

ANTI-TREM1 ANTIBODIES AND RELATED METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/802,161, filed February 6, 2019, and U.S. Provisional Application No. 62/889,994, filed on August 21, 2019, which are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 17, 2020, is named PII-010WO_SL.txt, and is 92,256 bytes in size.

BACKGROUND

[0003] Immunity plays a role in preventing tumor outgrowth. A complex microenvironment can develop within the lesion, and despite the recruitment of T-cells, there is often no effective control of the developing mass. Understanding the balance between tumor elimination and tumor escape may rely on a comprehension of the differential roles myeloid cells play in the tumor microenvironment.

[0004] Myeloid populations of the tumor microenvironment prominently include monocytes and neutrophils (sometimes loosely grouped as myeloid-derived suppressor cells), macrophages, and dendritic cells. Although intra-tumoral myeloid populations, as a whole, have long been considered non-stimulatory or suppressive, it has more recently been appreciated that not all tumor-infiltrating myeloid cells are functionally equivalent.

[0005] In normal tissues, many of these myeloid cells are essential for proper functioning of both innate and adaptive immunity and notably for wound repair. However, in the setting of cancer, a significant excess of macrophages and dysfunctional or skewed populations of these and other cell types are commonly described. When considered as an aggregate population defined by single markers, such as CD68 or CD163, "macrophage" infiltration is correlated with worse outcomes in patients across multiple tumor types ((de Visser, *Cancer Immunol Immunother*, 2008;57:1531–9); (Hanada et al., *Int J Urol* 2000;7:263–9); (Yao et al. *Clin Cancer Res*, 520, 2001;7:4021–6); (Ruffell et al., *PNAS*, 523 2012;109:2796–801)). But the phenotypic and functional subsetting of macrophages from the tumor microenvironment is complicated by the similarity of macrophages and dendritic cells, and is problematic in tumor biology. A morphologic criterion has been often applied to the issue; one approach to try to differentiate dendritic cells from macrophages was based on a more spikey or dendritic morphology for the former and more veiled or bulbous morphology for the latter (Bell et al., *J Exp Med* 555, 1999;190:1417–26). Other groups are trying to differentiate on the basis of genetic and cell-surface markers.

[0006] There is diversity in the antigen-presenting compartment within tumors, and T-cells can differentiate features of antigen-presenting cells (APC). Because T cells are a major driver of tumor

immunity, understanding the exact features of their cognate APCs will be important. Myeloid cells are prominent among cells capable of presenting tumor-derived antigens to T-cells and thereby maintaining the latter in an activated state. Antigen presentation occurs within the tumor itself and likely influences the functions of tumor cytotoxic T-lymphocytes (CTLs). T-cell activation by antigen presenting cells (APC) is an important component in antigen-specific immune responses and tumor cell killing. As these myeloid populations represent major T-cell-interacting partners and antigen-presenting cells for incoming tumor-reactive cytotoxic T lymphocytes, understanding their distinctions may guide therapeutic avenues.

[0007] Triggering Receptor Expressed on Myeloid Cells 1 (TREM1, but also known as CD354, HGNC: 17760, Entrez Gene: 54210, UniProtKB: Q9NP99) belongs to the Ig superfamily of receptors and is highly expressed on subsets of myeloid cells including neutrophils, monocytes and macrophages. TREM1 lacks signaling motifs and instead, receptor activation is mediated through the adapter DAP12 (DNAX-activating protein 12) that leads to amplification of inflammatory responses (Bouchon, et al (2000) J. Immunol.164 (10): 4991-4995). Specifically, crosslinking of TREM1 induces expression of IL-8, myeloperoxidase, TNF α and MCP-1. TREM1 expression is up-regulated on myeloid cells in response to Toll-Like Receptor stimulation (bacterial and fungi stimulation), and has been shown to contribute to, and amplify the acute inflammatory response during septic shock and infection (Cohen, (2001) Lancet. 358: 776-778). While the ligand for TREM1 has remained elusive, recently, PGLYRP1 (peptidoglycan recognition protein 1) has been identified as a potent ligand of TREM1 (Read et al, (2015) J of Immunol. 194: 1417-1421). In mice there are 5 activating forms of TREM receptors including TREM 1, 2, 3, 4, and 5, with a soluble form of TREM1 (sTREM1) released during infection. Mouse TREM1 and the human homolog TREM1 share relatively low sequence identity of 46% (Radaev, et al. (2003) Structure 11: 1527-1535). Structurally TREM1 consists of a single V-type immunoglobulin (Ig)-like domain (Ig-V) of about 108 amino acids, followed by a 70 amino acid stalk region. In addition to the role TREM1 plays in sepsis, it has also been linked to inflammatory bowel disease. However very little is known about the role of TREM1 in the tumor microenvironment. (Schenk, et al (2007) JCI. 117: 3097-3106).

[0008] An unmet need exists for novel cancer therapeutic approaches that involve selectively decreasing the amount of cells that are ineffective at stimulating T-cell responses or repolarizing such cells, thereby enhancing an immune response within the tumor microenvironment.

[0009] Related patent applications include: PCT/US2018/045680, filed August 7, 2018 which is herein incorporated by reference, in its entirety, for all purposes.

SUMMARY

[0009a] In one aspect, the present disclosure refers to an isolated antibody that binds to human TREM1 (SEQ ID NO: 1), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

- a. CDR-H1 comprises the sequence set forth in SEQ ID NO: 23,
- b. CDR-H2 comprises the sequence set forth in SEQ ID NO: 24,
- c. CDR-H3 comprises the sequence set forth in SEQ ID NO: 33,
- d. CDR-L1 comprises the sequence set forth in SEQ ID NO: 26,
- e. CDR-L2 comprises the sequence set forth in SEQ ID NO: 27, and
- f. CDR-L3 comprises the sequence set forth in SEQ ID NO: 28.

[0009b] In another aspect, the present disclosure refers to a method of producing an antibody comprising expressing the antibody as described herein from an isolated host cell and isolating the expressed antibody.

[0009c] In another aspect, the present disclosure refers to a kit comprising the antibody as described herein and instructions for use.

[0009d] In another aspect, the present disclosure refers to an isolated antibody that binds to human TREM1 (SEQ ID NO: 1), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:

- a. CDR-H1 comprises the sequence set forth in SEQ ID NO: 23,
- b. CDR-H2 comprises the sequence set forth in SEQ ID NO: 24,
- c. CDR-H3 comprises the sequence set forth in SEQ ID NO: 32,
- d. CDR-L1 comprises the sequence set forth in SEQ ID NO: 26,
- e. CDR-L2 comprises the sequence set forth in SEQ ID NO: 27, and
- f. CDR-L3 comprises the sequence set forth in SEQ ID NO: 28.

