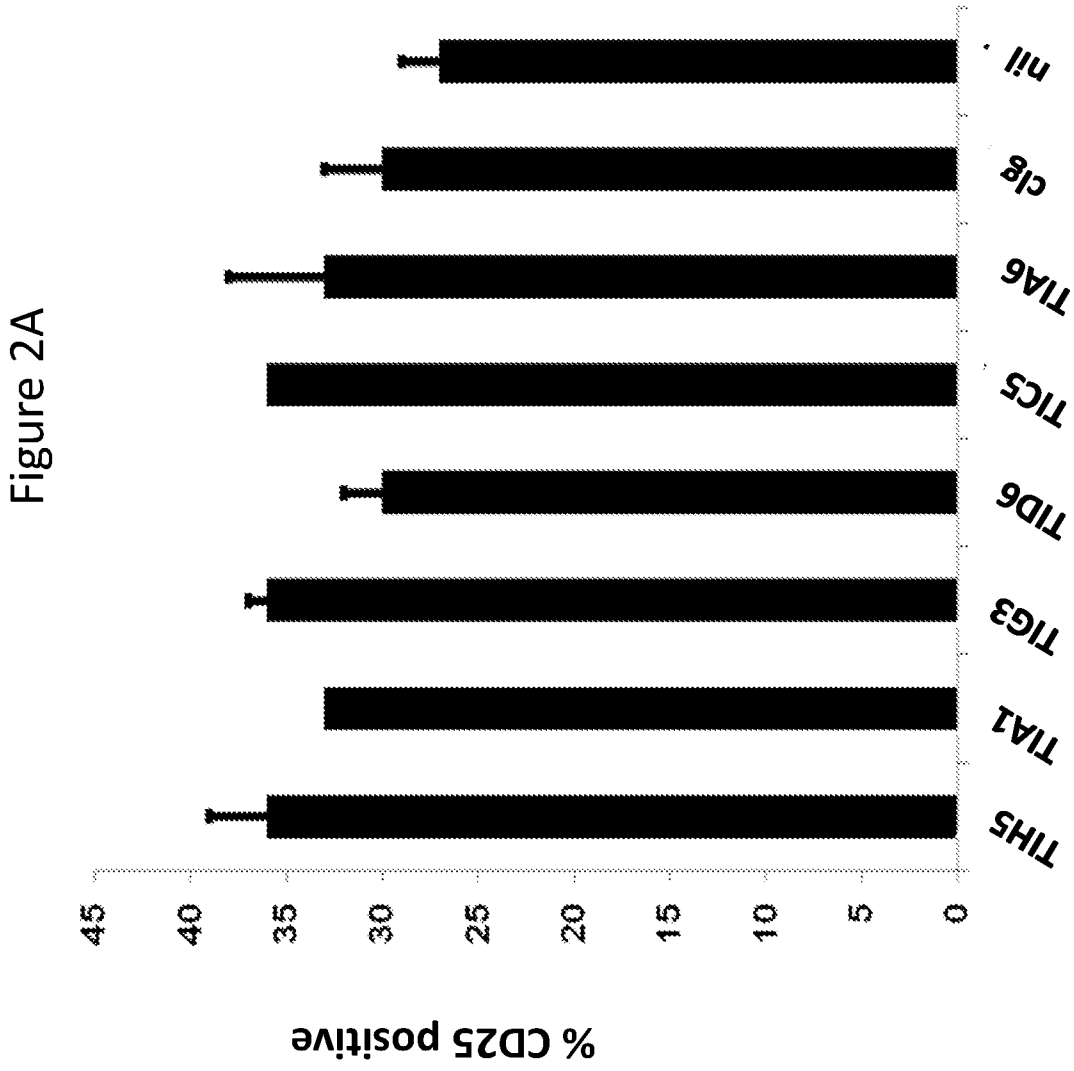

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Figure 2A

