

Streptococcus infection, *Campylobacter jejuni* infection, *Neisseria meningitidis* infection, type I HIV, and Haemophilus influenza. The methods provided herein also find use in inducing or promoting the survival, maturation, functionality, migration, or proliferation of one or more immune cells in an individual in need thereof. The methods provided herein find further use in decreasing the activity, functionality, or survival of regulatory T cells, tumor-imbedded immunosuppressor dendritic cells, tumor-imbedded immunosuppressor macrophages, neutrophils, natural killer (NK) cells, myeloid-derived suppressor cells, tumor-associated macrophages, neutrophils, NK cells, acute myeloid leukemia (AML) cells, chronic lymphocytic leukemia (CLL) cell, or chronic myeloid leukemia (CML) cell in an individual in need thereof

[0023a] In one aspect, the present disclosure refers to an isolated humanized antibody that binds to a human TREM2 protein, wherein the antibody decreases levels of amyloid beta (Abeta) peptide in an individual as compared to levels of Abeta peptide in a corresponding individual that is not treated with the antibody or that is treated with an isotype control antibody.

[0024] In some examples, tumor cells, such as acute myeloblastic leukemia (AML) cell, express TREM2. Accordingly, anti-TREM2 antibodies of the present disclosure also find use in treating cancers. In some examples, anti-TREM2 antibodies, including antibodies that display antibody-dependent cell-mediated cytotoxicity (ADCC) and/or TREM2 antibody drug conjugates, can be used to target and inhibit cancer, such as AML.

[0025] Certain examples of the present disclosure are based, at least in part, on the identification of two distinct classes of isolated antibodies that specifically bind to and modulate TREM2 proteins.

[0026] One class of antibodies relates to agonist antibodies that induce one or more TREM2 activities on, for example, human primary immune cells and TREM2-expressing cell lines, and when combined with one or more TREM2 ligands enhance one or more TREM2 activities induced by binding of the one or more TREM2 ligands to the TREM2 protein. Advantageously, such agonist anti-TREM2 antibodies can enhance ligand-induced TREM2 activity without competing with or otherwise blocking binding of the one or more TREM2 ligands to the TREM2 protein. In some examples, the agonist antibodies can activate and/or enhance the one or more TREM2 activities regardless of whether the antibodies are clustered or in solution. In some examples, the agonist antibodies can activate TREM2 in solution without the need to be clustered by secondary antibodies, by Fc receptors, or by binding to plates. In some examples, the agonist antibodies may activate TREM2 regardless of whether the mechanism for antibody clustering are present at the therapeutic site of action *in vivo*. In some examples, the agonist antibodies may have increased safety and efficacy. In some examples, the agonist antibodies can ensure that immune cells that express TREM2 will act primarily in the location where they are required for therapeutic efficacy and will be able to interact with their physiological targets. In some examples, the agonist antibodies do not block TREM2 activity that leads to increased disease risks similar to those observed with genetic mutations that reduce TREM2 activity.

[0027] The second class of antibodies relates to antagonist antibodies that specifically bind to and inhibit TREM2, and are incapable of activating TREM2 regardless of whether the antibodies are clustered or in solution. In some examples, the antagonist antibodies have increases safety and

pharmaceutical composition comprising the antibody of any of the preceding examples and a pharmaceutically acceptable carrier.

[0042a] In one aspect, the present disclosure refers to an isolated nucleic acid comprising a nucleic acid sequence encoding the antibody disclosed herein.

[0042b] In one aspect, the present disclosure refers to a vector comprising the nucleic acid disclosed herein.

[0042c] In one aspect, the present disclosure refers to an isolated host cell comprising the vector disclosed herein.

[0042d] In one aspect, the present disclosure refers to a method of producing an isolated humanized antibody that binds to a human TREM2 protein, comprising culturing the host cell disclosed herein so that the antibody is produced.

[0042e] In one aspect, the present disclosure refers to an isolated humanized antibody that binds to a human TREM2 protein produced by the method disclosed herein.

[0042f] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody disclosed herein and a pharmaceutically acceptable carrier.