[0010] In one example, provided herein are isolated antibodies that binds to human TREM1 (SEQ ID NO: 1), wherein the antibody *i*) binds within residues 21-34 (SEQ ID NO: 42), 103-109 (SEQ ID NO: 43), and 110-116 (SEQ ID NO: 44).

43), and 128-136 (SEQ ID NO: 44) of human TREM1 (SEQ ID NO: 1); and *ii*) comprises a human Fc region.

[0011] In one example, provided herein are isolated, humanized antibodies that binds to human TREM1 (SEQ ID NO: 1), wherein the antibody *i*) binds within residues 21-34 (SEQ ID NO: 42), 103-109 (SEQ ID NO: 43), and 128-136 (SEQ ID NO: 44) of human TREM1 (SEQ ID NO: 1); and *ii*) optionally comprises a human Fc region.

[0012] In one example, provided herein is an isolated antibody or antibodies that bind(s) to human TREM1 (SEQ ID NO: 1), comprising a variable heavy (VH) chain sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light (VL) chain sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence set forth in SEQ ID NO: 23, CDR-H2 comprises the sequence set forth in SEQ ID NO: 24, CDR-H3 comprises the sequence set forth in SEQ ID NO: 29, wherein X is leucine (L), glutamine (Q), methionine (M), isoleucine (I), or glutamic acid (E), CDR-L1 comprises the sequence set forth in SEQ ID NO: 26, CDR-L2 comprises the sequence set forth in SEQ ID NO: 27, and CDR-L3 comprises the sequence set forth in SEQ ID NO: 28. In one example, provided herein is an isolated antibody or antibodies that bind(s) to human TREM1 (SEQ ID NO: 1), comprising a heavy chain comprising a variable heavy (VH) chain sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a light chain comprising a variable light (VL) chain sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein: CDR-H1 comprises the sequence set forth in SEQ ID NO: 23, CDR-H2 comprises the sequence set forth in SEQ ID NO: 24, CDR-H3 comprises the sequence set forth in SEQ ID NO: 29, wherein X is leucine (L), glutamine (Q), methionine (M), isoleucine (I), or glutamic acid (E), CDR-L1 comprises the sequence set forth in SEQ ID NO: 26, CDR-L2 comprises the sequence set forth in SEQ ID NO: 27, and CDR-L3 comprises the sequence set forth in SEQ ID NO: 28.

[0013] In some examples, the antibody comprises a CDR-H3 comprising the sequence RXAAMDY (SEQ ID NO: 29), wherein X is leucine (L), glutamine (Q), methionine (M), isoleucine (I), or glutamic acid (E). In some examples, the antibody further comprises a CDR-H1 comprising the sequence set forth in SEQ ID NO: 23 and a CDR-H2 comprising the sequence set forth in SEQ ID NO: 24. In some examples, the CDR-H3 comprises the sequence set forth in SEQ ID NO: 33; and the antibody further comprises a CDR-H1 comprising the sequence set forth in SEQ ID NO: 23 and a CDR-H2 comprising the sequence set forth in SEQ ID NO: 24.

[0014] In some examples, the antibody further comprises a CDR-L1 comprising the sequence set forth in SEQ ID NO: 26, a CDR-L2 comprising the sequence set forth in SEQ ID NO: 27, and a CDR-L3 comprising the sequence set forth in SEQ ID NO: 28.

[0015] In some examples, the antibody comprises a VH sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18. In some examples, the antibody comprises the VH sequence set forth in SEQ ID NO: 17.

[0016] In some examples, the antibody comprises a VL sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22. In some examples, the antibody comprises the VL sequence set forth in SEQ ID NO: 20.

[0017] In some examples, the antibody comprises the VH sequence set forth in SEQ ID NO: 17, and the VL sequence set forth in SEQ ID NO: 20.

[0018] In some examples, the antibody is an scFv. In some examples, the antibody is an scFv and comprises the VH sequence set forth in SEQ ID NO: 17, and the VL sequence set forth in SEQ ID NO: 20.

[0019] In some examples, the antibody is an scFv and comprises a VH sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18 and a VL sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22. In some examples, the antibody comprises the VH sequence set forth in SEQ ID NO: 17, and the VL sequence set forth in SEQ ID NO: 20; and the human Fc region comprises wild-type, human IgG1 Fc.

[0020] In some examples, the antibody comprises the heavy chain sequence set forth in SEQ ID NO: 34 and the light chain sequence set forth in SEQ ID NO: 35.

[0021] In some examples, the antibody comprises the VH sequence selected from the sequences set forth in SEQ ID NOs: 4, 5, or 6.

[0022] In some examples, the antibody comprises a VL sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.

[0023] In some examples, the antibody comprises the VH sequence selected from the sequences set forth in SEQ ID NOs: 8, 9 or 10.

[0024] In some examples, the CDR-H3 comprises the sequence set forth in SEQ ID NO: 32, and the antibody further comprises a CDR-H1 comprising the sequence set forth in SEQ ID NO:23 and a CDR-H2 comprising the sequence set forth in SEQ ID NO:24.

[0025] In some examples, the antibody comprises the VH sequence selected from the sequences set forth in SEQ ID NOs: 12, 13 or 14. In some examples, the antibody comprises the VH sequence set forth in SEQ ID NO: 13.

[0026] In some examples, the antibody comprises a VL sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22. In some examples, the antibody comprises the VL sequence set forth in SEQ ID NO: 20.

[0027] In some examples, the antibody comprises the VH sequence set forth in SEQ ID NO: 13, and the VL sequence set forth in SEQ ID NO: 20. In some examples, the antibody is an scFv

and comprises the VH sequence set forth in SEQ ID NO: 13, and the VL sequence set forth in SEQ ID NO: 20.

[0028] In some examples, the antibody is an scFv and comprises a VH sequence selected from the sequences set forth in SEQ ID NO: 112, 13 or 14 and a VL sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.

[0029] In some examples, the antibody comprises the VH sequence set forth in SEQ ID NO: 13, and the VL sequence set forth in SEQ ID NO: 20; and the human Fc region comprises wild-type, human IgG1 Fc.

[0030] In some examples, the antibody comprises the heavy chain sequence set forth in SEQ ID NO: 36 and the light chain sequence set forth in SEQ ID NO: 37.