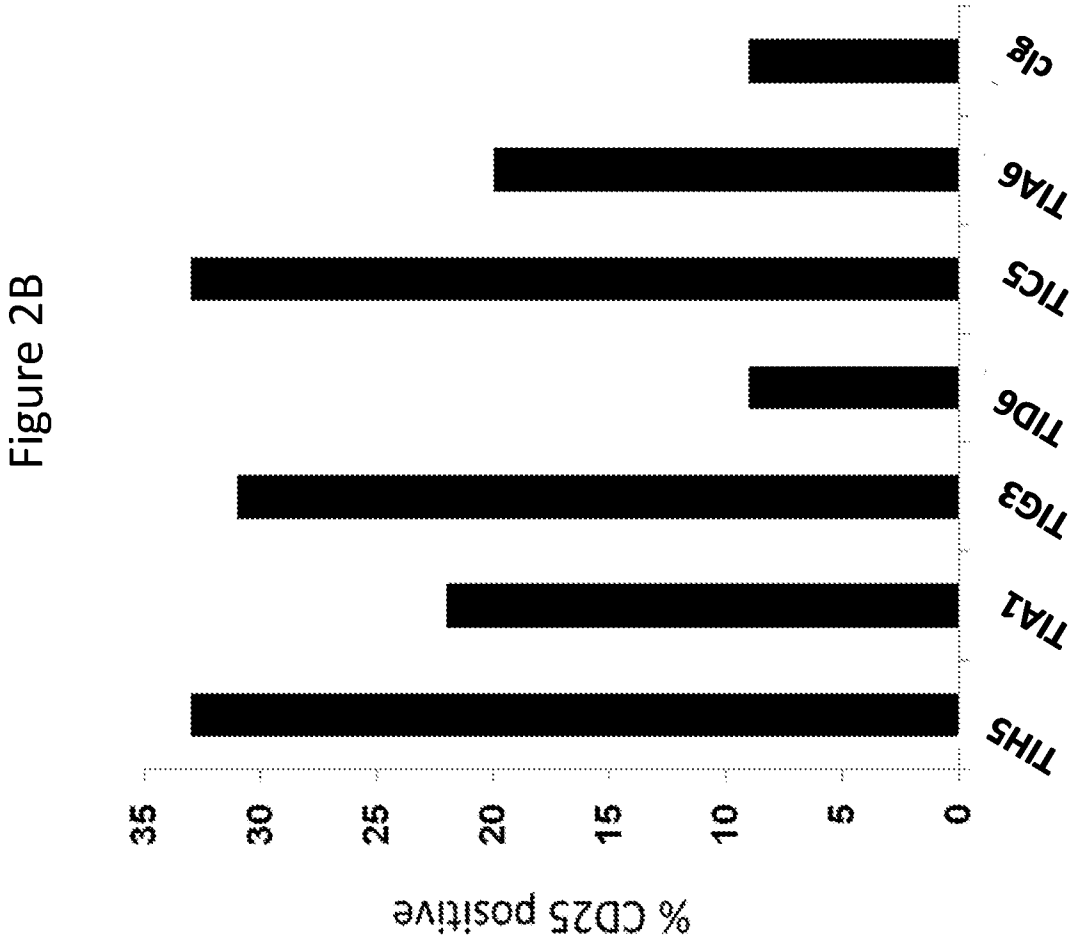
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Figure 2B