[0043] Other examples of the present disclosure relate to a method of preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, taupathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomatous disorders, sarcoidosis, diseases of aging, seizures, spinal cord injury, traumatic brain injury, age related macular degeneration, glaucoma, retinitis pigmentosa, retinal degeneration, respiratory tract infection, sepsis, eye infection, systemic infection, lupus, arthritis, multiple sclerosis, low bone density, osteoporosis, osteogenesis, osteopetrotic disease, Paget's disease of bone, bladder cancer, brain cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, kidney cancer, renal cell cancer, renal pelvis cancer, leukemia, lung cancer, melanoma, non-Hodgkin's lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, fibrosarcoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma, polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, primary or idiopathic myeloid-derived tumors, thyroid cancer, infections, CNS herpes, parasitic infections, Trypanosome infection, Cruzi infection, *Pseudomonas aeruginosa* infection, *Leishmania donovani* infection, group B *Streptococcus* infection, *Campylobacter jejuni* infection, *Neisseria meningitidis* infection, type I HIV, and Haemophilus influenza, comprising administering to an individual in need thereof a therapeutically effective amount of an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein. Other examples of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein for use in preventing, reducing risk, or treating an individual having a disease, disorder, or injury selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, amyotrophic lateral sclerosis, Huntington's disease, taupathy disease, Nasu-Hakola disease, stroke, acute trauma, chronic trauma, cognitive deficit, memory loss, lupus, acute and chronic colitis, rheumatoid arthritis, wound healing, Crohn's disease, inflammatory bowel disease, ulcerative colitis, obesity, malaria, essential tremor, central nervous system lupus, Behcet's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, cortical basal ganglionic degeneration, acute disseminated encephalomyelitis, granulomatous disorders,

L2 antibody, an anti-PD-1 antibody, an anti-B7-H3 antibody, an anti-B7-H4 antibody, and anti-HVEM antibody, an anti- B- and T-lymphocyte attenuator (BTLA) antibody, an anti-Killer inhibitory receptor (KIR) antibody, an anti-GAL9 antibody, an anti-TIM3 antibody, an anti-A2AR antibody, an anti-LAG-3 antibody, an anti-phosphatidylserine antibody, an anti-CD27 antibody, and any combination thereof. In some examples, the standard or investigational anti-cancer therapy is one or more therapies selected from the group consisting of radiotherapy, cytotoxic chemotherapy, targeted therapy, hormonal therapy, imatinib (Gleevec®), trastuzumab (Herceptin®), bevacizumab (Avastin®), Ofatumumab (Arzerra®), Rituximab (Rituxan®, MabThera®, Zytux®), cryotherapy, ablation, radiofrequency ablation, adoptive cell transfer (ACT), chimeric antigen receptor T cell transfer (CAR-T), vaccine therapy, and cytokine therapy. In some examples, the method further comprises administering to the individual at least one antibody that specifically binds to an inhibitory cytokine. In some examples, the at least one antibody that specifically binds to an inhibitory cytokine is administered in combination with the isolated antibody. In some examples, the at least one antibody that specifically binds to an inhibitory cytokine is selected from the group consisting of an anti-CCL2 antibody, an anti-CSF-1 antibody, an anti-IL-2 antibody, and any combination thereof. In some examples, the method further comprises administering to the individual at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein. In some examples, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is administered in combination with the isolated antibody. In some examples, the at least one agonistic antibody that specifically binds to a stimulatory checkpoint protein is selected from the group consisting of an agonist anti-CD40 antibody, an agonist anti-OX40 antibody, an agonist anti-ICOS antibody, an agonist anti-CD28 antibody, an agonist anti-CD137/4-1BB antibody, an agonist anti-CD27 antibody, an agonist anti-glucocorticoid-induced TNFR-related protein GITR antibody, and any combination thereof. In some examples, the method further comprises administering to the individual at least one stimulatory cytokine. In some examples, the at least one stimulatory cytokine is administered in combination with the isolated antibody. In some examples, the at least one stimulatory cytokine is selected from the group consisting of TNF- α , IL-10, IL-6, IL-8, CRP, TGF-beta members of the chemokine protein families, IL20 family member, IL-33, LIF, OSM, CNTF, TGF-beta, IL-11, IL-12, IL-17, IL-8, IL-23, IFN- α , IFN- β , IL-2, IL-18, GM-CSF, G-CSF, and any combination thereof.

[0044] Other examples of the present disclosure relate to a method of enhancing one or more TREM2 activities induced by binding of one or more TREM2 ligands to a TREM2 protein in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein. Other examples of the present disclosure relate to an isolated (e.g., monoclonal) antibody that binds to a TREM2 protein for use in enhancing one or more TREM2 activities induced by binding of one or more TREM2 ligands to a TREM2 protein in an individual in need thereof. Other examples of the present disclosure

[0050] Other examples of the present disclosure relate to a method of increasing memory, reducing cognitive deficit, or both in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated agonist antibody that binds to a TREM2 protein. Other examples of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in increasing memory, reducing cognitive deficit, or both in an individual in need thereof. Other examples of the present disclosure relate to use of an isolated agonist antibody that binds to a TREM2 protein in the manufacture of a medicament for increasing memory, reducing cognitive deficit, or both in an individual in need thereof. In some examples, the isolated agonist antibody is the agonist antibody of any of the preceding examples.