[0031] In some examples, the antibody consists of the VH sequence set forth in SEQ ID NO: 17, 13, or 9; and the VL sequence set forth in SEQ ID NO: 20. In some examples, the antibody consists of the VH sequence set forth in SEQ ID NO: 17; and the VL sequence set forth in SEQ ID NO: 20. In some examples, the antibody consists of the VH sequence set forth in SEQ ID NO: 13; and the VL sequence set forth in SEQ ID NO: 20. In some examples, the antibody consists of the VH sequence set forth in SEQ ID NO: 9; and the VL sequence set forth in SEQ ID NO: 20.

[0032] In some examples, the antibody the heavy chain consists of the heavy chain sequence set forth in SEQ ID NO: 34 and the light chain sequence set forth in SEQ ID NO: 35.

[0033] In some examples, the antibody consists of the heavy chain sequence set forth in SEQ ID NO: 36 and the light chain sequence set forth in SEQ ID NO: 37.

[0034] In some examples, the antibody is afucosylated.

[0035] In another example, provided herein are isolated antibodies that binds to human TREM1 (SEQ ID NO: 1), wherein the antibody is afucosylated, and the antibody comprises the VH sequence set forth in SEQ ID NO: 17, 13, or 9; and the VL sequence set forth in SEQ ID NO: 20. In some examples, the antibody comprises the VH sequence set forth in SEQ ID NO: 17, and the VL sequence set forth in SEQ ID NO: 20.

[0036] In some examples, the antibody comprises the heavy chain sequence set forth in SEQ ID NO: 34 and the light chain sequence set forth in SEQ ID NO: 35.

[0037] In some examples, the antibody comprises the VH sequence set forth in SEQ ID NO: 13, and the VL sequence set forth in SEQ ID NO: 20.

[0038] In some examples, the antibody is afucosylated, and the antibody comprises the heavy chain sequence set forth in SEQ ID NO: 36 and the light chain sequence set forth in SEQ ID NO: 37.

[0039] In some examples, the antibody comprises the VH sequence set forth in SEQ ID NO: 9, and the VL sequence set forth in SEQ ID NO: 20.

[0040] In some examples, the antibody is afucosylated, and the antibody comprises the heavy chain sequence set forth in SEQ ID NO: 38 and the light chain sequence set forth in SEQ ID NO: 39.

[0041] In some examples, the antibody is a humanized, human, or chimeric antibody. In some examples, the antibody is a humanized antibody. In some examples, the antibody comprises a heavy chain human constant region of a class selected from IgG, IgA, IgD, IgE, and IgM. In some examples, the antibody comprises an Fc region. In some examples, the Fc region is a human Fc region. In some examples, the human Fc region comprises a human heavy chain constant region of the class IgG and a subclass selected from IgG1, IgG2, IgG3, and IgG4. In some examples, the human Fc region comprises wild-type, human IgG1 Fc.

[0042] In some examples, the antibody consists of the VH sequence set forth in SEQ ID NO: 17, and the VL sequence set forth in SEQ ID NO: 20; and the human Fc region comprises wild-type, human IgG1 Fc.

[0043] In some examples, the Fc region comprises one or more amino acid substitutions, wherein the one or more substitutions result in increased antibody half-life, increased ADCC activity, increased ADCP activity, or increased CDC activity compared with the Fc without the one or more substitutions. In some examples, the Fc region binds an Fcγ Receptor selected from the group consisting of: FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa, and FcγRIIIb.

[0044] In some examples, the antibody is a monoclonal antibody.

[0045] In some examples, the antibody binds to human TREM1 with a KD of less than or equal to about 0.5, 1, 2, 3, 4, 5, 6, or 7x10⁻⁹ M, as measured by surface plasmon resonance (SPR) assay. In some examples, the antibody binds to human TREM1 with a KD of less than or equal to about 7 nM as measured by surface plasmon resonance (SPR) assay.

[0046] In some examples, the antibody is an agonistic antibody.

[0047] In some examples, the antibody induces increased expression of at least one cytokine or chemokine in a cell as compared to an isotype control antibody.

[0048] In some examples, wherein the at least one cytokine or chemokine is selected from the group consisting of: IFN-γ, IL-1α, IL-12, IL-2, TNFSF9, TNFSF10, CXCL9, CXCL10, CCL17, CXCL1, CXCL5, CXCL8, CXCL11, CXCL15, CCL3, CCL4, CCL2, FasL, CD274, CRTAM, granzyme A (GzmA), or granzyme B (GzmB). In some examples, the cytokine or chemokine is CXCL10 or IFN-γ.

[0049] In some examples, the antibody induces increased expression of at least one myeloid co-stimulatory protein in a cell as compared to an isotype control antibody.

[0050] In some examples, the myeloid co-stimulatory protein is HLA-DR, CD40, CD80, or CD86 in a cell.

[0051] In some examples, the antibody induces increased activation of the ERK and/or STAT3 intracellular signaling pathways in a cell as compared to an isotype control antibody.

[0052] In some examples, the antibody induces an anti-tumor memory response as compared to an isotype control antibody.

[0053] In some examples, the antibody: competes for binding to human TREM1 with human TREM-26 antibody; binds to human TREM1; binds to cynomolgus TREM1; stimulates TREM1 signaling; induces immune signaling pathways; induces cytokine or chemokine secretion; induces co-stimulatory molecule expression; kills, disables, or depletes myeloid cells; or is capable of any combination of a.- h.

[0054] In some examples, the antibody has antibody-dependent cell-mediated cytotoxicity (ADCC) activity, In some examples, the antibody has antibody-mediated cellular phagocytosis (ADCP) activity. In some examples, the antibody has complement-dependent cytotoxicity (CDC) activity.

[0055] In some examples, the cell is a TREM1+ cell.

[0056] In some examples, the TREM1+ cell is selected from the group consisting of: dendritic cells, tumor associated macrophages (TAMs), myeloid-derived suppressive cells (MDSCs), neutrophils, and tumor associated neutrophils (TANs). In some examples, the TREM1+ cell is a myeloid-derived suppressive cell or a tumor associated neutrophil.

[0057] In some examples, the antibody crosslinks TREM1 to TREM1 on the cell surface of a TREM1+ cell.

[0058] In some examples, the isolated antibody is for use as a medicament. In some examples, the isolated antibody is for use in the treatment of a cancer or infection. In some examples, the isolated antibody is for use in the treatment of a cancer, wherein the cancer is selected from a solid tumor and a liquid tumor.

[0059] In another example, provided herein are isolated polynucleotides or set of polynucleotides encoding the antibody as described herein, a VH thereof, a VL thereof, a light chain thereof, a heavy chain thereof, or an antigen-binding portion thereof; optionally cDNA.

[0060] In another example, provided herein are vectors or set of vectors comprising the polynucleotide or set of polynucleotides as described herein.