Figure 3A

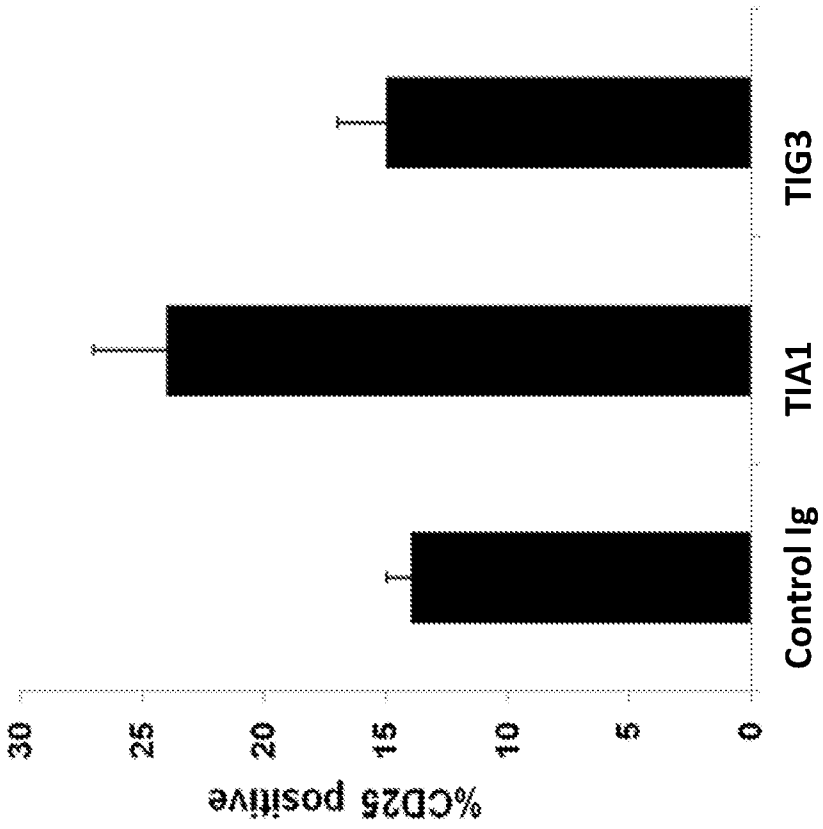
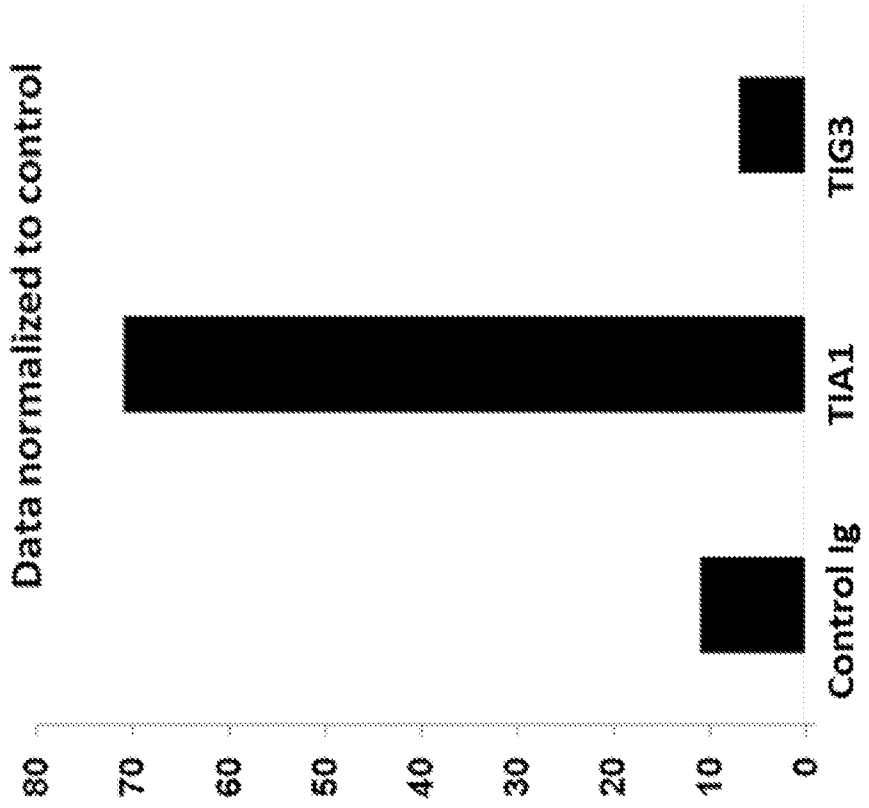


Figure 3B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