[0051] Other examples of the present disclosure relate to a method of increasing motor coordination in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated agonist antibody that binds to a TREM2 protein. Other examples of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in increasing motor coordination in an individual in need thereof. Other examples of the present disclosure relate to use of an isolated agonist antibody that binds to a TREM2 protein in the manufacture of a medicament for increasing motor coordination in an individual in need thereof. In some examples, the isolated agonist antibody is the agonist antibody of any of the preceding examples.

[0052] Other examples of the present disclosure relate to a method of reducing Abeta peptide levels in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated agonist antibody that binds to a TREM2 protein. Other examples of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in reducing Abeta peptide levels in an individual in need thereof. Other examples of the present disclosure relate to use of an isolated agonist antibody that binds to a TREM2 protein in the manufacture of a medicament for reducing Abeta peptide levels in an individual in need thereof. In some examples, the isolated agonist antibody is the agonist antibody of any of the preceding examples.

[0053] Other examples of the present disclosure relate to a method of increasing the number of CD11b⁺ microglial cells in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of an isolated agonist antibody that binds to a TREM2 protein. Other examples of the present disclosure relate to an isolated agonist antibody that binds to a TREM2 protein for use in increasing the number of CD11b⁺ microglial cells in an individual in need thereof. Other examples of the present disclosure relate to use of an isolated agonist antibody that binds to a TREM2 protein in the manufacture of a medicament for increasing the number of CD11b⁺ microglial cells in an individual in need thereof. In some examples, the isolated agonist antibody is the agonist antibody of any of the preceding examples.

[0054] Other examples of the present disclosure relate to a method of increasing levels of one or more of FLT1, OPNCSF1, CD11c, and AXL in an individual in need thereof, comprising

CLAIMS

What is claimed is:

1. An isolated humanized antibody that binds to a human TREM2 protein, wherein the antibody decreases levels of amyloid beta (Abeta) peptide in an individual as compared to levels of Abeta peptide in a corresponding individual that is not treated with the antibody or that is treated with an isotype control antibody.
2. The isolated humanized antibody of claim 1, wherein the antibody decreases levels of Abeta peptide in one or more cells in the individual as compared to levels of Abeta peptide in one or more cells in the corresponding individual that is not treated with the antibody or that is treated with an isotype control antibody.
3. The isolated humanized antibody of claim 1 or claim 2, wherein the antibody decreases levels of Abeta peptide in the brain of the individual as compared to levels of Abeta peptide in the brain of the corresponding individual that is not treated with the antibody or that is treated with an isotype control antibody.
4. The isolated humanized antibody of claim 3, wherein the antibody decreases levels of Abeta peptide in the brain of the individual by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or more, as compared to levels of Abeta peptide in the brain of the corresponding individual that is not treated with the antibody or that is treated with an isotype control antibody.
5. The isolated humanized antibody of claim 3 or claim 4, wherein the antibody decreases brain levels of Abeta peptide in the frontal cortex and/or hippocampus of the individual as compared to brain levels of Abeta peptide in the frontal cortex and/or hippocampus of the corresponding individual that is not treated with the antibody or that is treated with an isotype control antibody.
6. The isolated humanized antibody of any one of claims 3-5, wherein brain levels of Abeta peptide are assessed:
 - (a) based on a percentage of area of the brain that is positive for Abeta peptide; and/or
 - (b) based on levels of Abeta peptide in brain lysates.
7. The isolated humanized antibody of claim 6, wherein:
 - (a) the percentage of area of the brain that is positive for Abeta peptide is assessed by immunohistochemistry; and/or
 - (b) levels of Abeta peptide in brain lysates are assessed by enzyme-linked immunosorbent assay (ELISA).
8. The isolated humanized antibody of any one of claims 5-7, wherein:

- (a) the antibody decreases levels of Abeta peptide in the frontal cortex of the individual by at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50%, as compared to levels of Abeta peptide in the frontal cortex of the corresponding individual that is not treated with the antibody or that is treated with an isotype control antibody; and/or
 - (b) the antibody decreases levels of Abeta peptide in the hippocampus of the individual by at least about 20%, at least about 25%, or at least about 30%, as compared to levels of Abeta peptide in the hippocampus of the corresponding individual that is not treated with the antibody or that is treated with an isotype control antibody.
9. The isolated humanized antibody of any one of claims 1-8, wherein the Abeta peptide is Abeta42 or Abeta40.
 10. The isolated humanized antibody of any one of claims 1-9, wherein the antibody induces one or more TREM2 activities and enhances one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein.
 11. The isolated humanized antibody of claim 10, wherein the one or more TREM2 ligands are selected from the group consisting of E. coli cells, apoptotic cells, nucleic acids, anionic lipids, anionic lipids, APOE, APOE2, APOE3, APOE4, anionic APOE, anionic APOE2, anionic APOE3, anionic APOE4, lipidated APOE, lipidated APOE2, lipidated APOE3, lipidated APOE4, zwitterionic lipids, negatively charged phospholipids, phosphatidylserine, sulfatides, phosphatidylcholin, sphingomyelin, membrane phospholipids, lipidated proteins, proteolipids, lipidated peptides, lipidated amyloid beta peptide, and any combination thereof.
 12. The isolated humanized antibody of any one of claims 10-11, wherein the antibody induces the one or more TREM2 activities when the antibody is in solution and not clustered, and/or the antibody enhances the one or more TREM2 activities induced by binding of one or more TREM2 ligands to the TREM2 protein when the antibody is in solution and not clustered.
 13. The isolated humanized antibody of any one of claims 10-12, wherein the antibody:
 - (a) enhances the one or more TREM2 activities without blocking binding of one or more TREM2 ligands to the TREM2 protein; and/or
 - (b) enhances the one or more TREM2 activities by inducing or retaining cell surface clustering of TREM2, and/or when the antibody is clustered by secondary antibodies, by Fc receptors, or by binding to plates.
 14. The isolated humanized antibody of any one of claims 1-13, wherein the antibody:
 - (a) does not compete with one or more TREM2 ligands for binding to the TREM2 protein; and/or
 - (b) enhances binding of one or more TREM2 ligands to the TREM2 protein.

15. The isolated humanized antibody of any one of claims 1-14, wherein the TREM2 protein is a wild-type protein or a naturally occurring variant.

16. The isolated humanized antibody of any one of claims 10-15, wherein the one or more TREM2 activities are selected from the group consisting of:

- (a) TREM2 binding to DAP12;
- (b) DAP12 phosphorylation;
- (c) activation of Syk kinase;
- (d) modulation of one or more pro-inflammatory mediators selected from the group consisting of IFN- β , IL-1 α , IL-1 β , TNF- α , IL-6, IL-8, CRP, CD86, MCP-1/CCL2, CCL3, CCL4, CCL5, CCR2, CXCL-10, Gata3, IL-20 family members, IL-33, LIF, IFN-gamma, OSM, CNTF, CSF-1, OPN, CD11c, GM-CSF, IL-11, IL-12, IL-17, IL-18, and IL-23, optionally wherein the modulation occurs in one or more cells selected from the group consisting of macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, dendritic cells, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, and microglial cells;
- (e) recruitment of Syk to a DAP12/TREM2 complex;
- (f) increasing activity of one or more TREM2-dependent genes, optionally wherein the one or more TREM2-dependent genes comprise nuclear factor of activated T-cells (NFAT) transcription factors;
- (g) increased survival of dendritic cells, macrophages, M1 macrophages, activated M1 macrophages, M2 macrophages, monocytes, osteoclasts, Langerhans cells of skin, Kupffer cells, microglia, M1 microglia, activated M1 microglia, or M2 microglia, or any combination thereof;
- (h) modulated expression of one or more stimulatory molecules selected from the group consisting of CD83, CD86 MHC class II, CD40, and any combination thereof, optionally wherein the CD40 is expressed on dendritic cells, monocytes, macrophages, or any combination thereof, and optionally wherein the dendritic cells comprise bone marrow-derived dendritic cells;
- (i) increasing memory; and
- (j) reducing cognitive deficit.

17. The isolated humanized antibody of any one of claims 1-16, wherein:

- (a) the isolated antibody is of the IgG class, the IgM class, or the IgA class;
- (b) the isolated antibody is of the IgG class and has an IgG1, IgG2, IgG3, or IgG4 isotype;
- (c) the isolated antibody has a human or mouse IgG1 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: N297A, D265A, D270A, L234A, L235A, G237A, C226S, C229S, E233P,

L234V, L234F, L235E, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, L328E, P238D, S267E, L328F, E233D, G237D, H268D, P271G, A330R, and any combination thereof, wherein the numbering of the residues is according to EU numbering, or comprises an amino acid deletion in the Fc region at a position corresponding to glycine 236 according to EU numbering;