[0061] In another example, provided herein are host cells comprising the polynucleotide or set of polynucleotides or the vector or set of vectors as described herein.

[0062] In another example, provided herein are methods of producing an antibody comprising expressing the antibody with the host cell and isolating the expressed antibody.

[0063] In another aspect, provided herein are pharmaceutical compositions comprising the antibody as described herein and a pharmaceutically acceptable excipient.

[0064] In another example, provided herein are kits comprising an antibody or a pharmaceutical composition as described herein and instructions for use.

[0065] In another example, provided herein are methods of increasing an immune response comprising administering to a subject a composition comprising an anti-TREM1 antibody or antigen binding fragment thereof.

- [0066]** In some examples, the composition comprises an antibody or the pharmaceutical composition as described herein.
- [0067]** In some examples, the antibody has receptor-ligand blocking, agonist, or antagonist activity.
- [0068]** In some examples, the antibody has agonist activity.
- [0069]** In some examples, the antibody induces increased expression of at least one cytokine or chemokine in a cell as compared to an isotype control antibody.
- [0070]** In some examples, the at least one cytokine or chemokine is selected from the group consisting of: IFN- γ , IL-1 α , IL-12, IL-2, TNFSF9, TNFSF10, CXCL9, CXCL10, CCL17, CXCL1, CXCL5, CXCL8, CXCL11, CXCL15, CCL3, CCL4, CCL2, FasL, CD274, CRTAM, granzyme A (GzmA), or granzyme B (GzmB).
- [0071]** In some examples, the cytokine or chemokine is CXCL10 or IFN- γ .
- [0072]** In some examples, the antibody induces increased expression of at least one myeloid co-stimulatory protein as compared to an isotype control antibody.
- [0073]** In some examples, the myeloid co-stimulatory protein is HLA-DR, CD40, CD80, or CD86 in a cell.
- [0074]** In some examples, the antibody induces increased activation of the ERK and/or STAT3 intracellular signaling pathways in a cell as compared to an isotype control antibody.
- [0075]** In some examples, the antibody induces a memory immune response.
- [0076]** In some examples, the cell is a TREM1+ cell.
- [0077]** In some examples, the TREM1+ cell is selected from the group consisting of: dendritic cells, tumor associated macrophages (TAMs), myeloid-derived suppressive cells (MDSCs), neutrophils, and tumor associated neutrophils (TANs).
- [0078]** In some examples, the TREM1+ cell is a myeloid-derived suppressive cell or a tumor associated neutrophil.
- [0079]** In some examples, the antibody crosslinks TREM1 to TREM1 on the cell surface of a TREM1+ cell.
- [0080]** In some examples, the subject is human.
- [0081]** In another example, provided herein are methods of treating cancer, comprising administering to a subject a composition comprising an anti-TREM1 antibody or antigen binding fragment thereof.
- [0082]** In some examples, the composition comprises an antibody or a pharmaceutical composition as described herein.
- [0083]** In some examples, the antibody has receptor-ligand blocking, agonist, or antagonist activity.
- [0084]** In some examples, the antibody has agonist activity.

- [0085]** In some examples, the antibody induces increased expression of at least one cytokine or chemokine in a cell as compared to an isotype control antibody.
- [0086]** In some examples, the at least one cytokine or chemokine is selected from the group consisting of: IFN- γ , IL-1 α , IL-12, IL-2, TNFSF9, TNFSF10, CXCL9, CXCL10, CCL17, CXCL1, CXCL5, CXCL8, CXCL11, CXCL15, CCL3, CCL4, CCL2, FasL, CD274, CRTAM, granzyme A (GzmA), or granzyme B (GzmB).
- [0087]** In some examples, the cytokine or chemokine is CXCL10 or IFN- γ .
- [0088]** In some examples, the antibody induces increased expression of at least one myeloid co-stimulatory protein as compared to an isotype control antibody.
- [0089]** In some examples, the myeloid co-stimulatory protein is HLA-DR, CD40, CD80, or CD86 in a cell.
- [0090]** In some examples, the antibody induces increased activation of the ERK and/or STAT3 intracellular signaling pathways in a cell as compared to an isotype control antibody.
- [0091]** In some examples, the antibody induces an anti-tumor memory response as compared to an isotype control antibody.
- [0092]** In some examples, the antibody has antibody-dependent cell-mediated cytotoxicity (ADCC) activity.
- [0093]** In some examples, the antibody has complement-dependent cytotoxicity (CDC) activity.
- [0094]** In some examples, the antibody has antibody-mediated phagocytosis (ADCP) activity.
- [0095]** In some examples, the cell is a TREM1⁺ cell.
- [0096]** In some examples, the TREM1⁺ cell is selected from the group consisting of: dendritic cells, tumor associated macrophages (TAMs), myeloid-derived suppressive cells (MDSCs), neutrophils, and tumor associated neutrophils (TANs).
- [0097]** In some examples, the TREM1⁺ cell is a myeloid-derived suppressive cell or a tumor associated neutrophil.
- [0098]** In some examples, the antibody crosslinks TREM1 to TREM1 on the cell surface of a TREM1⁺ cell.
- [0099]** In some examples, the subject is human.
- [0100]** In some examples, the cancer is a solid cancer.
- [0101]** In some examples, the cancer is a liquid cancer.
- [0102]** In some examples, the cancer is selected from the group consisting of: melanoma, kidney, hepatobiliary, head and neck squamous carcinoma (HNSC), pancreatic, colon, bladder, urothelial, glioblastoma, prostate, lung, breast, ovarian, gastric, esophageal, renal, endometrial, cervical, testicular, and mesothelioma cancers.

[0103] In some examples, the cancer is gastric cancer, ovarian cancer, colon cancer, or breast cancer.

[0104] In some examples, the contacting enhances an immune response in the subject.

[0105] In some examples, the enhanced immune response is an adaptive immune response.

[0106] In some examples, the enhanced immune response is an innate immune response.

[0107] In some examples, the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

[0108] In some examples, the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; anti-PD1 antibody; anti-PDL1 antibody; anti-CTLA4 antibody; adoptive cell therapy; adoptive T cell therapy; CAR-T cell therapy; a dendritic cell vaccine; a STING agonist; a monocyte vaccine; Bacillus Calmette-Guerin vaccine; an antigen binding protein that binds both a T cell and an antigen presenting cell; a BiTE dual antigen binding protein; a toll-like receptor ligand; a cytokine; a cytotoxic therapy; a chemotherapy; a radiotherapy; a small molecule inhibitor; a small molecule agonist; an immunomodulator; an oncolytic virus; and an epigenetic modulator.

[0109] In some examples, the immunotherapy is selected from the group consisting of: an anti-PD1 antibody, an anti-PDL1 antibody; or an anti-CTLA4 antibody.

[0110] In another example, provided herein are methods of killing, disabling, or depleting myeloid cells that express Triggering Receptor Expressed on Myeloid Cells 1 (TREM1) on the cell surface, comprising contacting the myeloid cells with a antibody or a pharmaceutical composition as described herein.

[0111] In some examples, the antibody kills, disables, or depletes the myeloid cells by at least one of ADCC, CDC, and ADCP, optionally wherein the antibody kills, disables, or depletes the myeloid cells by ADCC, optionally wherein the antibody kills, disables, or depletes the myeloid cells by CDC, and optionally wherein the antibody kills, disables, or depletes the myeloid cells by ADCP.

[0112] In some examples, the antibody kills the myeloid cells by at least one of ADCC, CDC, and ADCP.

[0113] In some examples, the antibody disables the myeloid cells by at least one of ADCC, CDC, and ADCP.

[0114] In some examples, the antibody depletes the myeloid cells by at least one of ADCC, CDC, and ADCP.

[0115] In some examples, the antibody has antibody-dependent cell-mediated cytotoxicity (ADCC) activity.

[0116] In some examples, the antibody has complement-dependent cytotoxicity (CDC) activity.

[0117] In some examples, the antibody has antibody-mediated phagocytosis (ADCP) activity.

- [0118] In some examples, the antibody has receptor-ligand blocking, agonist, or antagonist activity.
- [0119] In some examples, the myeloid cells are stimulatory myeloid cells.
- [0120] In some examples, the myeloid cells are non-stimulatory myeloid cells.
- [0121] In some examples, the myeloid cells comprise at least one of dendritic cells, tumor-associated macrophages (TAMs), neutrophils, monocytes, or myeloid-derived suppressor cells.
- [0122] In some examples, the myeloid cells are neutrophils or tumor associated neutrophils.
- [0123] In some examples, the myeloid cells are tumor associated macrophages.
- [0124] In some examples, the myeloid cells are monocytic myeloid-derived suppressor cells.
- [0125] In some examples, the myeloid cells are intratumoral.
- [0126] In some examples, the myeloid cells are in a population of immune cells comprising stimulatory myeloid cells and non-stimulatory myeloid cells.
- [0127] In some examples, the contacting is in vitro or in vivo.
- [0128] In some examples, the contacting occurs in vivo in a subject, optionally wherein the subject has cancer.
- [0129] In some examples, the subject is human.
- [0130] In some examples, the cancer is a solid cancer.
- [0131] In some examples, the cancer is a liquid cancer.
- [0132] In some examples, the cancer is selected from the group consisting of: melanoma, kidney, hepatobiliary, head and neck squamous carcinoma (HNSC), pancreatic, colon, bladder, urothelial, glioblastoma, prostate, lung, breast, ovarian, gastric, esophageal, renal, endometrial, cervical, testicular, and mesothelioma cancers.
- [0133] In some examples, the cancer is gastric cancer, ovarian cancer, colon cancer, or breast cancer.
- [0134] In some examples, the contacting enhances an immune response in the subject.
- [0135] In some examples, the enhanced immune response is an adaptive immune response.
- [0136] In some examples, the enhanced immune response is an innate immune response.
- [0137] In some examples, the enhanced immune response comprises expression of at least one cytokine or chemokine.
- [0138] In some examples, the at least one cytokine or chemokine is selected from the group consisting of: IFN- γ , IL-1 α , IL-12, IL-2, TNFSF9, TNFSF10, CXCL9, CXCL10, CCL17, CXCL1, CXCL5, CXCL8, CXCL11, CXCL15, CCL3, CCL4, CCL2, FasL, CD274, CRTAM, granzyme A (GzmA), or granzyme B (GzmB).
- [0139] In some examples, the at least one cytokine or chemokine is CXCL10 or IFN- γ .

[0140] In some examples, the subject has previously received, is concurrently receiving, or will subsequently receive an immunotherapy.

[0141] In some examples, the immunotherapy is at least one of: a checkpoint inhibitor; a checkpoint inhibitor of T cells; anti-PD1 antibody; anti-PDL1 antibody; anti-CTLA4 antibody; adoptive cell therapy; adoptive T cell therapy; CAR-T cell therapy; a dendritic cell vaccine; a STING agonist; a monocyte vaccine; Bacillus Calmette-Guerin vaccine; an antigen binding protein that binds both a T cell and an antigen presenting cell; a BiTE dual antigen binding protein; a toll-like receptor ligand; a cytokine; a cytotoxic therapy; a chemotherapy; a radiotherapy; a small molecule inhibitor; a small molecule agonist; an immunomodulator; an oncolytic virus; and an epigenetic modulator.

[0142] In some examples, the immunotherapy is selected from the group consisting of: an anti-PD1 antibody, an anti-PDL1 antibody; or an anti-CTLA4 antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

[0143] These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description, and accompanying drawings, where:

[0144] **FIG. 1** shows the SPR binding kinetics of PI-4026-5.

[0145] **FIG. 2A** shows the binding of PI-4026-5 to HEK293 control cells. **FIG. 2B** shows the binding of PI-4026-5 to human TREM1 over-expressing HEK293 cells.

[0146] **FIG. 3A** shows the binding of PI-4026-5 to neutrophils in human peripheral blood. **FIG. 3B** shows the binding of PI-4026-5 to monocytes in human peripheral blood.

[0147] **FIG. 4A** show the binding of PI-4026-5 to cells expressing cynomolgus TREM1. **FIG. 4B** shows no binding of PI-4026-5 to cells expressing mouse TREM1.

[0148] **FIG. 5A** show FcγR signaling induced by PI-4026-5 using the hCD16 reporter assay systems. **FIG. 5B** show FcγR signaling induced by PI-4026-5 using the hCD32 reporter assay systems.

[0149] **FIGS. 6A** shows that PI-4026-5 does not induces ADCP of parental expi293 cells by primary human macrophages. **FIG. 6B** show that PI-4026-5 induces ADCP of expi293 cells expressing hTREM1 by primary human macrophages.

[0150] **FIG. 7A** shows the interaction of residues within the CDRH1 of the PI-4026 Fab and the TREM1 IgV domain. **FIG. 7B** shows the interaction of residues within the CDRH2 of the PI-4026 Fab and the TREM1 IgV domain. **FIG. 7C** shows the interaction of residues within the CDRH3 of the PI-4026 Fab and the TREM1 IgV domain. **FIG. 7D** shows the interaction of residues within the CDRL1 of the PI-4026 Fab and the TREM1 IgV domain. **FIG. 7E** shows the interaction of residues within the CDRL3 of the PI-4026 Fab and the TREM1 IgV domain.