(d) the isolated antibody has an IgG1 isotype and comprises an IgG2 isotype heavy chain constant domain 1(CH1) and hinge region, optionally wherein the IgG2 isotype CH1 and hinge region comprises the amino acid sequence of ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGVHTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDPHKPS NTKVDKTVERKCCVECPPCP (SEQ ID NO: 886), and optionally wherein the antibody Fc region comprises a S267E amino acid substitution, a L328F amino acid substitution, or both, and/or a N297A or N297Q amino acid substitution, wherein the numbering of the residues is according to EU numbering;

(e) the isolated antibody has an IgG2 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: P238S, V234A, G237A, H268A, H268Q, V309L, A330S, P331S, C214S, C232S, C233S, S267E, L328F, M252Y, S254T, T256E, H268E, N297A, N297Q, A330L, and any combination thereof, wherein the numbering of the residues is according to EU numbering;

(f) the isolated antibody has a human or mouse IgG4 isotype and comprises one or more amino acid substitutions in the Fc region at a residue position selected from the group consisting of: L235A, G237A, S228P, L236E, S267E, E318A, L328F, M252Y, S254T, T256E, E233P, F234V, L234A/F234A, S228P, S241P, L248E, T394D, N297A, N297Q, L235E, and any combination thereof, wherein the numbering of the residues is according to EU numbering; or

(g) the isolated antibody has a hybrid IgG2/4 isotype, and optionally wherein the antibody comprises an amino acid sequence comprising amino acids 118 to 260 of human IgG2 and amino acids 261 to 447 of human IgG4, wherein the numbering of the residues is according to EU numbering.

18. The isolated humanized antibody of any one of claims 1-17, wherein the antibody binds to one or more amino acids within amino acid residues 142-152 of SEQ ID NO: 1, or amino acid residues on a TREM2 protein corresponding to amino acid residues 142-152 of SEQ ID NO: 1.

19. The isolated humanized antibody of any one of claims 1-18, wherein the isolated humanized antibody competes for binding to TREM2 with an antibody comprising an HVR-L1 of SEQ ID NO: 11, an HVR-L2 of SEQ ID NO: 26, an HVR-L3 of SEQ ID NO: 36, an HVR-H1 of SEQ ID NO: 51, an HVR-H2 of SEQ ID NO: 69, and an HVR-H3 of SEQ ID NO: 88.

20. The isolated humanized antibody of any one of claims 1-18, wherein the isolated humanized antibody comprises an HVR-L1, an HVR-L2, an HVR-L3, an HVR-H1, an HVR-H2, and an HVR-H3, wherein the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence of SEQ ID NO: 11 having one or more conservative amino acid substitutions, the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 26 or an amino acid sequence of SEQ ID NO: 26 having one or more conservative amino acid substitutions, the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 36 or an amino acid sequence of SEQ ID NO: 36 having one or more conservative amino acid substitutions, the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 51 or an amino acid sequence of SEQ ID NO: 51 having one or more conservative amino acid substitutions, the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 69 or an amino acid sequence of SEQ ID NO: 69 having one or more conservative amino acid substitutions, and the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 88 or an amino acid sequence of SEQ ID NO: 88 having one or more conservative amino acid substitutions.
21. The isolated humanized antibody of any one of claims 1-16 and 18-20, wherein the antibody is an antibody fragment and the antibody fragment is an Fab, Fab', Fab'-SH, F(ab')₂, Fv or scFv fragment.
22. The isolated humanized antibody of any one of claims 1-21, wherein the antibody is a bispecific antibody, a multivalent antibody, and/or a conjugated antibody.
23. The isolated humanized antibody of any one of claims 1-22, wherein the antibody is a monoclonal antibody.
24. The isolated humanized antibody of any one of claims 1-23, wherein the antibody binds specifically to both human TREM2 and mouse TREM2.
25. The isolated humanized antibody of any one of claims 1-24, wherein the antibody has a dissociation constant (KD) for mouse TREM2 that ranges from 1.2 nM to 10.4 nM, wherein the KD is determined at a temperature of approximately 4°C.
26. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of claims 1-25.
27. A vector comprising the nucleic acid of claim 26.
28. An isolated host cell comprising the vector of claim 27.
29. A method of producing an isolated humanized antibody that binds to a human TREM2 protein, comprising culturing the host cell of claim 28 so that the antibody is produced.
30. An isolated humanized antibody that binds to a human TREM2 protein produced by the method of claim 29.

31. A pharmaceutical composition comprising the antibody of any one of claims 1-25 and a pharmaceutically acceptable carrier.