[0151] **FIG. 8** shows the SEC profiles of PI-4026-5 after exposure to differential concentrations of H₂O₂.

[0152] **FIG. 9A** shows that fucosylated PI-4026-5 antibodies bind to human peripheral monocytes. **FIG. 9B** shows that afucosylated PI-4026-5 antibodies bind to human peripheral monocytes.

Example 1: Sequencing and Humanization of anti-TREM1 antibody

[0512] A monoclonal mouse IgG1 Clone TREM-26 specific for human TREM1 was obtained and used for sequence determination and humanization. In brief, disulfide bonds in the antibody were reduced with dithiothreitol (DTT) and free sulfhydryl groups were alkylated with iodoacetamide. The alkylated antibody was digested with sequencing-grade endoproteinases, purified using spin columns, and sequence was determined by LC-MS/MS analysis (see below).

[0513] A chimera antibody (PI-4026) was constructed by grafting the mouse antibody VL and VH regions to human IgG1 constant regions. The chimera was further humanized by cloning the antibody CDRs into human variable domain frameworks and ten additional humanized variants were made with different framework mutations, 4 VH variants and 4 VL variants (PI-4026-1-10).

[0514] The VH and VL sequences were compared to libraries of known human germline sequences on the NCBI website (ncbi.nlm.nih.gov/igblast/; Ye, J. et al. Nucleic Acids Research 41:W34-W40 (2013)). The databases used were IMGT human VH genes (F+ORF, 273 germline sequences) and IMGT human VLkappa genes (F+ORF, 74 germline sequences).

[0515] For the humanized PI-4026 VH, human germline IGHV1-46(allele 1) was chosen as the acceptor sequence and the human heavy chain IGHJ4(allele 1) joining region (J gene) was chosen from human joining region sequences compiled at IMGT® the international ImMunoGeneTics information system® www.imgt.org (founder and director: Marie-Paule Lefranc, Montpellier, France).

[0516] For the humanized PI-4026 VL, human germline IGKV1-39(allele 1) was chosen as the acceptor sequence and human light chain IGKJ2(allele 1) joining region (J gene) was chosen from human joining region sequences compiled at IMGT® the international ImMunoGeneTics information system® www.imgt.org (founder and director: Marie-Paule Lefranc, Montpellier, France).

[0517] CDRs were defined according to the AbM definition (see the website of Dr. Andrew C. R. Martin www.bioinf.org.uk/abs/ for a table comparing CDR definitions). Alteration of human germline framework (i.e., non-CDR residues in VH and VL) positions to corresponding parental murine sequence were used, e.g., to optimize binding of the humanized antibody.

[0518] **Table 1A** shows VH and VL sequences of the humanized versions of mAb PI-4026 that were created. 4026 VH-1 and 4026 VL-1 are the parent, humanized VH and VL clones from which the other humanized versions were created via additional framework mutations. Three humanized clones of the VH (4026 VH-2, VH-3, VH-4) and VL regions were made (4026 VL-2, VL-3, VL-4). **Table 1B** shows the CDR sequences.

Table 1A		
SEQ ID NO	Name	Sequence
7	4026 VH-1	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYVINWVRQAPGQGLEWMGEIYPGSGSTFYAQKFQGRVTMTTRDTSTSTVYMEISSLRSEDTAVYYCARRMAAMDYWGQGLTVTVSS

8	4026 VH-2	QVQLVQSGAEVKKPGASVKVSKASGYTFTDYVINWVRQAPGQGLEWMGEIYPGSGST FYAQKFQGRVTMTADTSTSTVYMELSLRSSEDTAVYYCTRRMAAMDYWGQGTLLTVSS
9	4026 VH-3	QVQLVQSGAEVKKPGASVKMSCKASGYTFTDYVINWVRQAPGQGLEWIGEIYPGSGST FYAQKFQGRATLTADTSTSTAYMEVSSLRSSEDTAVYYCTRRMAAMDYWGQGTLLTVSS
10	4026 VH-4	QVQLVQSGAEVKKPGASVKMSCKASGYTFTDYVINWVRQAPGQGLEWIGEIYPGSGST FYAQKFQGRATLTADKSTSTAYMEVSSLRSSEDTAVYYCTRRMAAMDYWGQGTLLTVSS
19	4026 VL-1	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMHYQQKPGKAPKLLIYTTSNLASGVP SRFSGSGSGTDFTLTISLQPEDFATYYCHQWSGYPTFGQGTKLEIK
20	4026 VL-2	DIQLTQSPSSLSASVGDRVTITCSASSSVSYMHYQQKPGKAPKLLLYTTSNLASGVP SRFSGSGSGTDYTLTISLQPEDFATYYCHQWSGYPTFGQGTKLEIK
21	4026 VL-3	DIQLTQSPSSLSASVGDRITLTCSASSSVSYMHYQQKPGKAPKLLLYTTSNLASGVP SRFSGSGSGTDYTLTISVQPEDFATYYCHQWSGYPTFGQGTKLEIK
22	4026 VL-4	DIQLTQSPSSLSASVGDRITLTCSASSSVSYMHYQQKPGKAPKLLLYTTSNLASGVP SRFSGSGSGTDYTLTISVQPEDAATYYCHQWSGYPTFGQGTKLEIK

Table 1C – CDRs of humanized antibodies

Table 1B		
SEQ ID NO	Name	Sequence
23	CDR H1	GYTFTDYVIN
24	CDR H2	EIYPGSGSTF
25	CDR H3	RMAAMDY
26	CDR L1	SASSSVSYMH
27	CDR L2	TTSNLAS
28	CDR L3	HQWSGYPT

[0519] Ten humanized variants of TREM1 antibody were made using the different framework mutations. **Table 1C** shows the number of framework mutations and the heavy and light chain pairing used in each humanized variant.

Table 1C			
mAb	# of Framework mutations (VH + VL)	VH used	VL used
PI-4026 (chimera)	N/A	N/A	N/A
PI-4026-1	0 (CDR swap only)	1	1
PI-4026-2	5	2	2
PI-4026-3	8	2	3
PI-4026-4	9	2	4
PI-4026-5	11	3	2
PI-4026-6	14	3	3
PI-4026-7	15	3	4
PI-4026-8	12	4	2
PI-4026-9	15	4	3
PI-4026-10	16	4	4

α 1,6-fucosyltransferase (FUT8) by CRISPR/Cas9 editing (Alexander Weiss, University of Toronto). Once cells were transfected, they were expanded for up to 7 days after which media was harvested and antibodies purified by a one-step protein A column purification step (HiTrap MabSelect SuRe, GE Healthcare). Antibodies were subsequently buffer exchanged into PBS and assessed for endotoxin (LAL Endotoxin test, Charles River Laboratories), concentration (Nanodrop, ThermoFisher Scientific), and any aggregation by UHPLC (ThermoFisher Scientific). Antibodies are SEC purified to monomer dependent on their aggregation properties (monomericity below 95%). Afucosylation is validated by a western blot with an antibody against Lens Culinaris Agglutination (LCA) antigen (L-1040-10, Vector Biolabs) or assessing the full glycan profile of the antibody of interest (Bionova Scientific).

Results

[0548] As shown in **FIG. 8**, PI-4026-5 has an oxidation risk at Met100 in CDRH3 (RMAAMDY (SEQ ID NO: 25)) as assessed by SEC. The percent heterogeneity of the antibody increases and the percent monomer decreases in an H₂O₂ dose dependent manner. This is indicated by the double peaks observed in the SEC profiles of the samples treated with 0.3%, 0.1%, and 0.01% H₂O₂. **Table 3** provides quantification of the SEC results.

Table 3		
%H₂O₂	% monomer	% heterogeneity
0	100	0
0.3	60.43	39.57
0.1	67.57	32.43
0.01	86.63	13.37
0.001	96.73	3.27
0.0001	100	0

[0549] To address this, the methionine at residue 100 in PI-4026-7 was mutated to isoleucine and the mutant antibody was tested as described above. As shown in **Table 4**, mutation of the methionine residue (RMAAMDY (SEQ ID NO: 25)) to isoleucine (RIAAMDY (SEQ ID NO: 30)) eliminated the oxidation risk. Incubation of the PI-4026-7M100I antibody with H₂O₂ did not result in any increase in protein heterogeneity.

Table 4				
	PI-4026-7-M100		PI-4026-7-M100I	
% H₂O₂	% monomer	% heterogeneity	% monomer	% heterogeneity
0	100	0	100	0
0.3	54.37	45.63	100	0
0.1	71.74	28.26	100	0
0.01	86.81	13.19	100	0
0.001	100	0	100	0
0.0001	100	0	100	0

[0550] Next, additional mutations were made in PI-4026-5 to determine one or more preferred mutation(s) at this residue position for clinical development. M100 was mutated to isoleucine (M100I), glutamic acid (M100E), leucine (M100L), or glutamine (M100Q). These mutations were

rationally selected based on an analysis of the solved crystal structure of the interaction between the PI-4026 Fab and the TREM1 IgV domain (**Example 5**). **Table 5** shows a summary of the CDR-H3 substitutions and sequences.

Table 5			
M100x substitutions	CDRH3 mutation	CDRH3 sequence	SEQ ID NO:
PI-4026-5-M100	None	RMAAMDY	25
PI-4026-5-M100I	M→I	RIAAMDY	30
PI-4026-5-M100E	M→E	REAAMDY	31
PI-4026-5-M100L	M→L	RLAAMDY	32
PI-4026-5-M100Q	M→Q	RQAAMDY	33

[0551] Each PI-4026-5 CDRH3 mutant was characterized as previously described in **Examples 2, 3,** and **4** for binding affinity to human and cynomolgus TREM1, SEC, cellular binding and EC₅₀ to human monocytes, DSF, and FcγR signaling using the hCD16 reporter assay system.

[0552] In addition, binding of the antibodies to cells overexpressing cynomolgus TREM1 was assessed. The results for the PI-4026-5 CDRH3 mutants are summarized in **Table 6**.

Table 6										
Anti-hTREM1 mAb (fucosylated)	Human Avid K_D (nM)	Cyno Avid K_D (nM)	% Mono-mer SEC	Human Monomeric K_D (nM)	Human Monomeric 'K_{off}' (M)	Back-ground binding	EC₅₀ (nM) Monocytes (Human)	EC₅₀ (nM) Cyno TREM1 cells	hCD16 ADCC assay EC₅₀ (nM)	DSF (Tm2, °C)
PI-4026-5-M100 (parent)	0.68	1.76	>95	4.81	6.67e-4	N	0.3	4.61	2.54	77.4
PI-4026-5-M100I	0.88	11.8	>95	10.2	1.31e-3	N	0.94	28.62	6.92	76.7
PI-4026-5-M100E	0.19	6.19	>95	3.33	4.76e-4	Y	0.45	57.99	3.18	77.6
PI-4026-5-M100L	0.27	1.43	>95	4.93	6.33e-4	N	0.67	4.85	5.86	77.3
PI-4026-5-M100Q	0.37	0.66	>95	5.61	9.06e-4	N	0.65	6.04	8.60	78.1

[0553] Next, afucosylated PI-4026-5 CDRH3 mutant antibodies were similarly characterized.

[0554] The results for the afucosylated PI-4026-5 CDRH3 mutants are summarized in **Table 7**.

Table 7										
Anti-hTREM1 mAb (afucosylated)	Human Avid K_D (nM)	Cyno Avid K_D (nM)	% Mono-mer SEC	Human Monomeric K_D (nM)	Human Monomeric 'K_{off}' (M)	Back-ground binding	EC₅₀ (nM) Monocytes (Human)	EC₅₀ (nM) Cyno TREM1 cells	hCD16 ADCC assay EC₅₀ (nM)	DSF (Tm2, °C)
PI-4026-5-M100 (parent)	0.55	2.99	>95	6.21	9.26e-4	N	0.60	6.61	0.36	77.5
PI-4026-5-M100I	0.88	13.4	>95	10.1	1.31e-3	N	1.06	22.02	0.39	76.7

CLAIMS

1. An isolated antibody that binds to human TREM1 (SEQ ID NO: 1), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:
 - a. CDR-H1 comprises the sequence set forth in SEQ ID NO: 23,
 - b. CDR-H2 comprises the sequence set forth in SEQ ID NO: 24,
 - c. CDR-H3 comprises the sequence set forth in SEQ ID NO: 33,
 - d. CDR-L1 comprises the sequence set forth in SEQ ID NO: 26,
 - e. CDR-L2 comprises the sequence set forth in SEQ ID NO: 27, and
 - f. CDR-L3 comprises the sequence set forth in SEQ ID NO: 28.
2. The isolated antibody of claim 1, wherein the VH sequence comprises the sequence set forth in SEQ ID NO: 17, and the VL sequence comprises the sequence set forth in SEQ ID NO: 20.
3. The isolated antibody of claim 1, wherein the VH sequence comprises the sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18; and the VL sequence comprises the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
4. The isolated antibody of claim 1, wherein the antibody comprises a heavy chain sequence set forth in SEQ ID NO: 34 and a light chain sequence set forth in SEQ ID NO: 35.
5. The isolated antibody of claim 1, wherein the VH sequence consists of the sequence set forth in SEQ ID NO: 17; and the VL sequence consists of the sequence set forth in SEQ ID NO: 20.
6. The isolated antibody of claim 1, wherein the VH sequence consists of the sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18; and the VL sequence consists of the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
7. The isolated antibody of claim 1, wherein the antibody consists of the heavy chain sequence set forth in SEQ ID NO: 34 and the light chain sequence set forth in SEQ ID NO: 35.

- 8.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and wherein the VH sequence comprises the sequence set forth in SEQ ID NO: 17, and the VL sequence comprises the sequence set forth in SEQ ID NO: 20.
- 9.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and wherein the VH sequence comprises the sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18; and the VL sequence comprises the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
- 10.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and the antibody comprises the heavy chain sequence set forth in SEQ ID NO: 34 and the light chain sequence set forth in SEQ ID NO: 35.
- 11.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and wherein the VH sequence consists of the sequence set forth in SEQ ID NO: 17, and the VL sequence consists of the sequence set forth in SEQ ID NO: 20.
- 12.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and wherein the VH sequence consists of the sequence selected from the sequences set forth in SEQ ID NO: 16, 17, or 18; and the VL sequence consists of the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
- 13.** The isolated antibody of claim 1, wherein the antibody is afucosylated, and the antibody consists of the heavy chain sequence set forth in SEQ ID NO: 34 and the light chain sequence set forth in SEQ ID NO: 35.
- 14.** The isolated antibody of claim 1, wherein the antibody is afucosylated.
- 15.** The isolated antibody of claim 1, wherein the antibody comprises human Fc.
- 16.** The isolated antibody of claim 15, wherein the human Fc is a wild-type human IgG1 Fc.
- 17.** The isolated antibody of claim 1, wherein the antibody is afucosylated and comprises a wild type human IgG1 Fc, and wherein the VH sequence comprises the sequence set forth in SEQ ID NO: 17, and the VL sequence comprises the sequence set forth in SEQ ID NO: 20.
- 18.** The isolated antibody of claim 1, wherein the antibody binds to human TREM1 with a K_D of less than or equal to about 0.5, 1, 2, 3, 4, 5, 6, or 7×10^{-9} M, as measured by surface plasmon resonance (SPR) assay.

- 19.** The isolated antibody of claim 1, wherein the antibody is humanized.
- 20.** A method of producing an antibody comprising expressing the antibody of claim 1 from an isolated host cell and isolating the expressed antibody.
- 21.** A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable excipient.
- 22.** A kit comprising the antibody of claim 1 and instructions for use.
- 23.** An isolated antibody that binds to human TREM1 (SEQ ID NO: 1), comprising a variable heavy chain (VH) sequence comprising three heavy chain CDR sequences, CDR-H1, CDR-H2, and CDR-H3, and a variable light chain (VL) sequence comprising three light chain CDR sequences, CDR-L1, CDR-L2, and CDR-L3, wherein:
- a. CDR-H1 comprises the sequence set forth in SEQ ID NO: 23,
 - b. CDR-H2 comprises the sequence set forth in SEQ ID NO: 24,
 - c. CDR-H3 comprises the sequence set forth in SEQ ID NO: 32,
 - d. CDR-L1 comprises the sequence set forth in SEQ ID NO: 26,
 - e. CDR-L2 comprises the sequence set forth in SEQ ID NO: 27, and
 - f. CDR-L3 comprises the sequence set forth in SEQ ID NO: 28.
- 24.** The isolated antibody of claim 23, wherein the VH sequence comprises the sequence set forth in SEQ ID NO: 13, and the VL sequence comprises the sequence set forth in SEQ ID NO: 20.
- 25.** A pharmaceutical composition comprising the antibody of claim 23 and a pharmaceutically acceptable excipient.
- 26.** The isolated antibody of claim 23, wherein the VH sequence comprises the sequence selected from the sequences set forth in SEQ ID NO: 12, 13, or 14; and the VL sequence comprises the sequence selected from the sequences set forth in SEQ ID NOs: 20, 21, or 22.
- 27.** A pharmaceutical composition comprising the antibody of claim 2 and a pharmaceutically acceptable excipient.
- 28.** A pharmaceutical composition comprising the antibody of claim 4 and a pharmaceutically acceptable excipient.

- 29.** A pharmaceutical composition comprising the antibody of claim 5 and a pharmaceutically acceptable excipient.
- 30.** A pharmaceutical composition comprising the antibody of claim 7 and a pharmaceutically acceptable excipient.
- 31.** A pharmaceutical composition comprising the antibody of claim 8 and a pharmaceutically acceptable excipient.
- 32.** A pharmaceutical composition comprising the antibody of claim 10 and a pharmaceutically acceptable excipient.
- 33.** A pharmaceutical composition comprising the antibody of claim 11 and a pharmaceutically acceptable excipient.
- 34.** A pharmaceutical composition comprising the antibody of claim 13 and a pharmaceutically acceptable excipient.
- 35.** A pharmaceutical composition comprising the antibody of claim 17 and a pharmaceutically acceptable excipient.
- 36.** The antibody of claim 4, wherein the antibody comprises two heavy chain sequences, each having the sequence as set forth in SEQ ID NO: 34; and two light chain sequences, each having the sequence as set forth in SEQ ID NO: 35.
- 37.** The antibody of claim 4, wherein the antibody consists of two heavy chain sequences, each having the sequence as set forth in SEQ ID NO: 34; and two light chain sequences, each having the sequence as set forth in SEQ ID NO: 35.
- 38.** The antibody of claim 10, wherein the afucosylated antibody comprises two heavy chain sequences, each having the sequence as set forth in SEQ ID NO: 34; and two light chain sequences, each having the sequence as set forth in SEQ ID NO: 35.
- 39.** The antibody of claim 10, wherein the afucosylated antibody consists of two heavy chain sequences, each having the sequence as set forth in SEQ ID NO: 34; and two light chain sequences, each having the sequence as set forth in SEQ ID NO: 35.
- 40.** A pharmaceutical composition comprising the antibody of claim 36 and a pharmaceutically acceptable excipient.

- 41.** A pharmaceutical composition comprising the antibody of claim 37 and a pharmaceutically acceptable excipient.
- 42.** A pharmaceutical composition comprising the antibody of claim 38 and a pharmaceutically acceptable excipient.
- 43.** A pharmaceutical composition comprising the antibody of claim 39 and a pharmaceutically acceptable excipient.